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Bacterial biocomposites: production strategies and medical applications

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ABSTRACT

Cellulose, a vital structural component of the plant cell wall, is a linear polysaccharide polymer consisting of β (1→4) linked $(C_6H_{10}O_5)_n$ D-glucose units. However, cellulose can be produced by plants as well as bacteria, both of which are naturally occurring. Bacterial cellulose (BC), compared to native cellulose, has the same molecular formula, but it differs remarkably in macromolecular properties, characteristics, and a high degree of crystalline index, which allows the formation of ribbon-like microfibrils. BC has higher purity, greater hydrophilicity, greater tensile strength, a high degree of polymerization, and barely any lignin and hemicellulose. Possessing these unique properties makes BC more preferred over native cellulose, rendering the extraction of its purest form simplified without involving any pretreatment processes. A comparison of the structures of plant cellulose and BC reveals that they are chemically similar, but due to structural differences, both natural and BC have different applications in our daily lives. This paper emphasizes microbial cellulose, its production, and utilization, along with some other natural celluloses.

KEYWORDS

Cellulose; Polysaccharide; Glucose; Bacterial cellulose; Microfibril

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Introduction

Cellulose is a crucial component of plant biomass and is the most abundant renewable biopolymer on the planet. It is a linear homopolymer comprising a 1-4-linked β-D-glucopyranose unit. The term was first coined by Anselme Payen, a French scientist, in the early 19th century. Cellulose is a high molecular weight polysaccharide comprising glucose and is a major constituent of plant biomass. It is a valuable carbon source and is biocompatible. It is a bountiful source of raw material and has a number of applications. Apart from this, bacterial cellulose (BC) derived from bacteria is considered an essential reserve of cellulose due to its distinctive structure and properties. As the name suggests, bacterial celluloses can be synthesized by several species of bacteria like *Agrobacterium*, *Sarcina*, *Pseudomonas*, *Rhizobium*, and *Acetobacter xylinum* [1]. *Acetobacter xylinum* and *Glucanobacter xylinum* are noted as the most efficient producers of Bacterial cellulose. [2,3].

A comparison of the structures of plant cellulose and BC reveals that they are chemically similar and are composed of chains consisting of D-glucose units with C4-OH group and C1-OH group situated at each end. The stratified structure of both was combined with the hydrogen bonds [4]. BC had high purity when synthesized compared to plant cellulose, which is composed of lignin and hemicellulose and must be purified, which requires additional costs [5]. Due to such structural differences, both natural and BC have different applications in our daily lives. In medical science, there is a growing demand for the use of BC, mainly in tissue engineering for skin replacement, generation of artificial blood vessels, etc., due to its excellent biocompatibility [6]. Its other excellent features are described in Figure 1. Our paper mainly focuses on BC, its production, and its utilization, along with some other natural celluloses.

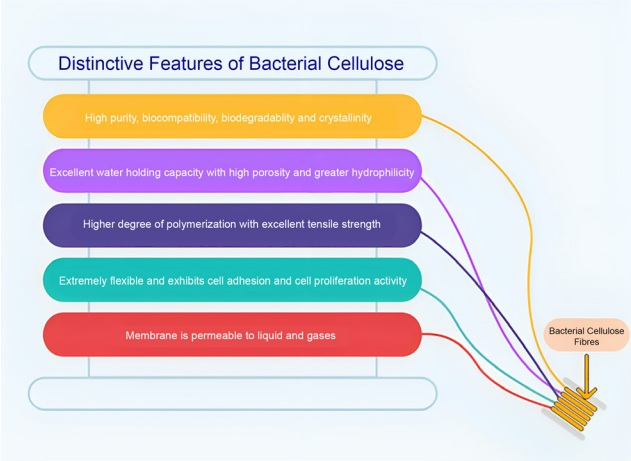

Figure 1. Bacterial Cellulose distinctive features.

Natural Biocomposites

Natural biocomposites are composite materials that are reinforced by natural fibers that are found to naturally exist in nature and most predominantly in the form of polysaccharides [7]. They can be from plant, animal, or cellulose-based. Since these biocomposites are easily biodegradable and harmless to the environment, it is known for their great ecological and economic importance. These biocomposites have drawn tremendous attention in industries for their distinctive applicability for various purposes. They were a perfect replacement for synthetic composites in several applications, such as food, construction, marine, automotive, etc., for their economic production, biodegradability, and exceptional physical and chemical characteristics. Some well-known natural fiber biocomposites include lignocellulosic plant fibers such as jute, palm oil, flax,

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polysaccharides like guar gum, and other reinforced fibers like cellulose, etc. [7,8].

Guar gum is a polysaccharide found in the species *Cyamopsis psoraloides*, where this biocomposite is well recognized for its gelling properties because of the presence of a large number of OH^- ions, which is responsible for enhancing the H-bond formation in water [8]. Because of these properties, guar gum biocomposites are widely used in the food industry as a thickening and stabilizing agent in varied no. of products like fruit juices, ketchup, syrup, etc. Guar gum, in its hydrolyzed form, is also used as a source of prebiotics, enhancing the activity of the gut microflora [9].

Other polysaccharides like chitosan are another remarkable example of the natural polymer-based biocomposite used in preparing scaffolds for bone tissue engineering. They exhibit excellent anti-microbial characteristics, do not induce an immunogenic response, and exceptionally carry a hydrophilic surface which is not usually found in other synthetic polymers [10]. These features allow it to play a potential role in biomedicine, where it is reported to enhance the adhesion of cells and stimulate osteoblast growth and mineralization. Chitosan, coupled with other polymers like ceramics, is used to treat defects in bone or simply used as a scaffold matrix in bone tissue engineering having high porosity [11].

Several automotive industries use these polyamide natural composites as molds instead of synthetic mold since they are highly impervious to temperature and other petroleum and chemical products. When these polyamides are reinforced with natural fibers like flax to form biocomposites, their tensile strength reportedly increases along with a significant increase in their water absorption capacity, toughness, and other mechanical properties. The enhanced mechanical property of this biocomposite increases its desirability in the automotive industry [12]. Other than polyamides, there are other biocomposites used in automotive industries, like a flax-sisal reinforced polyurethane biocomposite used by Audi as a trim panel in the door of its Executive cars [13]. Most of the parts of a vehicle are manufactured using biocomposites; for example, a hybrid biocomposite made from sisal and roselle is used in the fabrication of rear-view mirrors, indicator covers, and many other components. Hence, natural biocomposites have emerged as a promising biomaterial for their distinctive applicability [13].

There are various other uses of these natural biocomposites made from plant, animal, and cellulose derived from both plants and microbes. The following context describes various strategies for the production and application of microbial cellulose, discussed in brief.

Methods Used in Bacterial Cellulose Production

BC production is synthesized by several species of bacteria; some of those include *Gluconacetobacter xylinus* (formerly Acetobacter), *Komagataeibacter xylinus, Agrobacterium tumefaciens, Rhizobium leguminosarum, Salmonella enterica* [14,15]. Conventional methods for BC production implicate the use of fermentation techniques, which may either be static or submerged depending upon the nature of its application. In the static cultivation method, BC production is accomplished in a pellicle sheet configuration at the air-liquid interface of the culture. The continuous sheet produced solves the purpose of a skin- substitute and can be used as an artificial skin for the treatment of severe burn injuries [15]. On the other hand, circulating air is introduced in the submerged shaking cultivation method, increasing the dissolved oxygen concentration and resulting in enhanced production of BC in the form of small pellets or granules [16]. This method is advantageous from the industrial point of view. But both of these methods have their own drawbacks. The former is a time-consuming process. Also, the membrane is not oxygen permeable; cells present at the air-liquid interface only participate in cellulose production, and if the layer gets thick, the production rate decreases [6,17]. Whereas drawbacks associated with the latter process involve the production of cellulose-negative strain followed by a slow increase in the viscosity of the medium, disrupting the air distribution to the medium and lowering BC productivity [6,18]. Various strategies have been developed to optimize the culture conditions and improve the yield of BC. Some of them involve the use of advanced reactors with unique equipment to minimize the production of these cellulose-negative mutant strains as well as the cultivation period involving intensive labor.

Advanced Bioreactor Types

Stirred tank reactor

The complication associated with the traditional method of BC production is the aggregation of BC as a result of the insignificant rise in the viscosity of the culture medium. This additional increase interferes with the homogeneity and the mass transfer characteristics of the culture media and subsequently impairs oxygen from the medium [19]. Using a stirred tank reactor was a distinctive approach developed to address this problem.

In addition, these reactors are also sometimes equipped with baffles to enhance the heat transfer and increase the turbulence. As a result of these modifications, the pseudoplastic behavior of the culture medium was observed, favoring the conditions required for the generation of higher yields of BC [20]. According to a report, the production yield of BC and the stirrer speed were observed to find a correlation of direct proportionality. At a stirring speed of 600 rpm, the BC production yield was found to be 5g/L following a time period of 70 hr, whereas with a gradual increase in the stirring speed from 600 rpm to 800 rpm and finally to 12000 rpm, the observed yield was found to increase from 5g/L to 13g/L and 18g/L. The final yield was obtained after 45 hr, which confirms that the higher the stirring speed, the higher the BC yield obtained within a short period of time [20].

Modified airlift reactor

The conventional airlift reactor comprises a draft tube separating two channels - the riser and the comer to ensure proper circulation of the culture media in the chamber. But again, viscosity build-up in the reactor resulted in a decrease in the concentration of dissolved oxygen-limiting the productivity of the process. To address this problem, certain modifications were made to the draft tube of the reactor. A draft tube with a rectangular mesh was introduced in the reactor, as a result of which the surface area-to-volume ratio of the reactor was found to increase along with a discharge of reduced size bubble, which enhanced the dissolved oxygen circulation and mass transfer in the medium. The

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concentration of the dissolved oxygen increased by 50%, and the productivity of the reactor increased by five times [20].

A further modification was made in this airlift reactor, where the rectangular wire-mesh draft tube was replaced by a set of simple rectangular net plates. Wu and Li used 4, 6, 8, and 10 simple net plates to check the limiting concentrations of dissolved oxygen and observed that when they increased the number of plates from 4 to 6 and then gradually from 6 to 8 and then 10, there was no further decrease in the dissolved oxygen concentrations [21]. This, in fact, verifies that increasing the no. of plates decreases complications related to dissolved oxygen. The water holding capacity of the BC obtained through this method was also estimated, and it was concluded that BC obtained using 6 rectangular plates had the most suited water holding capacity that can hold up to 8 times more fluid when compared to the static cultivation method [21].

Rotary-disc reactor

A rotary disc reactor works on the idea of using sets of circular discs anchored over a rectangular shaft operated in usually submerged conditions. The BC-producing bacteria adhere over the surface of the disc, and while the shaft rotates, these bacteria are alternately exposed to the air and the culture medium [20]. In this way, the bacteria obtain a significant amount of oxygen as well as the nutrients required for the production of BC while being alternately exposed to air and the medium [22]. The yield of BC in these reactors is greatly influenced by a no. of factors like surface area-to-volume ratio, no. of the disc, as well as the rotating speed and pH. According to the data, pH-5 was reported to be the optimum yield to obtain maximum productivity of BC, and if the pH is increased beyond that, the resulting yield was found to decrease. Another data report that the maximum yield was obtained when the rotating speed was kept at 4 rpm with a surface area-to-volume ratio of 0.71 cm -1 cm and a total number of 8 discs. It was observed that if the no. of the disc were increased above 8, the yield decreased probably because of the reduced interstitial spaces between the discs that caused the accumulation of the resulting BC granule [22].

A study reported by Lin et al. showed that they successfully developed a modified version of the Rotary disk reactor using a plastic composite support [23]. The plastic composite support-rotating disk bioreactor (PCS-RDB) they developed was semi-continuous and didn't require re-inoculation for the production of bacterial cellulose, thereby maintaining its productivity for not less than 5 cycles. Their study further reported that the addition of substances like carboxymethylcellulose (CMC) and microcrystalline cellulose (Avicel) to the PCS-RBD tends to enhance BC productivity by 113% [23].

Reactors equipped with special membranes

Studies have reported the use of special membranes to enhance the productive yield of BC. Reactors equipped with silicon membrane is one such example [16,19]. This reactor consists of a cylindrical vessel whose base is layered with a thick silicon coating (100mm in thickness) along with a silicon airbag. Implementing the use of this membrane improved the yield as the pellicles were observed to form on both the oxygen-permeable silicon membrane as well as on the liquid surface. Here, the thickness of the membrane has to be taken care of because if the membrane is too thick, the oxygen permeability will decrease along with the total yield. The rate of BC production by this method was doubled compared to the traditional method of static cultivation [24].

Another special membrane-type reactor involves the use of a hydrophilic polyether sulfone membrane of 0.45 μm pore size [25]. This membrane has a higher surface area and acts as a unit of partial permeability where the BC-producing bacteria (*G. xylinus*) adhere on one side of the membrane, and the required nutrient for production diffuses from the alternative side of the membrane. This membrane separates the culture organisms from the fluid while exposing them to sufficient oxygen supply and reducing their subsequent separation cost in the later phases.

Both of these above-mentioned specialized membrane reactors are operated under static conditions. Furthermore, the submerged cultures, along with agitation, are well suited for better oxygen as well as a mass transfer but may reduce the productivity due to viscosity build-up cellulose negative mutant strains, whereas static cultures have the benefit of providing larger surface area-to-volume ratio required for enhanced production BC pellicles but lag behind when it comes to proper oxygen transfer rates so a Two-step fermentation technique was proposed where at the first stage BC producing cells were cultured in the agitated submerged reactors followed by the production of cellulose under static conditions [26]. This technique involves the benefit of both the conventional method of fermentation enhancing the productive yield of BC.

Production of BC Using the Appropriate Media

For the successful production of pure and desirable cellulose with extreme reliability, the elements present in the media of the culture play a key role. Carbon and nitrogen sources are the major elements that are responsible for affecting the growth of bacteria-producing bacterial cellulose, thereby having a significant effect on its yield. BC has acquired significant attention for being produced on a large scale, but the expensive media used for its synthesis makes this cellulose a little expensive for commercial use [27]. Therefore, researchers have tried to use various sources of carbon and nitrogen other than the ones used traditionally to bring down the expense consumed in the production. The conventional media were certainly modified in various experiments to increase productivity at a minimal expense [28-30]. Some of the successful strategies are mentioned in this context. BC is produced by different species of bacteria, including the acetic acid bacteria, Gram-negative and positive bacteria. Among the different species, *G. xylinum*, an acetic acid-producing gram-negative bacteria, is used as a prototype for the study of cellulose production because of the key role played by these organisms in the drug delivery to the target cell, regeneration of tissue, enhanced wound healing properties and several other biomedical related applications [31-33].

Hestrin and Schramm (HS), Yamanaka, and Zhou are some common conventional media used for cellulose production and use glucose as its major carbon source, but they differ in nitrogen content. Bacteria utilizing glucose in this media are at a disadvantage for the generation of gluconic acid as a side product. The acidic factor produced reduces the pH of the medium, which is another crucial factor to be considered for cellulose production [34]. The decrease in pH subsequently decreases the yield of the production. Mohammadkazemi et al. compared these three different media for BC production by strain *G. xylinum* [35]. First, they

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checked proper BC production from these 3 media and concluded that *G. xylinum* did not produce a considerable amount of BC in the Yamanaka medium, though the medium is rich in carbon because of the lack of a good amount of nitrogen sources like peptone in the medium and therefore demonstrated that nitrogen is an essential element required for the development of bacterial cellulose. In the next step, they changed the carbon sources in these media to check the yield of BC. They used sucrose, date syrup, mannitol, and food grade sucrose as the source of carbon and found that the maximum yield was obtained when sucrose and mannitol were used as a carbon source and the media used was HS compared to other carbon sources and media. Therefore, using HS media, changing its source of carbon, and supplementing it with more nitrogen might enhance the yield of cellulose [35].

Another study reported the use of *G. hansenii* for BC production by modifying the regular HS media by replacing the conventional nitrogen sources (yeast extract, peptone) with corn steep liquor to minimize the cost spent on using expensive culture media for production [36]. The Corn Steep liquor used was a by-product obtained from the corn-wet milling process, and it is highly nutritive, containing proteins, lactic acid, ash content, carbohydrates, and very low fat content. The result rendered up to 57.94% reduction in cost along with a decrease in the concentration of glucose by 25%. The reported productive yield was 73.55%, which was quite low when compared to the standard [36], but since the Corn Steep Liquor itself is waste generated by-product along with considering the expense, it was found to be the most cost-effective alternate technique that can be used for the production of BC in the near future.

Żywicka et al. developed a novel strategy in which vegetable oil was found to play a very significant role when added to the medium used for BC production to improve the yield [37]. The bacterial strain used in their experiment was *Komagataeibacter xylinus*, and the media to which 1% and 2.5% vegetable oil (rapeseed) were added to enhance the productivity is HS. The experiment used a control that was not supplied with vegetable oil to compare the results. The outcome of the experiment suggested that the addition of 1% vegetable oil was the optimum condition obtained, which enhanced productivity by 500% when compared to 2.5%, which tends to decline in the presence of a control. The cellulose pellicles obtained from 1% supplemented vegetable oil were extremely tensile (3 times of control) without showing any insignificant cytotoxicity and were reported to have a high-water holding capacity (2 times of control). This method of production can successfully replace the trend of using traditional expensive media and can be successfully implemented for large-scale commercial use [37].

Jahan et al. remarkably tried to minimize not only the expense associated with supplementing the culture media for BC production but also to address the issue of environmental abuse due to industrial (distillery) wastewater discharge [38]. The discharged wastewater is highly rich in carbon and nitrogen content, and so it was used as an alternate source of nutrients in the HS media. Therefore, crude distillery effluent was found to be an effective source of nutrients in the case of G. obedience, resulting in a scalable yield in the process of BC production. The yield was found to be 8.11g/L using crude distillery effluent compared to other similar kinds of studies performed, and the process was found to be economical [38].

Skiba et al. utilized pretreated oat hulls to improve the yield of BC derived from *Medusomyces gisevii* following enzymatic saccharification, which reportedly scaled up the process by 98% since they produced 80 tons of wet BC per 100 tons of oat hulls [39]. Moukamnerd et al. also demonstrated that passion fruit peel and banana peel can be used as a cheap carbon source for producing BC from *Komagataeibacter nataicola* TISTR 2661 by digesting these peels with the help of enzymes [28]. Table 1 gives a brief knowledge of the bacterial strain involved in various studies under different optimized systemic conditions, improving the yield of production.

Table 1. Cellulose yield from bacterial strains under different systemic conditions when various substrates are fed into the system.

Sl.No	Bacterial strains	Supplement	Carbon source	System	Duration	Yield (g/L)	Reference
1	*K. xylinus* K2G30=UMCC 2756	Glucose,ethanol	Glucose	Static	15 days	19.65	[14]
2	*K. xylinus* BCRC12334	Glucose	Glucose	Static	14 days	7.28	[40]
3	*K. xylinus* ATCC23767^{T}	CSL, Glucose, Xylose, Mannose, Acetic Acid	Glucose	Static	7 days	2.87	[41]
4	*K. xylinus* DSM46602	Glucose, Peptone, Phosphate,Yeast Extract, Disodium Citric acid, Vegetable oil.	Glucose	Static	7 days	-	[37]

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5	*Gluconacetobacter hansenii* UCP1619	Corn steep liquor (CSL),sugarcane molasses, citric acid monohydrate, disodium phosphate	Sugarcane Molasses	Static	10 days	0.30	[36]
6	*G. xylinus* BPR2001	Glucose	Glucose	-	-	2.6	[21]
7	*Gluconacetobacter xylinus* ATCC® 700178™	Fructose, peptone, yeast extract, Na_2HPO_4, critic acid	Fructose	Static	5 days	5.9	[42]
8	*Gluconacetobacter xylinus* FC01	Glucose, yeast extract,peptone, acetic acid and ethanol	Glucose	Static	6 days	2.520	[43]
9	*K.hansenii* M2010332	Glucose, citric acid, ethanol	Glucose	Static	7 days	16.31	[44]
10	*Komagataeibacter saccharivorans* BC1	Dextrose, mannitol, citric acid monohydrate, disodium phosphate agar, crude glycerol	Crude glycerol, dextrose	Static	7 days	1.26 g/100mL	[45]
11	*Acetobacter sp.* DR-1	Mannitol, yeast extract,peptone, citric acid, disodium hydrogen	Glucose	Static, submerged	10 days	1.38	[46]
12	*Gluconacetobacter sp.* RKY5	-	Glycerol	Submerged	144 hr	5.63	[47]

Biosynthetic pathway

Synthesis of cellulose by the bacterial species is regulated by a multi-step biosynthetic pathway involving various enzymes of the metabolic pathway, catalytic subunits of cellulose synthase complex, and regulatory proteins. The model organisms used for the study of the pathway are usually acetic acid-producing gram-negative bacteria, among which *Gluconobacter xylinus* is most extensively studied since it can utilize a large variety of carbon-derived sources [20,48,49]. The pathway of cellulose synthesis can be mainly categorized into two stages. The primary stage involves reactions associated with the formation of β-1-4 glucan chains, which further polymerize to form cellulose, followed by crystallization in the later stage [1,34,49]. Cellulose biosynthesis can metabolize a varied number of carbon sources to produce cellulose. Since the bacteria (*G. xylinum*) is the deficit of the enzyme phosphofructokinase (PFK-1), they are reported to perform either the pentose-phosphate pathway or the TCA cycle depending upon their physiological state followed by gluconeogenesis to metabolize glucose [20,34,50]. When it comes to enzymes utilized for the formation of cellulose, there are some major enzymes involved that play a key role during the formation of cellulose [1,49,51].

- The primary role is played by the enzyme glucokinase/hexokinase, which is responsible for the phosphorylation of glucose into glucose-6-phosphate.
- Enzyme phosphoglucomutase drives the isomerization of the glucose-6-phosphate to glucose-1-phosphate.
- Glucose-1-phosphate produced in the last step is acted upon by the enzyme UGPase and gets converted into UDP-glucose (UDPG)s.

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The UDP-glucose is the direct precursor that gets converted into cellulose. UDPG releases glucose monomer to form a β-1-4 glucan chain, which further polymerizes to form cellulose, but the process of polymerization is not completely known yet. Two very well-known hypotheses were proposed for this mechanism; one hypothesis put forward the probability of the involvement of a lipid intermediate where the glucose monomer is initially transferred to this lipid intermediate molecule from UDPG, establishing a lipid-glucose intermediate complex before forming the glucan chain. The other hypothesis was contradictory to the former theory and denied the involvement of any intermediate lipid complex. It suggests that the monomer of glucose from UDPG directly goes and attaches to the growing polymer chain one at a time, giving rise to the β-1-4 glucan chain [31,49,52]. The latter theory is considered to be more plausible since most studies related to this mechanism have suggested UDPG to be the direct precursor that gets converted into cellulose without any involvement of an intermediate step [49,52].

The final polymerization of cellulose from UDPG takes place in the cellulose synthase machinery [53]. The cellulose synthase involves four protein subunit complexes- bcsA, bcsB, bcsC, and bcsD. Here, c-di-GMP (cyclic diguanylic acid) plays a crucial role in activating the cellulose synthase machinery by regulating the activation of its subunits [40,51]. BcsA, a β-galactosyltransferase catalytic subunit of cellulose synthase, consists of a cytosolic domain to which the c-di-GMP binds. The presence of c-di-GMP activates the bcsA subunit by removing the gatling loop, which is responsible for blocking the active site of this subunit, giving access to the substrate-binding pocket [54]. Thus, bcsA makes a conducting loop to lengthen the cellulose (glucan) chain by adding the glucose monomer from the UDPG one at a time [14,52]. The pathway is described in Figure 2.

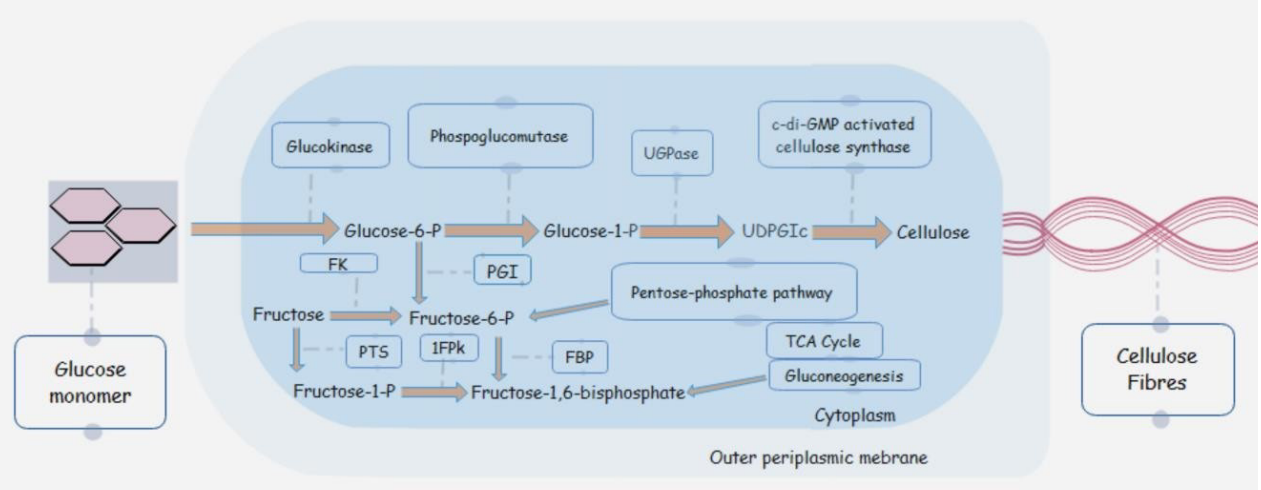

Figure 2. Biosynthesis of cellulose in G. xylinum.

The nascent cellulose chain continues to bind to the anomeric end of the UDPG monomer. BcsA is also bound with another protein subunit, bcsB, to form a bcsA-bcsB complex. BcsB was reported to be responsible for the displacement of the nascent cellulose chain. Other than this complex, bcsC is another protein subunit having its N-terminal associated with the periplasmic space and the C-terminal associated with the outer membrane. The N-terminal region of this protein is responsible for the protein-protein interaction, allowing the interaction of the bcsC with the bcsB protein governing the path of the glucan chain transport via the C-terminal region, whereas the C-terminal region is responsible for the formation of the β-barrel which further allows the transfer of the glucan chain in the outer membrane. BcsD is considered to play a crucial role in the length-wise arrangement of these terminal complexes and the packing of the glucan chain [14,51]. The glucan chain so formed is then weaved and combined together to form the protofibrils, which in size range from 2-4nm with respect to its diameter. These protofibrils give rise to the ribbon-shaped microfibrils of cellulose, which is ~ 80nm in size, resulting in a higher degree of crystallinity [34,51].

Bacterial Cellulose Applications

BC is generated by acetic acid bacteria, both in the synthetic and non-synthetic medium, by oxidative fermentation like *Gluconacetobacter, Agrobacterium, and Rhizobium* [55]. Nowadays, a lot of research is being done to overcome the high preparation cost and to achieve high cellulose production from bacteria [15]. As a biomaterial, BC has applications in the medical field, electrical instruments, and food ingredients [15]. It has extensive use in the field of regenerative medicine, such as wound dressings, vascular grafting, bone tissue engineering, and artificial skin [55]. Some important properties of BC are high water retention, wet strength, tensile strength, shape retention, and moldability in terms of shape and property. Moreover, BC, unlike cellulose, does not require much processing [56]. These properties are being largely exploited for various biomedical applications [56]. Some of the applications are described here. Figure 3 and Table 2 give us an overall idea of the applications of BC.

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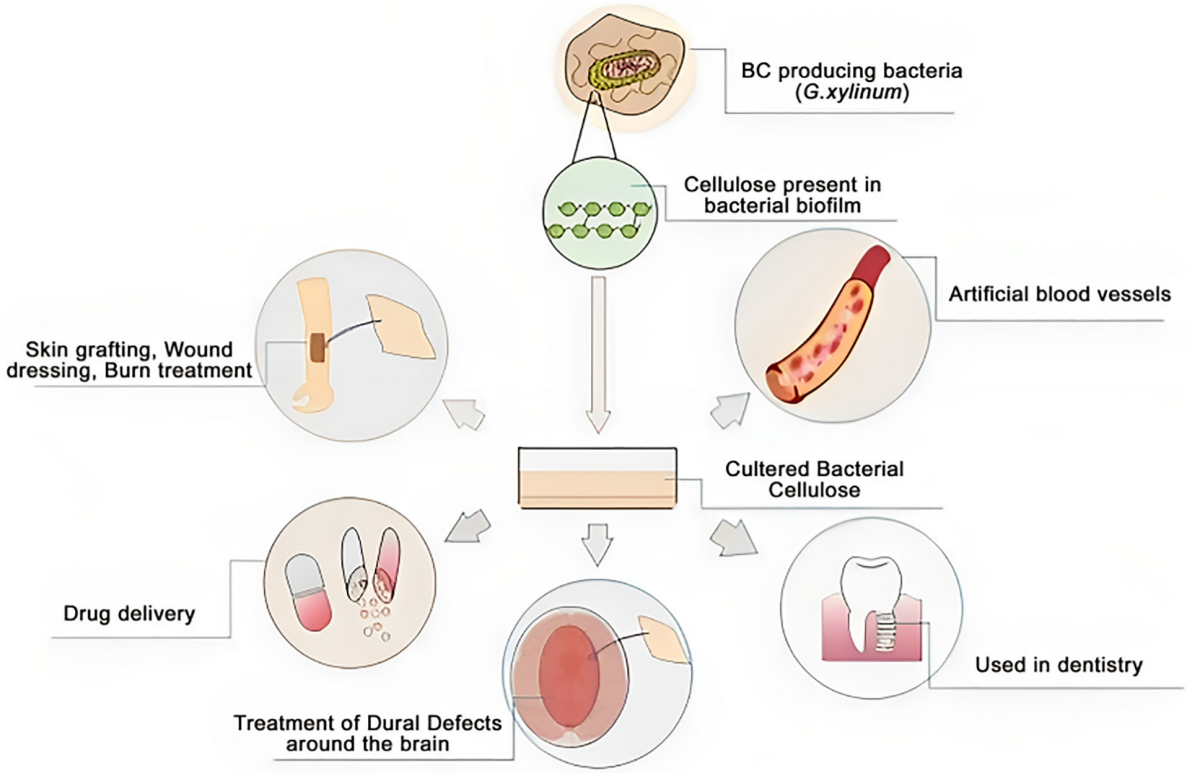

Figure 3. Applications of BC in various biomedical sectors.

Table 2. Application and action of BC derived from various bacterial strains.

Sl. No.	Application	Species of bacteria for BC production	Action	Reference
1	Burn wound treatment	*Acetobacter sp.*	Curative properties of BCM produced intreating second-degree burns.	[57]
2	Dentistry	Naturally occurring hydrous BC *Acetobacter sp.*	Eliminate infection and promote periodontal regeneration. Applicative potential of improved silicate cement with BC indentistry.	[58,59] [60]
3	Artificial blood vessel formation	*Gluconobacter* strains	Small diameter blood vessels were created from bio-designed cellulose.	[61]
4	Bone tissueformation	*Gluconobacter xyliuinus*	BC has its use in tissue engineering and can be used inbone regeneration.	[62]
5	Wound dressing	*Gluconobacter* and *Acetobacter* strains	BC are coupled with other materials. This enables it to be used as an ideal material for wound dressing as it not only reduces pain but also accelerates granulation.	[63]
6	Drug delivery in the form of capsules	*Acetobacter sp.*	Practicability of BC in both immediate and sustained drugrelease was seen.	[64]
7	Treatment of Dural Defect	Bacterial synthesis from sugarcane molasses	Non-toxic and low-cost solution to beused for treating dural defects.	[65]

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Wound healing

One of our most vital organs, the skin, is essential for various functions like temperature regulation, water and electrolyte balance, and sensation [66]. Loss of this barrier might be caused by traumas, and the problem must be addressed immediately [66]. Mostly, when the skin is wounded, the tissues start to repair by themselves following the four steps of healing viz, hemostasis, inflammation, proliferation, and remodeling, but the problem arises when wounds are large and deep, resulting in impaired function of the tissue [66,67]. So, wound dressings that can provide a favorable microenvironment for proper restoration of the wounded skin are necessary [68]. The ability to absorb, extrude, and prevent the growth of microorganisms are the main properties required in a good wound dressing [69]. BC, with its extraordinary hydrophilic nature, can effectively serve the purpose as they are known to heal ulcers and promote healing without pain [70]. However, the only limitation of BC is that it does not possess antibacterial properties, which need to be separately incorporated to prevent infection in the wound area [71]. Zmejkoski et al. used a dehydrogenative polymer of coniferyl alcohol (DHP) and BC and formulated a hydrogel composite. The DHP showed good antibacterial efficacy against gram-negative *S. typhimurium* and *P. aeruginosa* and gram-positive bacteria *L. monocytogenes* and *S. aureus* [72]. Similarly, Pal et al. functionalized BC with silver nanoparticles (AgNPs), which showed good antibacterial activity against *E. coli* [72]. To reduce toxicity from silver, they treated the composite with UV light and turned the silver ion into metallic silver. The composite was demonstrated to be stable in a moist environment and could be used for general wound-healing applications [73]. Another experiment by Lin et al. demonstrated the use of chitosan in BC. The membrane showed good cytocompatibility and antibacterial activity (*E. coli* and *S. aureus*) [71]. Animal experiments also demonstrate the performance of BC in wound healing. Khamrai et al. used curcumin as an antibacterial and wound-healing agent and fabricated a gelatin-based hydrogel patch with ionically modified self-assembled bacterial cellulose (iBC) [73]. This special patch containing iBC participated in self-healing by the formation of the ionic interlocking system only at a physiological pH of 7.4. Due to the presence of curcumin, strong antibacterial activity against Gram-negative E.coli and Gram-positive *S. aureus* was seen. Moreover, the wound healing capability was found to be high, as demonstrated in vitro by treating the patch with NIH 3T3 fibroblast cell line [73]. Qiu et al. synthesized bacterial cellulose-vaccarin (BC-Vac) membranes [74]. In comparison to the BC membrane, BC-Vac showed enhanced physical and mechanical properties and cell viability. Both membranes demonstrated a non-toxic impact on L929 cells with a cell relative growth rate above 74% (necessary for biomaterials). After 14 days of wound treatment on mice, the wound area was found to be 0.56mm and 0.5mm for BC and BC-Vac, respectively. Moreover, the removal of BC membranes from the wound was easy, while the petroleum gauze (PG) and nano silver dressing (ND) induced trauma on removal. Even in the histology study, the PG and ND groups showed an increased number of inflammatory cells and few necrotic cells.

However, the BC-treated group saw new neovascularization and fibroblasts and less inflammatory cells with more active fibroblasts and epithelialization. While both the BC membranes showed good performance, the BC-Vac was better, as vaccarin can promote cell growth and proliferation [74]. Full-thickness wounds are difficult to treat and might require split skin grafting or regenerative products, which might cause infection or immune response [66]. Loh et al. demonstrated the wound healing potency of bacterial cellulose/acrylic acid (BC/AA) hydrogel loaded with human epidermal keratinocytes (EK) and dermal fibroblasts (DF) for a full-thickness wound in mice [66]. The EK and DF were obtained from the patient's skin whose wound needs to be treated. With only visual observation, it was seen that the hydrogel with cell (HC) showed complete healing after 13 days of treatment than the hydrogel alone (HA) and non-treated cell (NT). This might be because BC/AA had some resemblance to natural soft tissue and showed 'excellent cell attachment, maintained cell viability with limited migration, and allowed cell transfer' in vivo. The percentage of wound closure on day 13 was 99.2 ± 1.3%, 91.9 ± 2.0%, and 87.8 ± 2.0% for HC, HA, and NT, respectively. Moreover, no scrab on the HC-treated cell was found, while the other two showed scrab formation [66].

Drug delivery

The biocompatibility and the 3D nanoporous structure of BC make it a good candidate for drug delivery systems [75]. Figure 4 shows the general functioning of a drug delivery system. BC, both in the form of hydrogels and capsules, can be used for drug delivery [63,75-78]. Silva et al. loaded bacterial nanocellulose (BCN) with different active pharmaceutical ingredients (APIs) like lidocaine, caffeine, ibuprofen, and diclofenac and investigated the storage stability of the Bacterial nanocellulose (BNC) membranes [75]. They found that with the increase in relative humidity (RH), the moisture uptake of the hydrophilic BNC membrane increased. Moreover, no significant variations in drug release, morphology, and structure of BNC were observed for the different conditions of RH and temperature (0% RH/40 ℃, 60% RH/25 ℃, and 75% RH/40 ℃). The drug release profile followed a general trend of 'initial burst, then a plateau (where the drug release rate reached a maximum value). Further, they checked the cutaneous compatibility of the membranes loaded with caffeine on human volunteers. No cutaneous response of skin irritation or any compromise of the skin barrier and hydration was seen for both plasticized and caffeine-loaded BNC. As the plasticization was done using 1% glycerol, the BNC provides moisture and hydration to the skin [75]. For controlled drug release, a novel BC/graphene oxide (GO) nanocomposite drug nanocarrier [77]. The drug release profile for both IBU-BC/GO and IBU-BC (control) was pH-dependent, i.e., fast in neutral and slow in acidic pH. They claim that this behavior might be due to the swelling of BC at different pH. The drug release followed a non-Fiskian diffusion mechanism for IBU-BC/GO, and it showed more sustained drug release than BC. Moreover, it is important that the amount of GO should be optimum so as not to hinder the porous nature of the BC for proper drug release and exchange of nutrients [77]. Badshah et al., using a circular-shaped disc fabricator, formulated BC matrices of 12mm diameter [76]. They selected highly water-soluble tizanidine and poorly soluble famotidine as test drugs. They saw that both hydrated and partially hydrated matrices showed greater drug diffusion as compared to the freeze-dried matrices due to the porous and hydrophilic nature of the former two. Moreover, BC with the loaded drug was chemically and thermally stable. Irrespective of the drug's solubility, it was found that within the initial 15 min, 80% of

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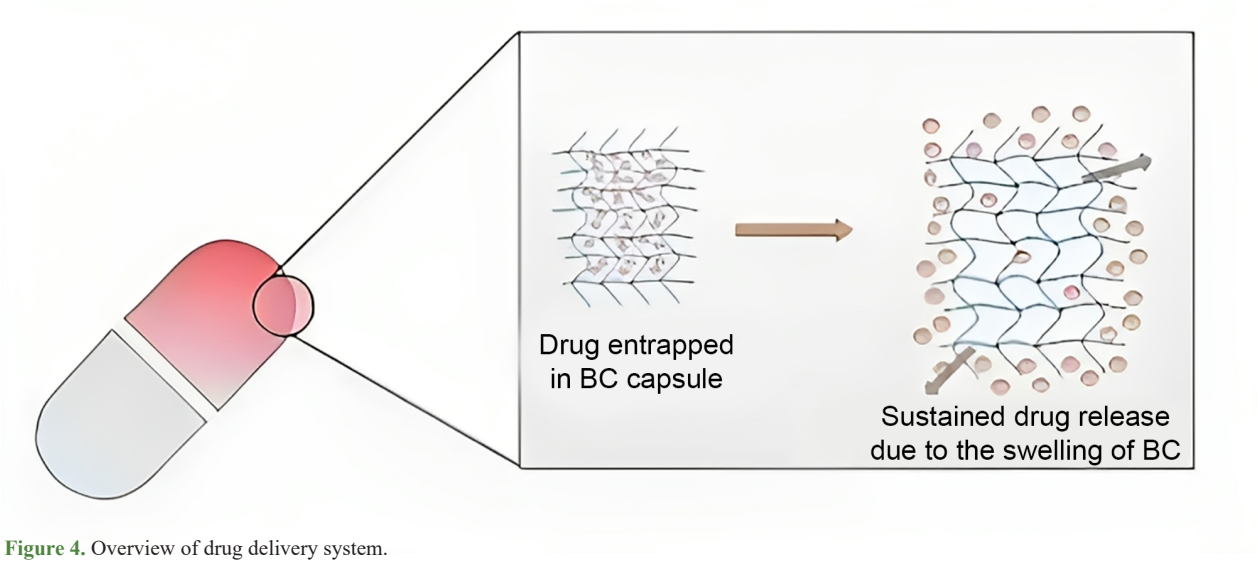

Figure 4. Overview of drug delivery system.

the drug was released, concluding that BC is a good candidate for immediate drug release and can replace conventional formulations where different excipients need to be added [77]. In another experiment by Ullah et al., they made capsules of BC loaded with salbutamol sulfate using Teflon pins [62]. They found that the BC capsules showed immediate drug release irrespective of the drying process used, the wall thickness, and the amount of drug loaded [63]. Moreover, by adding polymers, membrane-controlled matrix-based BC capsule shells can be fabricated, which can sustain drug release. This proved that BC could be used both for immediate and sustained drug release [63].

Tissue engineering

In the multidisciplinary field of tissue engineering, much attention is paid to cell interactions and antibacterial properties of the scaffolds [61]. Though BC is a good candidate for tissue engineering applications, it has a few other limitations in terms of pore size and biodegradability, which constricts its use [79]. To overcome these limitations and to be used on human tissues, proper modification (antibacterial properties, biodegradability, antioxidant activities) needs to be done [79]. Keskin et al. modified BC with human hair keratin by an in-situ method (during the culturing) and by post-manipulation [79]. As the structure of keratin is similar to that of intermediate filaments, its incorporation in BC enhanced the attachment of dermal fibroblasts and retained the original morphology of keratinocytes [79]. The performance of post-manipulated BC in terms of fibroblast proliferation was more likely because the in situ modified nanocomposite did not contain enough keratin for cell attachment. This BC/Keratin nanocomposite can be used for tissue engineering applications [79]. In an experiment by Kirdponpattara et al., they crosslinked thermally crosslinked gelatin and homogenized BC with glucose via the Maillard reaction to form a highly porous gelatin/BC sponge (GB) [80]. Due to this reaction, melanoidin, a reddish-brown substance, was formed, which is known to have antibacterial and antioxidant activity. Thus making this nanocomposite a good material for tissue engineering applications.

Moreover, these GB sponges displayed good biocompatibility, non-toxicity, high porosity, good swelling, and low weight loss against Vero cells [80]. An experiment by Palaninathan et al. used acetosulfation to functionalize BC with sulfate groups and make it soluble in aqueous solution [81]. Then, by using the electrospinning method, bacterial cellulose sulfate/polyvinyl alcohol (BCS/PVA) nanofibers were fabricated. In vitro studies with L929 mouse fibroblast cells suggested that BCS had antioxidant properties, and BCS/PVA nanofibers also allowed cell growth and proliferation with cell viability of more than 90%. Moreover, the BCS was also found to be hemocompatible i.e., it does not lyse human red blood cells RBCs and also maintains its integrity. All such properties of BCS give BCS/PVA nanofibres the potential to be used in regenerative medicines and tissue engineering applications [81]. In an experiment by Lamboni et al., they developed microstructured bacterial cellulose (mBC) modified with silk sericin (SS) for the regeneration of the gut muscle layer [82]. Poly (dimethyl siloxane) was used to make the stripes on the surface of BC to form mBC to mimic the gut morphology [82]. The physical property of the BC was altered, making it stiff and reducing its swell ability due to its high degree of crystallinity and fiber density. The SS, with its proangiogenic and antioxidant properties, created a suitable microenvironment for tissue regeneration, which supported the in vitro growth and differentiation of primary smooth muscle and enteric nervous system cells. Moreover, as compared to unmodified BC, the mBC showed improved functions in terms of cell attachment [82].

Bone regeneration

There are several causes of bone damage, including trauma, surgery, old age, or infection, and to regain function, bone regeneration is necessary [55]. Grafting may be a good option, but it has its limitations of graft rejection or pathogen transmission [55]. On the other hand, guided tissue regeneration (GTR) membranes can help overcome such problems [55]. Some of the important features that are necessary for such scaffolds or membranes used in bone regeneration are porous structure, biocompatibility, and good mechanical strength [41]. The porous structure might negatively influence the mechanical strength as the mechanical strength is an important property as it enhances cell migration and adherence [41]. The membrane is used as a barrier between the damaged bone and the connective tissues to provide space for the new bone to form [55]. Klinthoopthamrong et al. fabricated a bacterial cellulose membrane (BCM) grafted with poly (acrylic acid) (PAA) and

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containing plant-derived recombinant human osteopontin (p-rhOPN) [50]. Together called p-rhOPN-BCM. This product was compared to the commercial rhOPN derived from a mammalian cell line. They found that both types of membranes, as compared to BCM alone, were able to promote the adhesion of human periodontal ligament stem cells and osteogenic differentiation to a greater extent, and the prhOPN-BCM was more potent than the commercial rhOPN-BCM.

An experiment by Chen et al. focused on enhancing the mechanical strength of the tissue scaffold that mimics a natural bone [42]. They produced biodegradable 'silk fibroin (SF)/bacterial cellulose nano-ribbon (BCNR) composite scaffolds'. SF was obtained from the silkworm. It had outstanding biocompatibility, tunable biodegradability, antibacterial properties, and good permeability to water vapor and oxygen. The BC was obtained from *Acetobacter xylinum*. This three-dimensional scaffold achieved by a multi-stage freeze-drying method with temperature gradients had a radial lamellar pattern and gradient lamellar gap. The BCNRs increased the lamellar strength, and the intercalated fibers avoided slipping when stress was dispersed. The increased mechanical strength also allowed good cell adhesion and bone bonding. Moreover, the porous structure improved water uptake, swelling, nutrient uptake, and waste flow efficiently [42]. Similarly, Codreanu et al. fabricated 'bacterial cellulose modified poly(3-hydroxybutyrate) scaffolds (PHB/BC)' [65]. The osteogenic potential of the scaffolds was tested for calvaria defects under the critical-size mouse. For evaluating the in vitro biocompatibility of the scaffolds, a 3T3-L1 pre-adipocytes mouse cell line was used. It was found that the cell line proliferated and had good viability in the scaffolds, suggesting that the scaffolds were biocompatible.

Increased expression of Osterix (OSX- important for bone regeneration) and enhanced activity of Alkaline phosphatase (ALP) suggested enhanced osteoblast differentiation in vivo [83]. The formation of new bones was also observed by X-ray and histology analysis. In an experiment conducted by Gutiérrez-Hernández et al., multi-walled carbon nanotubes (MWNTs) were combined with BC to obtain a 3D scaffold to culture osteoblastic cells [61]. The scaffold showed enhanced mechanical properties, and its topography allowed favorable adhesion and proliferation of cells [61]. Basu et al. synthesized calcium phosphate (CaP) and incorporated it in BC polyvinylpyrrolidone (PVP) based hydrogel scaffolds, which had 80% porosity, significant degradability, and compressive strength of 0.21–0.31 MPa (similar to human cancellous bones) [84]. The human osteosarcoma Saos-2 cell line showed good viability and proliferation between day 1 and day 7. This confirmed the cytocompatibility of the scaffolds [84]. Luz et al. combined BC and hydroxyapatite (HA) and doped them with strontium ions (Sr2+) with two modes of synthesis [85]. In the physisorption mechanism, calcium ions in the hybrid' BC/CaHA' were exchanged for strontium ions in a strontium nitrate solution to form BC/CaHA/Sr hybrid. The chemisorption mechanism involves the precipitation and interaction of phosphate ions and strontium ions on the BC by ionic bonds to form the hybrid BC/SrAp. They found that due to the strong chemical bond of BC/SrAp, Sr was better absorbed, and there was sustained release for over 4 months [85].

Burn wound applications

Burn injuries may lead to serious health problems. It has a high chance of morbidity and mortality [86]. The severity of the injury is associated with the agent causing it and the extent and depth of the damaged area [86]. There are three types of burn injury, first-degree, second-degree, and third-degree, which is due to the damage of the epidermis, blisters on the skin, and a total loss of skin layers respectively [86]. The recovery from a deep burn injury is difficult as the tissue function gets impaired, leading to improper deposition of collagen fibers, which can lead to various issues. These include the prevention of the mobility of cells locally and the alteration of sensibility causing pain due to innervation [81]. For a wound to heal properly, there must be proper interaction between the extracellular matrix, growth factors, and cells [86]. The three stages of wound healing are inflammation, proliferation, and remodeling following in order [86].

Another problem that might arise during injury is an infection caused by bacteria [86]. So, a functional biological dressing may be a good option to solve such problems [86]. The use of BC is a good option for treatment as it provides a moist environment for proper wound healing [87]. Kwak et al. compared the effectivity of BCM with gauze (GZ) on second-degree burn wounds of Sprague Dawley (SD) rats [56]. The tensile strength, strain, crystallinity, gel fraction, and water vapor transmission rate were found to be 12.13 MPa, 12.53%, 17.63%, 90.2%, and 112.14 g × m2/hr, respectively. The BCM-treated group, compared to the GZ group, showed good angiogenesis and a high level of collagen formation in the mice specimens, suggesting the superior performance of BC in wound healing [57]. Brassolatti et al. investigated the efficacy of BCM and BCM loaded with lidocaine in the treatment of burn injury [86]. For the experiment, he used three sets of Wistar rats, subjected them to third-degree burn, and divided them into a control group (CG), BCM group (MG), and BCM with drug group (MGL). Both MG and MGL groups showed comparable results. After 10 days, it showed skin appendages, moderate inflammatory infiltrates, and better organization of collagen fiber. The presence of COX-2 and MMP-9 was seen in very low quantity. Compared to the control, the results were better for the other two groups [86]. Pandey et al. investigated the extent of wound healing and skin irritation caused by BC/acrylamide (AM) hydrogel on partial-thickness burn wounds in rat models [87]. Groups were treated with BC/AM, a positive control (Intrasite gel), and an untreated negative control [87]. After 7 days of treatment, 55% wound closure was achieved for the BC/AM treated group, the positive control showed 52% wound closure, and it was 28% for the untreated group. The 14th day showed a 14% higher wound contraction of the BC/AM treated wound than the untreated one. These microparticles were highly porous, had good swelling properties, showed good cytocompatibility with L929 cells and it was not irritant to the skin [87].

Mohamad et al. developed BC/AA hydrogel and added to it human dermal fibroblasts (HEF) and human epidermal keratinocytes (HEK) [88]. Then, an in vivo study was done on athymic mice with partial thickness burns on their hind legs. Three groups- untreated, treated with BC/AA, and treated with BC/AA containing HEK and HEF were studied. They saw a wound reduction of 64.79 ± 6.84%, 71.51 ± 2.35, and 77.34 ± 6.21, respectively, on the 13th day, suggesting that the BC/AA loaded with cells had better performance. Moreover, from the histology studies, they found collagen deposition was most common for BC/AA loaded with collagen [88]. To promote

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wound healing and to provide antibacterial efficacy on burn wounds, Khalid et al. developed BC and titanium dioxide (TiO_2) nanocomposites (BC–TiO_2) [89]. The healing potential of the dressing was demonstrated on mice with deep partial-thickness burns. The decrease in wound area after 15 days was 86.0 ± 3.4, 147.3 ± 3.0, 248.3 ± 2.8, and 76.6 ± 5.7, respectively, for BC–TiO2 treated, BC treated, Negative control, and silver sulfadiazine treated groups respectively. Inhibition of *E. coli* was 81 ± 0.4%, and *S. aureus* was 83 ± 0%, which suggested a good antibacterial property of BC–TiO_2 nanocomposite. In comparison to BC only, which showed partial epithelization and inflammation of the wound area, BC–TiO_2 showed healthy granulation tissue and re-epithelization. This can be correlated with the accelerated wound contraction ability of the BC–TiO_2 group [89]. Similarly, Wen et al. incorporated silver sulfadiazine (SSD) particles of the narrow size distribution in BC to form BC–SSD membranes, which also showed good antibacterial properties against *Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli* and had better wound healing efficacy than gauze [90].

Dental applications

Periodontal disease treatment, root canal operations, and other dental implants require the use of good biomaterials [58,59,91,92]. BC based biomaterials are coming into consideration due to their unique properties like softness, flexibility, self-attachment, and others, as previously mentioned [92]. A few applications of BC based composites are mentioned here. Zhang et al. evaluated the performance of polylactic-co-glycolic acid (PLGA)/multiwall carbon nanotubes (MWNTs)/bacterial cellulose (BC) composite membrane for tissue regeneration of maxillary canine periodontal bone defects [58]. For the GTR, they performed U insertion and made a defect on the buccal side of the maxillary canine of beagle dogs. For both untreated and PLGA/MWNTs/BC treated membranes, complete healing was seen after 12 weeks. However, the composite-treated defect was noted to show active proliferation because of the presence of abundant osteoblast at the bone's edge and the presence of clumps of lamellar bone. The new soft tissue formed in the experimental group was hard on probing as compared to the control, where the connective tissue was found soft on the decaying surface. Thus, the efficacy of the composite was determined [58].

Bioactive and bioabsorbable BC has important applications as dental medicines in periodontal diseases. For this purpose, a selectively oxidized BC membrane with loaded bactericides was made by Inoue et al. [91]. They prepared 2,3-dialdehyde bacterial cellulose membranes (DABC) by oxidation with sodium periodate at varying degrees of oxidation (DO). The DABC membrane with DO=6.8 showed optimum degradation in PBS solution compared to DO=15.5, which had excessive weight loss and was intact to be handled even after 90 days. The unmodified BC and DABC of DO=2.8 had no weight loss. The antibacterial studies against *E. coli, S. aureus, and C. albicans* revealed that both chlorhexidine and βcyclodextrin (CHX:β CD) loaded BC and DABC (DO=6.8) showed the highest mean value of inhibition zone in the agar diffusion test. Thus, DABC DO=6.8+CHX:βCD shows admirable properties to be used further in periodontal treatments [91].

For endodontic treatments like perforated channel filling, root channel obturation, or dentine mineralization, Voicu et al. used polygranular BC powder and mixed with silicate cement (SC) in a 9:1 ratio to form a dental cement [59]. The material showed notable mineralization and shortened setting time. Within vivo studies revealed that the composite can provide proper mesenchymal stem cell adhesion and proliferation [59].

Dural defect

The bilayer membrane between the skull and the brain surface is the dura mater [93]. Traffic accidents and various underlying diseases like tumor and brain surgeries are a major cause of the dural defect in humans [93,94]. On severe occasions, these defects may lead to the leakage of cerebrospinal fluid (CSF) [94]. Implantation is a good treatment option but it is accompanied by severe immune response and inflammation [58,93-95]. The criteria for ideal dural repair material are that it should have an easily available source and can be easily produced, it should be chemically stable, biocompatible, non-toxic, non-carcinogenic, and should not transmit diseases [58,93-95]. The material should have considerable toughness and flexibility and should not adhere dura mater to the brain tissue [58,88-90]. BC has already been reported to be a good substitute for dura mater due to its lack of adhesion to the brain tissue with low immune response [93]. Xu et al. derived BC from *Acetobacter xylinum* and studied its performance against a commercially available dural patch in China called NormalGEN® (control) on dural defects of rabbits [95]. They observed that under 30 days BC was covered by connective tissue, and by day 90, it was blended with the surrounding tissue. The expression of iNOS, COX-2, and inflammatory cytokines like IL-6, IL-1β, and TNF-α in BC, was less than that of the control. Also, they observed no adhesion of BC with the brain surface, proving its efficacy as a dural implant [90]. Again, in another experiment, Xu et al. aimed to use the drug vancomycin (VAN) in BC to prevent bacterial infection due to the implant [93]. For the in vivo study, he made dural defects on rabbits and inoculated them with S. aureus. The control (BC without drug) showed infection, while the experimental sample showed no infection after seven days of treatment. This was due to the sustained release of VAM (both in vitro and in vivo).

Moreover, a much lower level of inflammatory cytokines was observed in the experimental group [94]. In an experiment by de Lima et al., they prepared BC using sugarcane molasses [64]. The performance of the BC was compared to polytetrafluoroethylene (ePTFE) on dural defects made on adult Wistar rats after 120 days of treatment. The performance of both groups was comparable, with no cases of infection or CSF leak. However, the ossification on the BC was more than ePTFE, suggesting that BC was more biocompatible [64].

Artificial blood vessels

Due to the growing unhealthy lifestyle, smoking, old age, and diabetes, there is an increase in cardiovascular diseases causing death worldwide every year [96]. To treat pathologies like stroke, myocardial infraction, etc., vascular grafts are necessary [96,97]. Allograft rejections and limited sources of autologous blood vessels can lead to limitations in the treatment [97]. For this reason, much research is being done on the development of artificial blood vessels [97]. BC, due to its unique properties, has been certified as a promising biomaterial and can be used in arterial stent coating [98].

Moreover, the extraordinary network structure of BC

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resembles the extracellular matrix, which has a collagen network and can facilitate the transmission of nutrients and metabolites [98]. Some experiments done for this purpose are mentioned. Zang et al. prepared BC tubes with polydimethylsiloxane (PDMS) as a tubular template material from *G. xylinum* [98]. The dimensions of the tube were 100 mm length 1 mm thick and the outer diameter was varied i.e., 4mm or 6 mm. The Young's modulus of the BC tubes of both diameters was found to be three times more than the porcine carotid artery, indicating the good tensile strength of BC tubes. As the degradation temperature of the BC tubes was found to be above 300 °C, it could be rightly concluded that our body temperature (37 °C) won't affect it [96]. Moreover, enzymes or acids present in our body are unable to degrade cellulose. The BC tubes demonstrated good biocompatibility and its surface was beneficial for cell attachment, proliferation, and ingrowth of endothelial, smooth muscle, and fibroblast cells. For the *in vivo* study of the BC graft, it was implanted in the femoral artery of the rabbit. The experiment revealed complete endothelialization of the BC with a confluent layer of endothelial cells and without any inflammation around the implants [98]. To enhance the compliance of bacterial nanocellulose (BCN) tubes, Tang et al., introduced poly (vinyl alcohol) (PVA) in the tubes [94]. They found that in comparison to pristine BNC tubes and PVA tubes, BNC/PVA demonstrated better water retention and mechanical strength [99]. In another experiment by Li et al., they fabricated chitosan (CH) deposited BNC tubes in double-silicone-tube bioreactors, after which heparin (Hep) was grafted chemically using EDC/NHS crosslinking [97]. The incorporation of CH greatly improved the physical, chemical, and mechanical properties of BNC tubes and enhanced the grafting of Hep, but the cell proliferation of pig iliac endothelium cells was slightly inhibited by CH. Also, the incorporation of Hep improved anticoagulation and endothelialization significantly. This formulation could be useful for small-caliber artificial blood vessels [97].

Conclusions and Future Prospects

BC has done wonders in the field of biomedicine. However, the technology still needs further improvement when it comes to its production, along with the nature of the application to be used. The conventional methods used for the production of BC are not very economical with respect to the reactor system and media used. The aim of the production should be to generate a low expense, higher yield productivity, which the conventional system has failed to deliver. Recent studies have pointed out the potential of using agro-waste or other industrial waste materials as the source of nutrients for BC production. This can serve as a progressive, environmentally friendly, and economical method of producing a desirable yield. Various approaches and extensive research in this area may enhance productivity at a low expense, and so this area requires considerable attention.

Disclosure statement

No potential conflict of interest was reported by the authors.

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