

# Bacterial nanocellulose production and application: a 10-year overview

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**Abstract** Production of bacterial nanocellulose (BNC) is becoming increasingly popular owing to its environmentally friendly properties. Based on this benefit of BNC production, researchers have also begun to examine the capacity for cellulose production through microbial hosts. Indeed, several research groups have developed processes for BNC production, and many studies have been published to date, with the goal of developing methods for large-scale production. During BNC bioproduction, the culture medium represents approximately 30 % of the total cost. Therefore, one important and challenging aspect of the fermentation process is identification of a new cost-effective culture medium that can facilitate the production of high yields within short periods of time, thereby improving BNC production and permitting application of BNC in the biotechnological, medical, pharmaceutical, and food industries. In this review, we addressed different aspects of BNC production, including types of fermentation processes and culture media, with the aim of demonstrating the importance of these parameters.

**Keywords** Bacterial nanocellulose · Biopolymers · Biomaterial · Bioprocess · Bioproducts · Fermentation process · *Gluconacetobacter xylinus*

## Introduction

Ten years of advances in biopolymer research have demonstrated the importance and potential of biopolymers for a variety of applications, particularly for biopolymers produced by microorganisms, including bacterial nanocellulose (BNC). Many types of BNCs have been developed for various applications, including tissue regeneration, drug delivery systems, vascular grafts, and scaffolds for tissue engineering in vitro and in vivo (Czaja et al. 2007; de Azeredo 2013; Almeida et al. 2014; Oliveira Barud et al. 2015; Martínez-Sanz et al. 2016).

Depending on the purpose of the application, BNC can provide improved mechanical qualities to the biomaterial owing to its biocompatibility, biofunctionality, lack of toxicity, and ease of sterilization (Klemm et al. 2011). For this reason, there are currently several methodologies for large-scale production of BNC. Researchers have focused on improving the efficiency of the production process, resulting in satisfactory yields that are compatible with the demand for this type of cellulose (Lin et al. 2014; Zhang et al. 2014; Cakar et al. 2014; Li et al. 2015).

The culture medium is the most important factor for the total cost of production of BNC. Therefore, one important aspect in BNC production is to identify a low-cost culture medium that can improve the yield of BNC and be used as an economically viable solution for application in a range of fields (Cakar et al. 2014; Padmanaban et al. 2015).

Therefore, the aim of this review is to discuss advancements in BNC production within the last 10 years. To this

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end, we will describe the types of processes and culture media used for BNC production. We also discuss the potential applications of BNC.

## Cellulose

Cellulose is the most common natural polymer worldwide. According to a worldwide estimate,  $10^{14}$  t of cellulose pulp are produced each year, emphasizing the economic importance of this polymer (Donini et al. 2010; Lin et al. 2014). Due to the presence of components other than cellulose, different chemical treatments employing highly polluting chemical products, such as chlorine gas, caustic soda, carbon disulfide, carbon monoxide, and carbon dioxide, are often needed prior to use in order to obtain pure cellulose (Basta and El-Saied 2009; Klemm et al. 2011).

Donini et al. (2010) compared the productivity of cellulose from plants and microorganisms in order to determine the advantages of producing cellulose from microorganisms. In their analysis, they compared the production of cellulose from 1 ha of eucalyptus with a mean annual increment (MAI) of  $50 \text{ m}^3$ , providing a basic density of  $500 \text{ kg/m}^3$ ; this generated an MAI of 25 t/ha/year. With 7 years from planting to cultivation, yielding about 45 % cellulose contents, this process would yield about 80 t of cellulose/ha after 7 years of cultivation. The authors found that the same production could be achieved with bacteria to a hypothetical yield of 15 g/L in 50 h of culture (average of 0.3 g/h) in a bioreactor of  $500 \text{ m}^3$  in approximately 22 days. This more efficient production method also yielded pure and ecologically sustainable BNC as the product.

Unlike plant cellulose, BNC is produced in the pure form, devoid of lignin, hemicellulose, pectin, or any other compound present in the plant pulp and does not contain components of animal origin. In addition, it has superior mechanical properties compared with plant cellulose (Fu et al. 2013).

The anhydroglucose units and various bacterial cellulose fibrils interact closely with each other to form a crystalline structure through internal and external hydrogen bonds, resulting in the compaction of fibers that are completely insoluble in water but that can be hydrated (Lynd et al. 2002; Conley et al. 2016). The thin nanofibers have a diameter of 20–100 nm, with a large surface area per unit; this feature, combined with the hydrophilic nature of BNC, results in high water absorption capacity, better adherence, and increased moisture content (Fu et al. 2013; Numata et al. 2015b). These properties, combined with the distinct physical and mechanical properties of the molecule, including its insolubility, rapid biodegradability, tensile strength, elasticity, durability, and nontoxic and nonallergenic features, make BNC ideal for the

production of several products with high added value, such as artificial skin used as a temporary substitute in the treatment of burns and other dermal injuries (Thompson and Hamilton 2001; Rehim et al. 2014; Cakar et al. 2014).

BNC is a highly crystalline linear polymer of glucose synthesized mainly by the bacterium *Gluconacetobacter xylinus* (formerly named *Acetobacter xylinus*). Although BNC production has been studied primarily in *G. xylinus*, other microorganisms also exhibit the ability to synthesize this biopolymer, such as other species of *Gluconacetobacter*, *Agrobacterium tumefaciens*, *Rhizobium* spp., and Gram-positive *Sarcina ventriculli* (Tanskul et al. 2013; Mohammadkazemi et al. 2015).

*G. xylinus* is the primary microbial producer of BNC and has become a model system for the study of the biosynthetic mechanisms of BNC in bacteria (Keshk 2014). For cellulose production, *G. xylinus* builds a nanofibrillar film with a denser lateral surface and a gelatinous layer on the opposite side (Kurosumi et al. 2009; Cai and Kim 2009). The biochemical process of cellulose synthesis by *G. xylinus* consists of three main steps: (i) polymerization of glucose residues in  $\beta$ -1-4 glucan, (ii) extracellular secretion of linear chains, and (iii) organization and crystallization of glucan chains through hydrogen bonds and van der Waals forces arrayed in a hierarchy into strips. Thus, microfibril cellulose is produced (Donini et al. 2010; Klemm et al. 2011).

Despite the above studies, the metabolic pathways through which microorganisms regulate BNC production remain unclear. Moreover, it is still necessary to identify new microorganisms that can produce this biopolymer.

## Biotechnology-based production of BNC

The production of environmentally friendly products is becoming increasingly important; in this context, the production of nanocellulose through microbial pathways is advantageous. Indeed, BNC production using microorganisms is industrially important because such microorganisms exhibit rapid growth, allowing for high yields and year-round availability of product (Santos-Ebinuma et al. 2013).

There are two main methods for producing BNC using microorganisms: static culture, which results in the accumulation of a thick, leather-like white BC pellicle at the air-liquid interface (Kuo et al. 2015), and stirred culture, in which cellulose is synthesized in a dispersed manner in the culture medium, forming irregular pellets or suspended fibers (Krystynowicz et al. 2002; Czaja et al. 2004). The choice between these two types of production (i.e., static or stirred culture) depends on the final application of BNC since the morphological, physical, and mechanical properties of the

formed polymer vary according to the method of cultivation. For example, cellulose produced by stirred culture has low mechanical strength compared with that produced by static culture. Moreover, stirred culture results in lower yields than static cultures and a higher probability of mutations in the microorganism, which may affect the production of BNC. On the other hand, static culture requires a larger cultivation area and a longer culture time (Chawla et al. 2009; Keshk 2014; Cakar et al. 2014; Lee et al. 2014; Jeon et al. 2014; Tyagi and Suresh 2015).

Some considerations must be taken into account when determining the conditions necessary to produce BNC. The cost-benefit from the culture medium in terms of yield of BNC is an important factor, and therefore, the composition and volume of the medium should be considered. The composition of the culture medium can directly affect the profitability of the biotechnological process and is therefore critical for the production of any bioproduct, including BNC (Ruka et al. 2012; Lee et al. 2014; Mohammadkazemi et al. 2015).

The fermentation medium must contain, at minimum, a carbon source, a nitrogen source, and other macro- and micronutrients required for the growth of the microorganism, such as phosphorus, sulfur, potassium, and magnesium salts (Krystynowicz et al. 2002; Chawla et al. 2009; Mohammadkazemi et al. 2015).

The synthesis of cellulose is susceptible to chemical agents and the physical influence of the compounds present during its production. Thus, regardless of the method of production, factors such as yield, morphology, structure, and physical properties may be affected by the culture medium used (Jung et al. 2010; Ruka et al. 2012; Mohammadkazemi et al. 2015).

The culture medium typically used for the production of BNC, regardless of the use of static or stirring culture, was first described in 1954 by Hestrin and Schramm (HS) (Schramm and Hestrin 1954). This medium is composed of 2 % glucose (the major carbon source), 0.5 % peptone, 0.5 % yeast extract, 0.27 % of anhydrous disodium phosphate, and 0.15 % citric acid monohydrate. However, HS medium can increase the final production cost of the biopolymer and is considered unfeasible for commercial production of BNC due to its high cost (Tyagi and Suresh 2015; Huang et al. 2016). For this reason, various studies have been performed over the last 10 years to improve BNC production based on several fermentation parameters, such as pH control, and alternative carbon sources, including sugar cane, molasses, sucrose, and rotten fruit, as well as culture in a static and agitated environment (Table 1).

*Gluconacetobacter* can use several carbon sources to synthesize BNC. Glucose is the most often used because it is both an energy source and the ideal precursor for obtaining cellulose during the biosynthesis process. However, BNC yield may be low because of the presence of glucose

dehydrogenase, which converts glucose into gluconic acid, thereby decreasing the pH of the culture and potentially affecting BNC biosynthesis, is present in the cell membrane of *G. xylinus* (Kuo et al. 2015)).

Beginning in 2006, Keshk and Sameshima studied the use of HS culture medium alone and in the presence of 1 % liginosulfonate (HSL) in six strains of *G. xylinus* (*G. xylinus* IFO 13693, 13,772, 13,773, 14,815, and 15,237) in static culture to produce BNC. The strains *G. xylinus* IFO 13693 and 13,773 exhibited the highest BNC production in HSL (around 16.32 g/L for both strains), which was higher than that obtained in HS (close to 7.92 g/L).

According to the authors, the presence of liginosulfonate promotes an increase in BNC production due to the inhibition of gluconic acid formation in the presence of antioxidant polyphenolic compounds in the liginosulfonate. In experiments performed with liginosulfonate, the pH was closer to 4.0 for all strains, whereas under other conditions, the final pH was around 3.0, which could be explained by gluconic acid production. Furthermore, FT-IR results showed that the BNC produced in the presence of liginosulfonate displayed a higher crystallinity index and  $I_{\alpha}$ -rich cellulose.

In 2009, Mikkelsen and coworkers studied the production of BNC by *G. xylinus* ATCC 53524 under static culture conditions using modified HS medium by replacing glucose with different carbon sources, i.e., mannitol, glycerol, fructose, sucrose, and galactose. Sucrose and glycerol showed the highest cellulose yields of 3.83 and 3.75 g/L, respectively, after 96 h of fermentation, whereas mannitol, fructose, and glucose (in the original HS medium) resulted in yields below 2.5 g/L.

Cross-polarization/magic angle spinning (CP/MAS)  $^{13}\text{C}$ -NMR spectroscopy showed that irrespective of the carbon source used, the cellulose produced by was pure and crystalline. These findings demonstrate the ability of *G. xylinus* to metabolize different sources of carbon to produce BNC. According to the authors, although the rate and extent of cellulose production was characteristic for the carbon source, the microscopic and molecular organization of cellulose produced was highly conserved, suggesting that differences in productivity due to the carbon source were due to substrate limitations, rather than changes in polymerization.

In the same year, Kurosumi and collaborators reported the production of cellulose by *Acetobacter xylinum* NBRC 13693 using juices (orange, apple, pineapple, Japanese pear, and grape) as culture media. The authors evaluated different conditions for these juices: fruit juice adjusted pH 6 with a nitrogen source of HS medium (medium I), fruit juice adjusted to pH 6 (medium II), and sugar reagents (glucose, fructose, and sucrose) with a nitrogen source in HS medium (medium III). The content and type of sugar present in each fruit juice varied, and the authors suggested that appreciable amounts of the bacterial cellulose could be produced from fruit juices containing an abundance of sucrose and fructose. The authors found a

**Table 1** Conditions, yields, production methods and microorganisms used to produce bacterial nanocellulose described in the literature starting in 2006

Carbon source	BNC Yield (g/L)	Production method	Microorganism	Reference
HS in the presence of 1 % lignosulfonate	16.32	Static culture at 28 °C for 168 h	<i>G. xylinus</i> IFO 13693	(Keshk and Sameshima 2006)
Sucrose	3.83	Static culture at 30 °C for 96 h	<i>G. xylinus</i> ATCC 53524	(Mikkelsen et al. 2009)
Orange juice containing nitrogen sources of HS	5.90	Static culture at 30 °C for 96 h	<i>Acetobacter xylinum</i> NBRC 13693	(Kurosuni et al. 2009)
Glucose in the presence of MCP-1	1.20	Stirred culture at 30 °C and 125 rpm for 288 h	<i>Acetobacter xylinum</i> JCM 9730	(Hu and Catchmark 2010)
Molasses and corn steep liquor in the presence of acetic acid	3.12	Stirred culture at 30 °C and 200 rpm for 168 h	<i>Acetobacter</i> sp. V6	(Jung et al. 2010))
Glucose	2.70	Static culture at 30 °C for 96 h	<i>G. sacchari</i>	(Trovatti et al. 2011))
Glucose (HS broth supplemented with <i>n</i> -butanol)	1.33	Static culture at 30 °C for 144 h	<i>A. xylinum</i> 186	(Lu et al. 2011)
HS broth supplemented with thin stillage	10.22	Static culture at 30 °C for 168 h	<i>G. xylinus</i> (BCRC 12334)	(Wu and Liu 2012)
Industrial residues from olive oil production	1.28	-	<i>G. sacchari</i>	Gomes et al. (Gomes et al. 2013)
Molasses	1.64	Static semicontinuous process for 168 h	<i>G. xylinus</i> (FC01)	Çakar et al. (Çakar et al. 2014)
Waste beer yeast treated with ultrasonication	7.02	Stirred culture at 30 °C and 150 rpm	<i>G. hansenii</i> CGMCC 3917	Lin et al. (Lin et al. 2014)
Rotten fruit culture	60	Static culture at 30 °C and 96 h	<i>G. xylinus</i> ATCC 53582	(Jozala et al. 2015))
Wood hot water extract	0.15	Static culture at 28 °C for 672 h	<i>Acetobacter xylinum</i> 23,769	(Erbaş Kızıltas et al. 2015b)
Waste water of candied jujube hydrolysate	2.25	Static culture at 30 °C for 144 h	<i>G. xylinus</i> CGMCC 2955	(Li et al. 2015)
Citrus Juice and sucrose	–	Static culture at 30 °C	<i>G. sp. gel</i> _SEA623-2	(Kim et al. 2015)
Lipid fermentation wastewater	0.66	Static culture at 28 °C for 5 days	<i>G. xylinus</i> CH001	(Huang et al. 2016)

HS Hestrin-Schramm culture medium, MCP-1 methylcyclopropane-1

higher cellulose yield (5.9 g/L) in culture medium containing orange juice supplemented with a nitrogen source after 96 h of bioprocessing. The BNC produced from this experiment was not characterized; therefore, it is not possible to determine whether the sugars present in different fruit juices generated BNC molecules with differential characteristics.

Jung et al. (2010) employed molasses and corn steep liquor to reduce the cost of the culture media in stirred culture. The authors found that the final pH in the presence of molasses was around 5.0 under several conditions, resulting in reduced production of gluconic acid because molasses components have lower amounts of glucose. The authors also evaluated whether the presence of organic acids (i.e., acetic acid, citric acid, lactic acid, pyruvic acid, and malic acid) would promote an increase in BNC biosynthesis. As result, the presence of acetic acid generated the highest yield (3.12 g/L). Moreover, FT-IR spectra of the BNC produced from the molasses and complex media showed similarities, indicating that the microorganisms could metabolize different carbon sources, producing BNC with the same characteristics.

Trovatti et al. (2011) first reported the production of BNC by *Gluconacetobacter sacchari*, isolated from Kombucha tea.

The strain harvested in HS medium containing glucose, sucrose, fructose, mannitol, or glycerol as the carbon source yielded the highest cellulose production (2.7 g/L in 96 h) when glucose was the carbon source. This value was consistent with that obtained from other cellulose-producing strains, and the structure of the cellulosic matrix obtained was identical to that produced by other bacteria.

Lu et al. (2011) studied the effects of six different alcohols (methanol, ethylene glycol, *n*-propanol, glycerol, *n*-butanol, and mannitol) added in the HS medium on cellulose production by strain *A. xylinum* 186 in static culture at 30 °C for 6 days. Interestingly, the addition of 1 % methanol produced a yield of 1.04 g/L, whereas the addition of 0.5 % ethylene glycol, *n*-propanol, or *n*-butanol produced yields of 1.06, 0.96, and 1.33 g/L BNC, respectively. The use of 3 % glycerol yielded 1.08 g/L BNC, and the addition of 4 % mannitol yielded 1.25 g/L BNC. Therefore, alcohols could be classified (in order from highest to lowest) based on BNC yield, as follows: *n*-butanol > mannitol > glycerol > ethylene glycol > methanol > *n*-propanol.

Wu and Liu (2012) studied HS broth supplemented with thin stillage (TS), which is the liquid portion of distillery

stillage from the fermentation of grain-based feedstock rich in organic acids and amino acids. The authors observed that complete replacement of glucose with TS enhanced the production of BNC, achieving a BNC yield of 10.22 g/L under conditions in which the TS was 100 % after 7 days of cultivation. According to the authors because TS is rich in organic acids, it could support the growth of *G. xylinus*, and the glucose in HS medium could be employed for BC biosynthesis. Therefore, the production of gluconic acid was low, promoting the highest production of BNC.

Gomes et al. (2013) studied the production of BNC by *G. sacchari* using industrial residues from olive oil (DOR) as nutrients and a carbon source. BNC production without the addition of any nutrients was around 0.80 g/L after 96 h of incubation, whereas conventional HS medium produced around 2.5 g/L BNC. Supplementation with olive oil residues containing nitrogen and phosphate sources [(NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> and KH<sub>2</sub>PO<sub>4</sub>, respectively] resulted in a 2-fold increase in BNC production compared with unsupplemented medium. The BNC produced employing DOR as carbon source exhibited a typical homogeneous three-dimensional network of nano- and microfibrils of cellulose, as previously reported for BNC.

Çakar et al. (2014) evaluated the production of cellulose using a static semicontinuous process in molasses medium. The authors achieved a maximum cellulose yield (1.64 g/L) when using a molasses ratio of 1:2 for 7 days. The use of molasses as a carbon source produced BNC with structure that changed from thin fibrils to a web-like pattern according to the incubation period. However, in general, the BNC produced exhibited a dense fibril structure.

Lin et al. (2014) used waste beer yeast (WBY) to improve BNC production by *Gluconacetobacter hansenii* CGMCC 3917. WBY hydrolysates, treated with ultrasonication, exhibited a high cellulose yield (7.02 g/L), almost 6-fold higher than that from untreated WBY (1.21 g/L). This result can be explained by the fact that the uncentrifuged samples after pretreatment had a high sugar concentration (and showed the highest sugar yields), which could inhibit BNC production

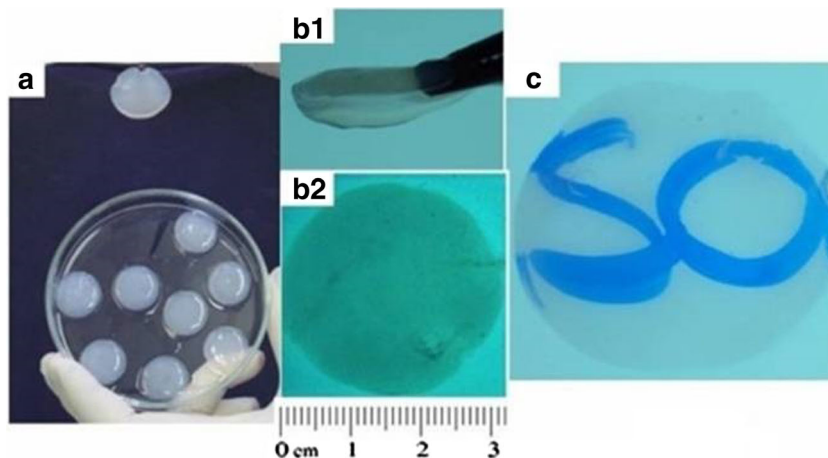
and reduce the supply of oxygen by the liquid medium. The properties and microstructure of BNC produced by WBY hydrolysates were as good as those obtained from the conventionally used chemical media.

Jozala et al. (2015) evaluated HS broth, milk whey, rotten fruit (plums, green grapes, pineapples, and apples) and combined milk whey/rotten fruit at different proportions as alternative sources to produce BNC by *G. xylinus* ATCC 53582 at 30 °C in a static culture for 0, 24, 48, 72, or 96 h. The highest production was observed after 96 h of bioprocessing using rotten fruit as main carbon source. The production achieved with this alternative medium was higher than obtained with HS medium (standard medium) and those reported in several previous reports. Figure 1 shows BNC produced by culture medium containing rotten fruits.

Li et al. (2015) studied the use of wastewater of candied jujube (WWCJ) for *G. xylinus* CGMCC No. 2955 under static culture to obtain BNC. According to the authors, WWCJ contained mainly glucose, glucan, and very low levels of other carbohydrates, providing an interesting carbon source with which to obtain BNC. WWCJ was used in three different conditions, namely WWCJ media containing ammonium citrate, sodium dihydrogen phosphate, and calcium carbonate, WWCJ without ammonium citrate, and WWCJ hydrolysate at 80 °C. The bioprocess took 6 days and promoted the production of BNC in all conditions analyzed. However, the WWCJ without ammonium citrate media generated the lowest BNC yield (0.25 g/L), indicating that ammonium citrate could be a key factor for BNC production. With WWCJ and the hydrolysate, the BNC yields were 1.50 and 2.25 g/L, respectively.

Kim et al. (2015) isolated a new BCN-producing strain identified as *G. sp. gel\_SEA623-2* from citrus fruit juice. The authors evaluated BNC production through five fruit juices, including orange, grape, apple, and pear juices, at several pH values (2.0, 2.5, 3.0, 3.5, 4.0, and 5.0), temperatures (20, 30, 35, and 40 °C), and brix values (5, 10, 20, and 30) during static culture. Among the fruit juice sources examined,

**Fig. 1** Bacterial Nanocellulose produced by culture medium composed by rotten fruits. *A* After treatment with NaOH; *B1*, *B2* size and thickness, *C* transparency. (source: personal files)



unshu juice was the most favorable for BNC production by *G. sp. gel\_SEA623-2*, showing that this bacteria had a high productive capacity in a citrus processing medium. The optimum pH and temperature for BNC production were 3.5 and 30 °C, respectively.

Erbas Kiziltas et al. (2015b) evaluated wood hot water extract (HWE), a residual material originating from pulp mills and lignocellulosic biorefineries for the production of BNC using *A. xylinum* 23,769. This source had mainly monomeric sugars, organic acids, and organics compounds. The cultivation was performed under static culture by varying the pH range from 5 to 8 and temperature range from 26 to 30 °C for BC production from *A. xylinum* 23,769 in HWE. Although an acidic pH generally promotes high BNC production, the authors found that the maximum production of BNC (0.15 g/L) was achieved at a pH of 8 and a temperature of 28 °C. In addition, the results achieved by the authors showed that the fractured surface morphology of the BNC pellicles from wood HWE exhibited a smaller cellulose fibril diameter compared with the BC pellicles from the HS medium.

Kuo et al. (2015) evaluated the effects of 100 mM acetate buffered at different pH on BNC production by static cultivation of *G. xylinus*. After 8 days of cultivation, the maximum amount of BNC produced was 2.98 g/L when 20 g/L glucose was employed in 100 mM acetate-buffered medium at pH 4.75. In contrast, the BC produced in yeast extract-peptone-dextrose broth (YPD) and HS media was only 0.66 and 1.23 g/L, respectively. The final pH of acetate-buffered medium (buffered at pH 4.75, 5.50, and 6.00) was close to its initial value. However, the final pH of YPD and HS media was lower than 3.5. Acetate-buffered medium can maintain a pH environment suitable for BC biosynthesis for a longer time as compared with traditional unbuffered HS medium. These results clearly showed the effects of pH on BNC production.

Huang and co-authors (2016) were the first to use lipid fermentation wastewater (fermentation broth after separation with yeast biomass) as a substrate for BNC production by *G. xylinus*. The chemical oxygen demand (COD) value of lipid fermentation wastewater was 25.59 mg/L, which could result in low BNC yield. According to the authors, the pretreatment of lipid fermentation wastewater to hydrolyze the extracellular polysaccharides may make the wastewater more biodegradable and could improve BNC production by reducing the production cost of BNC. Moreover, the lipid fermentation wastewater environment had only minor effects on the structure of BNC.

During the last 10 years, several groups have tested alternative carbon sources aiming to increase BNC yields and decrease production costs (Table 1). Carbon sources with low sugar contents have generated interesting results. Although the use of alternative carbon sources can improve BNC production, it is also necessary to control the environmental conditions, such as pH and temperature. Temperature is a crucial

factor that affects the growth of microorganisms, thereby influencing cellulose production.

In addition to temperature and pH, the dissolved oxygen concentration in the culture medium is an important factor that can affect the production of cellulose. In static cultures, the substrate must be transported entirely by diffusion, and because the carbon sources are generally available, the low availability of oxygen can become the limiting factor for cell metabolism and can have a negative effect on cellulose production and quality (Chawla et al. 2009). Ruka and collaborators (2012) found that the production of cellulose increases as the surface area of static medium and medium volume increase; however, this enhanced yield is also associated with increased cost and production time.

During the biosynthesis of BNC, if the culture broth contains different components, such as organic, inorganic, or polymeric materials, these components can be incorporated into the membrane of BNC, promoting the functionalization of BNC. There are two basic synthetic approaches for creating BNC matrix composites: in situ and ex situ. In the in situ method, secondary components can be introduced into the BNC culture media at the beginning of the BNC synthesis process. For the ex situ method, secondary components can be introduced into the BNC matrix by the solution impregnation method (Erbas Kiziltas et al. 2015a).

The effects of chondroitin sulfate and hyaluronic acid in bacterial cellulose production were studied by Molina de Olyveira et al. (2013). The authors analyzed BNC production using transmission infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM). FTIR analysis showed an interaction between bacterial cellulose nanobiocomposites and calcium phosphate. Thus, the addition of different compounds in the culture medium can direct the formation of bacterial cellulose with specific characteristics.

Kiziltas et al. (2015b) studied the biosynthesis of BNC by *A. xylinum* 23,769 in the presence of different nanoparticles (cellulose nanofibrils [CNFs], exfoliated graphite nanoplatelets [xGnPs], and nanoclay [NC]) using an in situ approach. All BC-based nanomaterials produced exhibited good dispersion of the NPs within the BC matrix, and the NPs were found embedded among the voids and microfibrils. The thermal stability and residual mass of BNC-xGnP and BNC-NC nanomaterials were significantly increased compared with that of pure BNC. CNF incorporation into the BNC matrix did not change the thermal stability and residual mass of the BNC matrix.

The cultivation method is also an important parameter that should be analyzed in greater detail. Static culture is the most commonly used method; however, many bioreactors contain a stirred tank, conventional airlift, and modified airlift with a rectangular wire-mesh draft tube. The BNC obtained from these types of bioreactors is fibrous or in pellet form

(Kralisch et al. 2010; Lee et al. 2014; Wu and Li, 2015), and this technology may generate promising results. Therefore, further studies are needed to examine BNC functionalization during its biosynthesis, which may be a key factor to promote the market expansion of this biomaterial.

## Applications of BNC

Based on the properties of BNC, including its high purity, high degree of crystallinity, high density, good shape retention, high water-binding capacity, and higher surface area as compared to native cellulose, BNC may have applications in a variety of contexts, such as the textile industry, nonwoven cloth, paper, food, pharmaceuticals, waste treatment, broadcasting, mining, and refineries (Table 2) (Wu and Liu 2012; Ashjaran et al. 2013; Lin and Dufresne, 2014). These distinctive properties have facilitated the use of BNC in the fabrication of several different products, including tires, headphone membranes, high performance speaker diaphragms, high-grade paper, make-up pads, diet foods, and textiles (Shah et al. 2013).

Fragmented BNC has potential applications in papermaking, allowing the production of flexible/durable paper and paper with high filler content, which is ideal for banknote paper (Chawla et al. 2009; Ashjaran et al. 2013), and its use as a binding agent in papermaking has been investigated (Basta and El-Saied 2009). Mautner et al. (2015) demonstrated that BNC-based nanopaper was suitable for tight ultrafiltration operations, while Li et al. (2015) developed a low-cost and environmentally friendly paper-based energy-storage device using bacterial cellulose–polypyrrole nanofibers in combination with multiwalled carbon.

Chemically pure cellulose can be used in processed foods as a thickening and stabilizing agent or for the promotion of gelling and water binding. Moreover, BNC is a type of dietary fiber and has been classified as a “generally recognized as safe” (GRAS) food, approved for marketing by the US Food and Drug Administration (FDA) in 1992 (Shi et al. 2014). The first use of BNC in the food industry was in “Nata” in the Philippines; Nata is made from a BNC gel and is a traditional dessert in Southeast Asia (Chawla et al. 2009; Shi et al. 2014). There are many types of Nata, including Nata de coco and Nata de pina, and the flavors of these products are controlled by the culture medium source. For example, Nata de coco uses coconut as the source, whereas Nata de Pina uses pineapple as the source (Shi et al. 2014).

Cellulose-producing microorganisms can be grown in culture medium sources, such as fruit syrup, that allow the produced cellulose to acquire the nature flavor and pigment of the fruit. Moreover, BNC can be produced to have a variety of shapes and textures, giving BNC many different applications in foods (Shi et al. 2014).

Owing to its unique nanoscaled 3D network structure, BNC can serve as a natural scaffold material for the regeneration of a wide variety of tissues (Fu et al. 2013). The most exciting applications of this biomaterial are in the biomedical field, where BNCs have been used as wound dressing materials, artificial skin, vascular grafts, scaffolds for tissue engineering, artificial blood vessels, medical pads, and dental implants (Shah et al. 2013). The many advantages of BNC, including its biocompatibility, conformability, elasticity, transparency, ability to maintain a moist environment in the wound, and ability to absorb exudates during the inflammatory phase, provide great potential for applications in wound healing systems. A thorough review of the most recent developments in

**Table 2** Bacterial nanocellulose applications in different areas

Area	Application
Cosmetics	Stabilizer of emulsions like creams, tonics, conditioners, nail polishes.
Textile industry	Sports clothing, tents and camping equipment
Mining and refinery	Sponges to collect leaking oil, materials for absorbing toxins.
Waste treatment	Recycling of minerals and oils
Sewage purification	Urban sewage purification, ultra filtration water
Communications	Diaphragms for microphones and stereo headphones
Food industry	Edible cellulose (nata de coco)
Paper industry	Artificial replacement of wood, special papers
Medicine/ biomedical	Temporary artificial skin for burns and ulcers, dental implant components; Antimicrobial wound dressing, Nanofilm, Drug Delivery, Drug excipient.
Laboratories	Protein immobilization, chromatographic techniques, tissue culture medium
Electronics	Opto-electronics materials (liquid crystal displays)
Energy	Membrane fuel cell (palladium)

BNC-based skin tissue repair materials was published by Chawla et al. (2009).

Besides improving the existing properties of BNC, composite materials have imparted BNC with new features displayed by typical inorganic or organic nanomaterials; these features include antibacterial effects; optical, electrical, and magnetic properties and catalytic and biomedical activities (Hu et al. 2014). For example, Shah et al. (2013) reviewed the applications of BNC composites in biomedical products, conducting materials, electrical devices, separation and waste purification, and composites with high mechanical strength for industrial applications. Additionally, Hu et al. (2014) reviewed the potential advantages and different applications of BNC-based functional nanomaterials, focusing mainly on application as sensors, photocatalytic nanomaterials, optoelectronic materials and devices, and magnetically responsive membranes.

The architecture of BNC materials can be engineered over length scales ranging from nano- to macro-sized by controlling the biofabrication process. Additionally, surface modifications have a vital role in determining the in vivo performance of biomaterials. Molina de Olyveira et al. (2013) studied the potential of gamma irradiation treatment for the modification of the surface properties of BNC, enhancing its potential for biomedical applications. Samples did not show significant variations in thermal properties; however, a higher pore density was produced in irradiated samples than in non-irradiated samples, resulting in slower diffusion than that observed in nonirradiated membranes.

BNC has a potential role in drug delivery systems. Müller et al. (2013) studied the applicability of BNC as a drug delivery system for proteins using serum albumin as a model drug. They found that freeze-dried samples showed lower uptake capacity for albumin than native BNC, which could be explained by changes in the fiber network during the freeze-drying process. The integrity and biological activity of proteins could be retained during the loading and release processes. Rajwade et al. (2015) recently published a review of the applications of BNC in the biomedical field, such as scaffolds, carriers for drug delivery, and wound-dressing materials. Numata et al. (2015a) studied the combination BNC gel and amphiphilic block copolymer nanoparticles as a drug delivery system, and Cacicedo et al. (2015) created a hybrid microparticle system utilizing BNC and stereospecific nucleation of mesoporous hybrid microspheres composed of  $\text{CaCO}_3$ . This hybrid system can be potentially used as an implantable drug delivery system for personalized oncological therapies.

Through enzymatic or acidic hydrolysis, BNC can form cellulose nanocrystals (NCCs), cellulose acicular particles with high crystallinity and with widths and lengths of 5–70 nm and between 100 nm and several micrometers, respectively (Klemm et al. 2011). NCCs also have many beneficial

properties, including biocompatibility, biodegradability, and a lack of toxicity, making NCCs an excellent candidate for pharmaceutical applications. Owing to its negative charge and large surface area, abundant amounts of drugs may be conjugated to the NCC surface. Furthermore, the hydroxyl groups on the surface of NCC can be modified with different functional groups, allowing the loading and release of drugs to be controlled (Akhlaghi et al. 2013).

According to Basmaji et al. (2014), the use of BNC as a part of the extracellular matrix is a novel biotechnology and unique medicine indicated for chronic wound treatment and management, drug delivery, tissue engineering, and skin cancer. Additionally, this material offers a tangible, effective solution to a serious medical and social problem, promoting rapid healing in lesions caused by diabetes, burns, ulcers of the lower limbs, or any other circumstances involving loss of epidermal or dermal tissue. In this context, novel antimicrobial peptides (AMPs) and bacterial cellulose/polyhexanide biguanide (PHMB), which are produced by symbioses culture between PHMB and green tea culture medium, result in a pure 3D structure consisting of an ultrafine network of novel matrix comprising biocellulose/PHMB nanofibers (2–8 nm) that is highly hydrated (99 % in weight), has a high molecular weight, and exhibits good biocompatibility. Nimeskern et al. (2013) evaluated the potential applications of BNC as a graft material for replacement of ear cartilage. Moreover, Bäckdahl et al. (2011) evaluated the applications of BNC as vascular grafts.

## Future trends

In 10 years, many attempts have been made to isolate strains that exhibit efficient production of cellulose, and many sources have been shown to enhance BNC production. However, most studies have been performed using *G. xylinus*, and further analyses are needed to determine whether other bacterial strains may exhibit higher productivity. Additionally, studies on the cost-effectiveness of culture medium have provided improvements to BNC yield and productivity. Because BNC is a material of great industrial interest, with applications in a variety of fields, further efforts are necessary to make this biotechnological material a competitive product and economically viable. In brief, although several studies have investigated the applicability of BNC, many more studies are needed to explore the feasibility of biotechnological production, particularly the cost effectiveness of culture medium. Thereby, permitting more applications of BNC especially on nanotechnological area (i.e., nanoparticles for drug delivery, cosmetics, and food) and environmental (i.e., reduction of organic solvents or metals).



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### Compliance with ethical standards

**Ethical statement/conflict of interest** The authors, whose names appear on the submission, declare have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results. This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal. There are no conflicts of interest to declare and this research not involved human participants or animals.

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