Applied Chemical Engineering (2023) Volume 6 Issue 3
doi: 10.24294/ace.v6i3.2170

REVIEW ARTICLE

Bacterial nanocellulose-Robust preparation and application—A literature review

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ABSTRACT

Increasing attention is being paid to bacterial nanocellulose (BNC) because of its environment-friendly properties. Researchers investigated the role of microbial hosts in BNC production due to the benefits of cellulose produced by microbes. Several research groups have developed techniques to make BNC on a large scale with the goal of developing new methods. A 3D network of micro and nanofibrils in BNC synthesized from several bacterial strains makes these BNC useful for reinforcing nanostructured composites that have increased Young's modulus, tensile strength, purity, crystallinity, and water holding capacity. To overcome the barriers associated with the industrial scale production of BNC, different production techniques will be used, including static culture, cell-free production, agitated/shaking culture, using a variety of receptors for fermentation, and low-cost substrates as carbon sources. By in-situ and ex-situ fermentation processes, metal/metal oxide nanoparticle composites are among the most widely used materials in diagnostic and regenerative medicine. The purpose of the review is to update the researchers regarding the lucid production process and versatile applications of bacterial nanocellulose in biomedical field. We shall mainly discuss about the different methods for bacterial cellulose production and some of its applications in this mini-review.

Keywords: bacterial nanocellulose; production of BNC; biomedical applications; tissue engineering; biosensing

ARTICLE INFO

Received: 29 May 2023
Accepted: 2 August 2023
Available online: 14 November 2023

1. Introduction

The cellulose synthesis of bacteria results in the production of bacterial nanocellulose (BNC), which is a natural, biodegradable material. A highly ordered three-dimensional network of thin, microfibrillar strands of cellulose is formed. Several unique properties like high toughness, high strength, and high modulus of BNC make it suitable for a wide range of applications including packaging material, wound dressing, artificial skin, tissue engineering scaffolds, and cosmetics[1,2]. In composite materials, BNCs can serve as reinforcements (combined with polymers or biopolymers to enhance its properties) as well as standalone materials (like scaffolds for tissue engineering, and wound dressing). Material containing BNC fibers are usually reinforced by a matrix (e.g., polymer). The polymer matrix is the continuous phase that surrounds and binds the reinforcement material to improve the mechanical properties of composites over the matrix alone by using these materials[3]. The production of BNC can be accomplished in a variety of ways, including the traditional fermentation process, involving cultivating bacteria in liquid media, and the more recent electrospinning method, which involves applying an electric field to produce BNC fibers. With various additives, BNC can be tailored for specific applications in sheets, films, and fibers[4].

BNC is suitable for structural applications due to its high strength (σ = 2–7.7 GPa) and modulus ($E \approx 140$ GPa) compared to steel[5]. Steel can be replaced with this material in certain applications like lightweight structural components, biomedical implants, and biodegradable packaging and containers due to its similar tensile strength and modulus to high-strength steel. In addition to being tough, BNC can also withstand a great deal of deformation without breaking. Microorganisms can break down the material into natural substances, making it potentially sustainable compared to synthetic materials[6]. As a barrier material, BNC is suitable for packaging applications. Food products can be protected against gas penetration by its low moisture absorption rate, making it a good option for extending their shelf life[4,7]. Non-bacterial cellulose fibers vary significantly is shape and size, depending on the source and extraction process but BNC has unique nanofibrillar structure with highly uniform and intertwining. BNC is stronger than most non-BC material because of its excellent mechanical properties including high stiffness and tensile strength[8]. Furthermore, BNC is highly porous and has highly pronounced physical and mechanical properties, so it can be used in filtration and separation applications. Water treatment and desalination membranes have been developed from it as filters and membrane materials. Overall, BNC has many potential applications due to its unique combination of properties[9].

It is important to address some challenges in order to fully utilize the potential of BNC. In addition to the high cost of production, BNC has not been widely adopted because of its high cost. The cost of BNC will likely decrease as production methods improve and become more efficient, allowing it to be used in a broader range of applications. Availability of BNC is also a challenge. In order to meet the demand for BNC, it is necessary to develop methods for large-scale production[10]. Currently, BNC is produced on a small scale having an area of 29,400 cm^2 and weight ranging from 16.24 to 17.04 kg[11].

In order to optimize BNC's use in numerous applications, further research and development are required to fully understand its properties and behavior. It is also important to understand how to manufacture sheets, films, and fibers from BNC by functionalizing it with a variety of additives to tailor its properties to specific applications. The purpose of this review is to provide an update to the previously published articles regarding increasing the production of bacterial cellulose in large scale, and focusing on their use in environmental and biomedical applications.

2. Cellulose—A versatile polymer

Cellulose is the primary structural component of the cell wall of plants, algae and certain bacteria. In comparison to other biopolymers on earth, cellulose is the most common natural polymer used worldwide. Cellulose is the most abundant organic compound and a complex carbohydrate. Cellulose is produced by plants and some microbes through complex chemical processes, such as photosynthesis, glucose formation, polymerization, microfibril formation, and cell wall construction[12]. It is a biopolymer made up of monomers (repeating units of glucose or simple sugar). Beta-D-glucose is cellulose's basic building block or monomer, a simple sugar with the molecular formula $C_6H_{12}O_6$. The linear and unbranched polymer chain of cellulose is formed by glucose molecules attached through beta-1,4-glycosidic bonds. The molecular formula of cellulose is $(C_6H_{10}O_5)n$, here "n" represents the number of sugar units that are linked together to form the polymer chain[13]. A long and fibrous chains are formed due to the specific arrangement of these glucose monomers and the strong bond between them. The production of cellulose pulp worldwide each year exceeds 10^{14} t, showing the huge consumption and thereby the importance of polymers and their use in daily life[14]. Lignocellulosic pulp consist of long cellulose fibers, lignin, and hemicelluloses are obtained from lignocellulosic biomass (wood or non-wood plant materials, and agricultural residues), and is primary used in paper and fibreboard industries[15]. Nanocellulose can be produced from various cellulose like wood pulp and bacterial cellulose by breaking down (mechanical or chemical treatment) the cellulose material into nanoscale dimensions. It has applications including drug delivery system, tissue engineering scaffolds, food packaging, electronics, and sensors[16]. Ranby first described sulphuric acid hydrolysis as a method for producing colloidal cellulose (cellulose that exists in colloidal form) almost 70 years ago[17]. Because of the strong intermolecular and intramolecular hydrogen bonds between its molecules, cellulose is insoluble in most common solvents and water. A wide range of applications are possible with cellulose due to its poor solubility. Chemical modifications like etherification, esterification, oxidation, carboxymethylation, and acetylation are performed on cellulose to improve its processing ability[18]. Various industrial applications and biomedical applications use cellulosic (cellulose derivatives) that are biocompatible, generally strong, reproducible, biodegradable, and recyclable[19]. Carbon monoxide, carbon dioxide, chlorine gas, carbon disulphide, and caustic soda are some of the pollutants used in the production of pure cellulose, which makes it a potentially hazardous to environment environment.

Plants, microbes, and enzymes are able to produce cellulose through a variety of processes. There is a wide range of cellulose synthesis in plants through photosynthesis, which converts carbon dioxide and water into glucose[20], such as cotton fibres that produce 90%, wood that produces 70%, and dried hemp that produces 40%–50%. Cellulose is produced by a variety of microorganisms, including algae, fungi, and bacteria. Microfibrillated cellulose (MFC) is a three-dimensional network made of aggregated cellulose chains, each of which is made up of an assembly of several glucose molecules, that are linked together through van der Waals and hydrogen bonds to form the three-dimensional structure (**Figure 1**). It consists of long, slender cellulose microfibrils that have high length-to-width ratio[21].

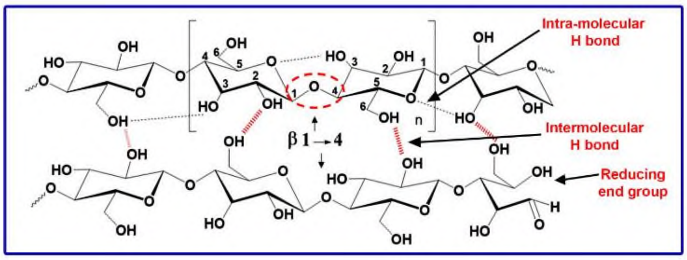

Figure 1. The molecular structure of Microfibrillated cellulose. The figure is adapted from the study of Tayeb et al.[1].

It is possible to disintegrate MFCs into cellulose nanostructures using a variety of methods, including mechanical treatment. The disintegration process is however highly energy-intensive and inefficient[22]. The hydrogen bonds between cellulose nanostructures can be broken by chemical treatment as an alternative method. The mechanical treatment primarily affects the amorphous region of cellulose, while chemical treatment targets both amorphous and crystalline region. As a result, cellulose fibers can be functionalized with a surface charge, which creates repulsion between them, eventually resulting in the disintegration of cellulose nanofibers and nanocrystalline cellulose[23,24], which are also known as cellulose nanocrystals (CNC). Depending on the cellulose source and preparation conditions, CNCs have been classified into four categories: CNC, CNF, bacterial nanocellulose (BNCC), and hairy nanocellulose (HNC)[25]. BNCC is typically generated by bacteria, such as *Gluconacetobacter xylinus*, by producing cellulose in aqueous culture media. Despite the fact that these bacteria produce ribbon-like nanofibrils, they cannot be isolated mechanically. The diameter of BNCC is larger than the diameter of CNF, but the lengths are similar[26]. The crystallinity, purity, and mechanical properties of BNCC are higher than those of CNF[27,28]. To list out the advantages of microbes over plants when it comes to producing cellulose, Donini et al. compared cellulose produced by microbes and plants[29]. Plant cellulose contains pectin, hemicelluloses, lignin, and other compounds, whereas bacterial cellulose is pure and free from these contaminants. The mechanical properties of bacterial cellulose are higher than those of plant cellulose[30].

3. Bacterial nanocellulose (BNC)

Acetobacter xylinum was the first bacterium used by Brown to produce cellulose in 1886, then multiple strains were used thereafter. The microbial strains that produce cellulose are pure, and this means that it does not contain any of the compounds typically found in plant pulp, such as lignin, pectin, hemicelluloses, etc.[31]. Moreover, BNC has many unique characteristics, including its high purity, large surface area, crystallinity, high degree of water holding capacity, and excellent mechanical properties, on top of its large surface area. In addition to its unique properties, BNC is also known as bacterial cellulose (BC), which finds a wide range of applications, such as drug delivery, production of polymer nanocomposites, food applications, and tissue engineering.

Many wild and recombinant microbial strains have been reported to produce cellulose by utilizing multiple carbon sources, including wastes as their substrate. BC is produced by both Gram-negative and Gram-positive bacterial species; they are *Agrobacterium, Achromobacter, Aerobacter, Azotobacter, Alcaligenes, Rhodobacter, Rhizobium, Dickeya, Sarcina, and Pseudmonas*. The *A. Pasteurianus*, *A. Xylinum*, and *A. Hansenni* are the most effective strains used for BC production and in recent, *A. Xylinum* has been an aerobic Gram-negative strain used for large-scale BC production[32]. Several mutant strains have been developed using genetic engineering principles to improve BC production and yield by improving its structural features. This method effectively increased the production of BC up to 100%[33].

Bacterial strains such as *Gluconacetobacter xylinus* produce BNC in large quantities and have become the primary model for studying bacteria's biosynthesis of the compound. An outer layer of gelatinous material and a denser lateral surface are created by *G. xylinus* during the production of cellulose. The synthesis of cellulose by *G. xylinus* in the biochemical process consists of three major steps: polymerization of glucose residues in glucan molecules, linear chain extracellular secretions, and crystallization and organization of glucan chains through Van der Waals force and hydrogen bonds arrayed in a hierarchy into strips; exhibiting that the cellulose is produced[34]. **Figure 2** shows the production of bacterial nanocellulose.

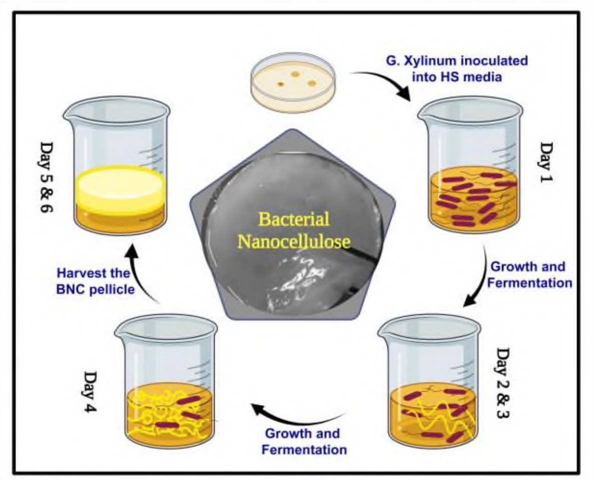

Figure 2. The production of bacterial nanocellulose using *Acetobacter Xylinum*.

4. Properties of bacterial cellulose

Plant cellulose (PC) and BNC have similar chemical properties but differ in physical characteristics, macromolecular properties, and purity. Due to the absence of pectin, lignin, and hemicellulose, BNC is highly purified and more polymerizable and crystallizable than PC. Replacing the PC with BNC will decrease pollution by avoiding the long and restrictive purification process. In BNC, ultrafine fibers with a diameter of 20 nm–100 nm are assembled in a network of ultrafine fibers, which are about 100 times thinner than PC fibers[35]. BNC has special nanomorphology, allowing it to hold dry weight up to 200 times in water, making it excellently conformable, elastic and highly sensitive to wet conditions. Some of the properties of bacterial nanocellulose (BNC) cannot be achieved with plant cellulose, certain differences between the two make BNC unique. Both PC and BNC are composed of same cellulose polymer, but their production process and resulting structures lead to different material properties[36]. These unique properties of BNC are used to create bandages in medical field. The porous nature of BNC allows antibiotics and other drugs to pass through and get loaded, while serving as a physical barrier against external infections. BNC improves the re-epithelialization of wet wounds by retaining water, thereby speeding up the healing process[37]. Due to its outstanding physical and chemical characteristics, BNC can be used for developing effective food packaging systems due to its high-water absorbency, high degree of crystallinity, large surface area, excellent mechanical strength, and high permeability.

BC has higher strength and stability in a wet state like innate blood vessels but has lower elasticity. However, fibrin exhibits a maximum of 330% extensibility (elasticity) but has very low strength when subjected to physiological environments[38]. The elastic and stiff fibres of composites found in real blood vessels are responsible for mechanical properties. Similarly, a composite structure has the potential to be used to develop a replacement for a real blood vessel. Brown et al. used glutaraldehyde as a crosslinker to prepare the BC/fibrin composites by immersing the never-dried BC sheets in a fibrin solution. They showed enhanced tensile strength and improved stretching over to normal BC. Compared to small diameter blood vessels, the composites have higher tensile strength, time dependent and modulus driven viscoelastic properties[39].

5. Culture method

Culture methods play a key role by influencing the BC's properties, microstructure, and morphology. Additionally, more studies are needed to improve BNC production and their yields in a cost-effective manner. Because BNC has a great interest in industrial production with multiple applications, more efforts are needed to make this material economically viable and competitive. In recent years, multiple culture methods like static, bioreactor, and shaking or agitated culture methods with different carbon sources and microbes are used to improve BC production (**Table 1**).

Table 1. Different microorganisms, cultivation methods and carbon sources used to produce BNC.

S. No	Microorganism	Cultivation method	Culture duration	BNC yield (g/l)	Carbon source	Advantages	Drawbacks	Reference
1.	*Gluconacetobacter xylinus* CGMCC2955	Static culture	6 days	2.55	Wastewater of candied jujube hydrolysate	Low cost, easy hydrolysis of abundant raw material into glucose.	pH of the medium decreased around 2–3.	[40]
2.	*Gluconacetobacter xylinus* CH001	Static culture	5 days	0.66	Liquid fermentation wastewater	Increase in water holding capacity, and low cost.	Shorter lag phase than other substrates, and influence on BC structure.	[41]
3.	*Gluconacetobacter xylinus* ATCC 700178	Static culture	9 days	3.20	Carob and haricot bean medium	Higher yield with better morphological and mechanical properties.	Sudden pH drop.	[42]
4.	*Komagataeibacter haeticus*	Static culture	7 days	6	Cashew tree exudates	Increased thermal stability and mechanical properties.	Change in surface morphology.	[43]
5.	*Acetobacter xylinum* TISTR 107	Static culture	5 days	5.89	Rambutan juice	Pure and contaminant-free BC were produced.	Higher sugar level.	[44]
6.	*Acetobacter xylinum* ATCC 23767	Static culture	7 days	2.86	Cornstalk	Higher BC production.	At low temperature, incomplete reaction and incomplete degradation of hemicellulose would occur.	[45]

Table 1. (*Continued*).

S. No	Microorganism	Cultivation method	Culture duration	BNC yield (g/l)	Carbon source	Advantages	Drawbacks	Reference
7.	*Gluconacetobacter sucrofermentans* B–11267	Agitate culture d	3 days	6.19	Thin stillage	Higher BC production and large amount of BC in low pH media.	Influence on the micro-morphology and crystallinity.	[46]
8.	*Komagataeibacter haeticus*strain PG2	Static culture	10–15 days	8.7	Glycerol	Cost effective and high yield of BC with good structural characteristics.	Low thermal stability	[47]
9.	*Komagataeibacter xylinus* BPR 2001	Static culture	9 days	7.5	Sugarcane molasses	Higher BC production and low cost	Low thermal stability.	[48]
10.	*Gluconacetobacter xylinus* KCCM 41431	Static culture	7 days	6.95	Crude glycerol	Eco-friendly BC production	BC production inhibited by low pH and salt (NaCl/KCl)	[49]
11.	*Komagatacibacter xylinus* PTCC 1734	Static culture	10 days	1.80	Vineasse	Increased thermal stability.	The thickness of BC was reduced.	[50]
12.	*Komagataeibacter hansenii* GA2016	Static culture	21 days	3.92	Citrus peels	High water holding capacity, thermal stability, crystallinity and thin fiber diameter.	-	[51]
13.	*Gluconacetobacter xylinus* ATCC 10245	Static culture	6 days	4.70	Potato peel	Higher thermal stability, crystallinity, and increased surface volume.	Needs high amount of sugar.	[52]
14.	*Acetobacter xylinum* ATCC 23767	Static culture	15 days	2.07	Solid kitchen waste	Increase in crystallinity and tensile strength.	Higher glycerol volume reduces the yield of BC.	[53]
15.	*Gluconobacter xylinus* KCCM 41431	Static culture	7 days	3.40 & 2.93	Glycerol & Crude glycerol	Increase in mechanical properties and thermostability.	Substrate inhibition, and low water holding capacity.	[54]

Other than the culture method, nutrient, oxygen concentration, pH, and bacterial strain play a key role and impact on BC properties.

5.1. Static culture

This method is a simple, conventional, and mostly used technique for BNC production. The BNC formed at the air-culture medium interface was produced by a comprised hydrogel pellicle. The cellulose sub-fibrils are constantly crystallizing into microfibrils and extruding from the linear pores on the bacterial membrane. They are formed by overlapping, self-assembling, and intertwined cellulose ribbons in parallel plane results; gelatinous cellulose membranes are accumulated at the top of the culture medium[55]. Depending on the culture time, the membrane thickness will differ. In lab-scale production of BC, mostly this technique was used because of its low shear environment, but the major limitation of this method is low productivity and long cultivation time[56].

5.2. Agitated/shaking culture

The agitated or shaking culture method overcomes the drawbacks of static fermentation, and this method increases the production rate of BC[57]. A higher level of agitation during fermentation increased oxygen transfer to fermentation broth, resulting in a higher rate of growth and a higher BC level. The shapes are very different from the static culture method and are related to BC's intrinsic mechanical and lower crystallinity properties. Some bacteria may be genetically unstable under agitated conditions, which may also reduce the productivity of BC.

5.3. Cell-free production

It is possible to overcome several limitations associated with the conventional BC fermentation process by using a cell-free system. By the enzymatic cascade systems, cellulose is synthesized in vitro. Compared to whole-cell fermentation, this process provides several advantages, including a continuous production system, preventing unwanted product accumulation and cofactor regeneration[58].

5.4. Use of multiple receptors in the fermentation process

Many attempts on the reactor design have been done to achieve industrial-scale BC production, which reduces the cultivation time, increase productivity, and low production cost. The BC elasticity, crystallinity, and polymerization degree were lower than the static or agitated method. Because of cellulose-negative mutants, acids accumulation, and BC broth adhesion to the reactor wall, the production of BC in agitated culture is reduced[59]. These limitations are overcome by several reactors like airlift bioreactors, rotary biofilm contractors, stirred tank reactors, rotating disk reactors, trickling bed reactors, silicone membrane reactors, and bioreactors with spin filters which are further used for BC production.

5.5. Productivity enhancement

Other than culture methods and reactor design, the production of BC was increased by additives like agar, organic acids, alcohols, and carboxy methyl cellulose added in the fermentation process[60]. Lu et al. reported the effect of 6 different alcohols after static fermentation of *Acetobacter xylinym* 186 at bacterial culture with 1% methanol, 0.55% ethylene glycol, 0.5% n-propanol, 3% glycerol, 0.5% n-butanol, and 4% mannitol were added in the medium to produce 21.8%, 24.1%, 13.4%, 27.4%, 56% and 47% higher production of BC than the control groups, respectively[61].

6. Bacterial nanocellulose production

Multiple sources have been shown to increase BNC production, and more efforts have been made to isolate bacterial strains that produce cellulose efficiently. Most of the studies are reported or conducted on the *G. xylinus* strain, and further research is required to determine whether other bacterial strains may produce higher levels of BNC. To increase the BNC production, in-situ fermentation and ex-situ fermentation processes are used.

In situ & Ex situ fermentation process

In BC polymeric matrix, several augmentation materials or additives are incorporated to enhance the interactions with BC nanofibrils and give a number of new properties to the BC matrix. In the in-situ fermentation process, a hydrogen bridge is formed in the BC matrix by interacting with exogenous molecules and OH moieties. The in-situ method mostly uses water-soluble and hydrophilic molecules[62] and without changing the chemical composition of the BC membrane, this method alters the physical properties and morphology of the BC. The BC matrix structural modification occurs after purification and production in ex-situ fermentation. The ex-situ modification is classified into the physical modification and chemical modification. In the physical modification, the additives were immersed in a purified BC matrix[63], and as a result of physical adsorption, strong hydrogen bonds were formed between the hydroxyl groups of cellulose chains and the absorbed molecules. Alternatively, chemical modifications were carried out between BCs and reagents during ex-situ chemical modification. The physiological condition changes and improper binding due to the leaching out of bounded molecules are the major disadvantages of this method.

The in-situ and ex-situ fermentation process for the synthesis of bacterial cellulose nanocomposite involves the following steps:

1). In-situ fermentation process:

a. Bacterial culture: Selecting and preparing a bacterial strain (like *Gluconacetobacter xylinus*, and *Komagataeibacter spp*) capable of producing cellulose is the first step.
b. Inoculation: The selected bacterial strain inoculated into a suitable growth medium typically consists of nitrogen, carbon source, and mineral salts.

c. Fermentation: The inoculated medium is subjected to fermentation process, it is carried out in a fermentation tank or bioreactor at a controlled temperature and pH.

d. Bacterial cellulose synthesis: By polymerizing glucose molecules, bacteria consume carbon sources from the medium to produce cellulose.

e. Nanocomposite formation: During cellulose synthesis, nanoparticles are introduced into the fermentation medium. By interacting with nanoparticles, cellulose fibrils form a nanocomposite material with enhanced properties compared to pure bacterial cellulose.

f. Harvesting and post-processing: After the process, the bacterial cellulose nanocomposites is harvested from the medium, then washed, and dried to remove impurities[64,65].

2). Ex-situ fermentation process:

g. Bacterial culture and fermentation: As same as in situ fermentation process, the bacterial strains are inoculated into suitable medium under controlled conditions. The bacteria secrete cellulose during fermentation, forming a thick, gel-like layer of cellulose.

h. Harvesting bacterial cellulose and purification: After completing the fermentation process, the bacterial cellulose is harvested from the medium through various methods like filtration and centrifugation. Then it is washed thoroughly to remove the bacterial remnants or impurities.

i. Nanoparticle incorporation: The purified bacterial cellulose is immersed in a nanoparticle solution. Nanoparticles can be absorbed into cellulose fibers, resulting in their incorporation into the matrix.

j. Drying and Post-processing: The bacterial cellulose nanocomposite is carefully dried to remove excess water and to allow nanoparticles to adhere firmly to the cellulose matrix after nanoparticle incorporation[66,67].

The schematic representation of in situ and ex situ fermentation process for BNC production is given in **Figure 3**.

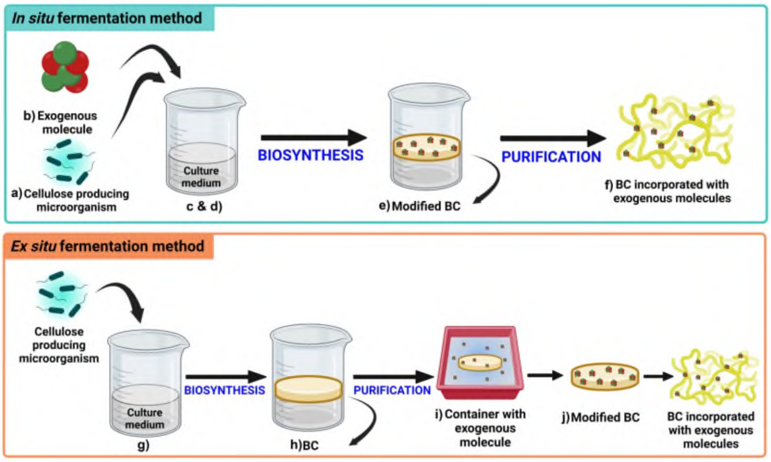

Figure 3. Schematic representation of in situ and ex situ fermentation process for the synthesis of bacterial nanocellulose using cellulose producing microorganisms.

7. Bacterial cellulose incorporated with different nanostructures

Nanotechnology is a field of science which has profound applications in biomedical research such as biosensing[68–71], multimodal imaging[72–75], theranostics[76–80], nanoformulation of nutraceuticals[81,82], tissue engineering[83,84], targeted drug delivery[85], food technology[86], photocatalysis[87] etc. Among the different types of nanomaterials, nanocomposites have specifically gained a lot of attention. BNC was amalgamated with different types of natural and artificial nanostructures to yield superior nanocomposites with improved properties.

7.1. In photocatalysis and wastewater remediation

Inorganic nanoparticles are used as decorative elements in multifunctional laminates synthesized from bacterial cellulose fibrils. Different nanoparticles can be used in each layer, and they have selected two metals (Au, Ag) and two semiconductors (TiO_2 and Fe_2O_3). On cellulose fibers, inorganic nanocrystals were nucleated and grown in situ using microwave-assisted synthetic routes. After that, functionalized bacterial cellulose films were layered and dried at 60 ℃ to create a millefeuille construct. They form a thicker and more integrated film after drying. It was determined that the laminates would be structurally, functionally, and mechanically sound. Surface adhesion energy of cellulose fibrils between two cellular structures was computed by molecular dynamics simulations, and the resulting films constituted by up to four types of particles were spatially confined in an orderly manner throughout[88]. In catalytic support applications, nanocellulose surfaces possess hydroxyl groups (naturally present) or sulfate ester groups (modified via acid hydrolysis), which facilitate the reduction of metal ions to metal nanoparticles. Furthermore, cellulose's supramolecular structure allows metal nanoparticles to disperse and prevent aggregation. A nanocellulose matrix was presented in this context in order to immobilize noble metal nanoparticles and then be applied to organic catalysis[89]. Another study prepared Au and Ag nanoparticles impregnated on bacterial nanocellulose films using *Punica granatum* peel extract induced in situ deposition. In addition to reducing Au and Ag ions, bacterial nanocellulose was an eco-friendly and excellent platform for the interaction of the biomolecules in the *Punica granatum* peel. To reduce 4-nitrophenol, these metal nanoparticles incorporated in bacterial cellulose were used. For four consecutive cycles, Au and Ag nanocellulose films showed excellent catalytic reduction properties. Aside from enabling superior antioxidant activity, cellulose nanofiber films incorporating Au and Ag showed improved mechanical properties[90]. MoS_2 nanostructures have gained a lot of attention in biomedical field in recent years[91]. A hybrid aerogel membrane prepared by combining BNC and MoS_2 nanostructures has been reported by researchers. In this composite, bacterial nanocellulose (BC)-based macro/mesoporous scaffolds are combined with adsorption-cum-photocatalytic properties of MoS_2 nanostructures, resulting in excellent mechanical stability and excellent textural properties. Based on a detailed study using a membrane photoreactor containing the developed photoactive/adsorptive BC/MoS_2 hybrid membranes, it was shown that the modification of BC with nanostructured MoS_2 enhanced the removal of pollutants through both adsorptive and photocatalytic mechanisms. It is important to note that the BC/MoS_2 airgel membranes demonstrated excellent performance for removing heavy metal ions (88% Cr (VI)) and organic dye molecules (96% within 120 min, Kobs = 0.0267 min^{-1})[92].

7.2. BNC for energy storage

In terms of energy storage material, nanocellulose can be classified based on the source of origin and morphology as nano fibrillated cellulose (NFC), nanocrystalline cellulose (NCC), or bacterial nanocellulose (BNC). Despite its insulative properties, nanocellulose is an excellent material for fabricating electrode composites by converting it into activated carbon. Carbon-based materials such as CNT2,6 can also be bonded to it, making it a flexible substrate for conductive polymers. Using nanocellulose as a separator is one of the most important uses of nanocellulose because it can be adapted in terms of porosity, pore distribution, functional layer, so that the energy storage device can be improved. Lithium-metal and Lithium-Sulfur batteries benefit greatly from such kind of active separators. Additionally, it can be synthesized using large-scale paper printing processes or sequential filtration of aqueous solutions and can be used as a current collector, electrode, separator or a complete device. By combining three-dimensional networks of BNCs in a conductive matrix, it is possible to achieve superior electrochemical performance is due to the ability to extract ions effectively, which is critical to the rapid charging and discharging of energy storage devices. In a review published recently, a number of recent studies have been done on the use of BNCs for energy storage systems, such as Lithium-ion batteries, ultracapacitors, and Lithium-S batteries, among others[93]. Platinum nanoparticles were synthesized using microwave assisted synthesis on BNC as a green material. Pt/BNC, the synthesized bacterial nanocellulose-platinum catalyst, was characterized using different photophysical tools, such as differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), X-ray diffractometry (XRD) and transmission electron microscopy (TEM). Pt-based catalysts were successfully synthesized based on the results obtained. As a result of electrocatalytic testing, it was found that Pt/BNC catalyst exhibits high electrocatalytic performance in methanol oxidation with promising application as fuel cells[94]. In a previous review, cellulose-derived nanostructures (CNS) or carbonized-CNS based materials have been demonstrated to be effective in the development of sustainable energy storage devices. The CNS based materials also included the BNC materials[95].

7.3. Biomedical applications

In temporary wound healing system[96] as well as tissue regeneration and drug delivery[97,98], BNC and its composites are constantly being used[99]. BioFill, a type of wound dressing, was the first biomedical application of BNC, used for the treatment of severe burns, wounds that required skin grafting, and chronic skin ulcers[100]. A BNC-based artificial blood vessel for microsurgery was invented in 2001 as the next biomedical application of BNC[101]. Productivity, however, determines whether BNC can be utilized. Commercialization of BNC at low cost is hampered by the high capital investment and costly production process. As a result of intra-molecular and strong hydrogen bonds between the polymer chains of the cellulose polymer, BNC is insoluble in water and many other solvents used in the biomedical field. To increase wound healing, varying the ratio of BNC to other constituent scaffolding materials can be highly beneficial for improving the porosity, adherence, stiffness, hydrophilicity, and surface area of the scaffold. Adding polyurethane, gelatin, alginate, silk fibroin, chitosan, to BNC can alter nanoscale fiber dimensions and promote the adhesion and migration of cells within the matrix[102]. By blending bacterial cellulose, tri-calcium phosphate, and hydroxyapatite, scaffolds with pores up to nanometers have been prepared. As mineralization occurs on the hydroxyapatite, such scaffolds can be used to form bone tissue engineering implants[103–105]. BNC is the preferred material combination for bone tissue engineering because it can combine with natural materials such as nano-hydroxyapatite and tricalcium phosphate. Mesenchymal stem cells (MSCs) derived from fibrous synovium were shown to have excellent biocompatibility with these spongy BNC membranes, penetrating and multiplying on them for 7 days at a distance of 150 μm[106]. An ice-templating and freeze-drying technique using liquid nitrogen was used to fabricate a BNC/chitosan composite. In combination with chitosan, this technique provided a scaffold with high microporosity and well-interconnected nano-fibrous pores. The pore size of the scaffold was increased when chitosan was added to BNC at 1% and 1.5%[107]. As scaffolding materials, biopolymers obtained from mutant strains are highly promising. Researchers from the University of Minnesota have recently improved the strain *Komagataeibacter hansenii* ATCC 23769 through genetic manipulation to obtain modified BNC pellicles with enlarged pores (around 1.48 micrometers) when compared with wild-type BNC membrane that has pores of approximately 0.16 micrometers[108]. There are other methods that are used to create pores of different sizes, including using porogens, varying cultivation times, inoculum volumes, and post-treatments with alkaline solutions[109].

A peripheral nerve autograft is currently the gold standard for treating peripheral nerve injury (PNI), but a donor nerve is not always available, and secondary injuries can also complicate the procedure. Injured nerves can be regenerated in nerve guidance conduits (NGC), which may be a replacement for autografts. Using the ion gel method, nerve growth factor (NGF) encapsulated chitosan nanoparticles (CSNPs) were initially constructed in situ on an oxidized bacterial cellulose (OBC) conduit, after which a solution of CS/NGF was introduced under pressure to facilitate a sustained release of NGF. Researchers successfully developed an antibacterial NGF@CSNPs/OBC nanocomposite characterized by biodegradability, and porous microstructure. Schwann cells adhered and multiplied more readily to the nanocomposite in vitro. Four weeks after application of the nanocomposite, the sciatic nerve defect of rats was successfully repaired with a 10 mm nerve defect present before treatment. It appears that the NGC effectively promoted regeneration and function recovery of the regenerated nerve at week 9, based on its diameter, morphology, histology, and functional recovery. Clearly, NGF@CSNPs/OBC has great potential as a new NGC for treating PNI[110]. It is possible to promote bacterial nanocellulose's anticoagulant properties while promoting its endothelialization to improve long-term patency of artificial blood vessels. BNC conduits were treated with and without heparin (Hep) by injecting silk fibroin nanoparticles (SFNP) onto the luminal wall surface. Two methods were used to introduce Hep: (1) embedding SF nanoparticles in HepNPs for construction of the BNC-SF-HepNP conduit, and (2) chemically grafting Hep onto BNC and BNC-SFNP for construction of the BNC-Hep and BNC-SFNP-Hep conduits. A toluidine blue staining confirmed that Hep was successfully grafted onto BNC and BNC-SFNP. A comparison of the hemocompatibility and cytocompatibility of the five samples was performed in vitro (BNC, BNC-SFNP, BNC-SF-HepNP, BNC-Hep, and BNC-SFNP-Hep conduits). A heparinized BNC-Hep conduit and a BNC-SFNP-Hep conduit improved anticoagulant properties, while BNC-SFNP-Hep stimulated endothelial cell proliferation in the umbilical vein, while limiting excessive smooth muscle proliferation in the arterial walls, facilitating rapid endothelialization and improving lumen patency. After 4 weeks of subcutaneous implantation, there were no significant inflammatory reactions or material degradation. All conduits had autogenous tissues around them, with cells infiltrating deep into their edges, the BNC-SFNP conduit showing the greatest infiltration, thereby providing an appropriate environment for angiogenesis in small-caliber blood vessels. Conduits BNC-Hep and BNC-SFNP-Hep exhibited few inflammatory cells. The outcome of this study indicated that, BNC-SFNP-Hep conduits have anticoagulant properties and stimulate endothelialization, suggesting they may be used as small-caliber artificial blood vessels in clinical settings[111].

A new method for depositing ad hoc NPs patterns on the surface of a flat BC film has been developed using a screen-printing process to deposit superparamagnetic iron oxide nanoparticles (SPIONs). Using microwave-assisted synthetics, BC fibers were blended into an ink solution for screen printing, which was then coated with SPIONs. Furthermore, an ex vivo test has been conducted to see if a BC/SPIONs implant can be identified easily by magnetic resonance imaging (MRI). Despite being a transverse relaxation (T2) contrast agent, SPIONs in the BC performed exceptionally well. Thus, by functionalizing BC films, they could be applied as bioimplants and monitored noninvasively for adhesions and deformations[112].

7.4. Antimicrobial applications

Cellulose surfaces contain a high number of reactive groups (i.e., hydroxyl groups), allowing for its functionalization with aldehydes, carboxylic acids, and amines. Proteins, polymers, metal nanoparticles, and antibiotics can also be grafted on the surface of cellulose due to the ease of surface modification. As a support for antibacterial agents, cellulose nanofibers and nanocrystals are used in many studies. In contrast, it is unclear how cellulose chemical modification affects its biocompatibility or antibacterial activity. Researchers have analyzed different surface modification techniques for cellulose nanostructures and their derivatives along with their antibacterial and biocompatibility properties to develop non-leaching and durable antibacterial materials[113]. In addition to being hydrophilic and highly porous, bacterial nanocellulose is a highly suitable matrix for creating antimicrobial, photoluminescent, and ultraviolet blocking carbon dots (CDs). Using Lactobacillus acidophilus supernatants, hydrothermal CDs were synthesized and characterized. CDs were tested against Gram-negative Escherichia coli and Gram-positive Listeria monocytogenes for antimicrobial activity. To fabricate antimicrobial/ultraviolet protective nanopaper, the as-prepared CDs were embedded into nanocellulose by an ex-situ method. The photoluminescent CDs were synthesized with an average size of 2.8 nm and a large amount of hydroxylated groups. Both bacteria were inhibited by the CDs at a concentration of 500 mg mL^{-1}. Additionally, nanopaper exhibited fluorescence under ultraviolet light. The fluorescence appearance of CDs can make them a suitable antimicrobial and ultraviolet protective material for use in nanocellulose films in order to produce forgery-proof antimicrobial packaging[114].

A previous study used the fibrillar network of BNC as a template to disperse chitosan in a matrix of BNC to form nanoparticles (CSNPs) via ionic gelation, resulting in the development of composites of chitosan nanoparticles embedded in bacterial nanocellulose (CSNPs-BNC). In order to achieve homogeneous dispersion of monodisperse CSNPs between 580 and 700 nm, BNCs were used as matrix supports. Antibacterial activity of the CSNP-BNC composites was found to be excellent, which suggested their potential application in clinical field. Schwann cells easily adhered to CSNPs-BNC composites and demonstrated good biocompatibility in vitro and in vivo. As a result of the experiments, CSNPs-BNC were found to offer promising biomedical applications[115]. Through the reduction (R) and UV-assisted (UV) methods, silver nanoparticles (AgNPs) were incorporated into bacterial nanocellulose (BNC) to produce an environmentally friendly antimicrobial film. When mixed with 3 weight percent polyvinyl alcohol (PVA), the films' elongation at break was improved up to 20 times. Oxygen barrier capacity and water vapor permeability were also improved in the films. In liquid medium and on raw beef, R and UV films displayed antimicrobial activity against Escherichia coli O157:H7 with CFU/mL reductions of 7 and 3 logs, respectively. For at least 10 days at 4 ℃, the films inhibited the growth of naturally present bacteria on raw beef. AgNP/PVA/BNC films could be thus applied to food packaging, according to the findings of this research[116].

7.5. Biosensing applications

In this study, researchers have developed a simple, low-cost, and well-designed synthetic method of generating hybrid composites made from Ag nanoparticles and bacterial nanocellulose (Ag-NPs@BNC) as flexible substrate for surface-enhanced Raman scattering (SERS) with ultrahigh SERS sensitivity, excellent signal reproducibility, and stability. A networked hybrid substrate with uniformly distributed SERS "hot spots" was created through the in-situ growth of homogenously distributed Ag-NPs on the networked BNC fibers. In addition to their ultrahigh sensitivity and good reproducibility, Ag-NPs@BNC substrates exhibit these unique 3D hot spots. As a result of the hydrophilic nature of the BNC material, it possesses good permeability and adsorption performance, which may allow for the adsorption of target molecules in highly active hotspot areas, thereby making SERS even more sensitive. Therefore, this method has been found to be highly effective in the detection of dye molecules (rhodamine 6G), as well as toxic organic pollutants such as 2-naphthalenethiol and thiram, with sensitivities of 1.6 and 3.8×10^{-9} M, respectively. Detecting toxic organic pollutants rapidly and quantitatively would be made possible by the good linear response of the intensity and logarithmic concentration. In addition, this self-supported Ag-NPs@BNC substrate was stable and flexible under a variety of detection conditions. As such, Ag-NPs@BNC substrates are versatile, ultrasensitive, and stable and can be used for a wide variety of rapid organic molecule identification applications[117]. In another study, by sputtering gold nanoparticles onto bacterial nanocellulose (AuNPs@BNC), low-cost, ecofriendly and efficient SERS substrates were successfully constructed. SERS performance of AuNPs@BNC substrates was investigated systematically using sputtering times from 25 to 200 s. An optimal AuNPs-150@BNC substrate contained Au nanoparticles of 18.5 nm diameter uniformly distributed on the nanocellulose matrix. Also, AuNPs-150@BNC substrates exhibited excellent reproducibility, good stability, and high sensitivity for rhodamine 6G detection with a detection limit of 10^{-9} M. Additionally, finite-difference time-domain (FDTD) simulations and 2D Raman mappings demonstrated the excellent SERS performances of AuNPs-150@BNC substrates. The engineered flexible AuNPs-150@BNC SERS sensor was successful in detecting pesticide residue on irregular fruit surfaces and cypermethrin at high sensitivity (10^{-7} M). This leads to a promising application of the AuNPs@BNC sensor, fabricated by means of magnetron sputtering technology, as an eco-friendly and scalable SERS substrate for the detection of hazardous substances[118].

8. Conclusions

Bacterial nanocellulose with its unique properties has become an indispensable alternative of plant cellulose in biomedical applications. High tensile strength, and modulus makes the BNC comparable to steel and any nanostructure made from it can withstand a huge amount of deformity. Moreover, it can be degraded by microbes making its application sustainable also. In this review we have discussed about the different methods used for BNC production using a versatile range of microorganisms and culture conditions. A detailed description of cellulose has been provided and the supremacy of BNC from other cellulose has been mentioned. The applications of BNC in photocatalysis and remediation of wastewater, energy storage, biomedical applications, especially wound healing materials, antimicrobial and biosensing applications are discussed. The sustainability of the BNC can warrant many more efficient applications in future.

Acknowledgment

We are grateful to Chettinad Academy of Research and Education for providing the CARE Seed Grant (004/Regr./AR-Research/2022-06). AnbazhaganThirumalai is grateful to Chettinad Academy of Research and Education for the PhD scholarship provided.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

BNC	Bacterial nanocellulose
BC	Bacterial cellulose
PC	Plant cellulose
HS-media	Hestrin-Schramm medium
PVA	Poly (vinyl alcohol)
PEG	Poly (ethylene glycol)
PLA	Polylactic acid
Ag	Silver
Au	Gold
Cu	Copper
N-C	Nitrogen-doped carbon dots
Fe^{3+}	Iron(III)
AgNP	Silver nanoparticle
UV method	Ultraviolet method
PET	Polyethylene terephtalate
ePTFE	expanded Polyethylene tetreflurothylene

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