

BACTERIAL NANOCELLULOSE MEMBRANES AS POTENTIAL CHRONIC WOUND DRESSING: INFLUENCE OF ALTERNATIVE CULTURE MEDIA ON NANOFIBER DIAMETER - A BRIEF REVIEW¹

MEMBRANAS DE NANOCELULOSE BACTERIANA COMO POTENCIAL CURATIVO PARA FERIDAS CRÔNICAS: INFLUÊNCIA DE MEIOS DE CULTURA ALTERNATIVOS NO DIÂMETRO DAS NANOFIBRAS - UMA BREVE REVISÃO

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ABSTRACT

Chronic wounds are a major health problem worldwide. Mainly associated with chronic diseases and aging, this condition decreases life quality and expectancy in patients. Biomaterials are a growing trend in the biomedical industry due to their composition includes substances and similar structures to the human body, what brings the possibility of discovery and use of certain protein bindings and other physiological signs that can aid in the healing and biointegration process. Bacterial nanocellulose is a biomaterial formed by an interlaced fitting of nanofibrils about 100 nm in diameter, making it an excellent material for chronic wounds dressings due to its specific characteristics, such as (i) liquid absorption capacity, (ii) high crystallinity, (iii) purity, (iv) three-dimensional structure, (v) permeability to gases and (vi) biocompatibility. To overcome one of its limitations, - the absence of antimicrobial activity - there is the need of structural modifications. These modifications can be *in-situ* (during the membrane formation) or *ex-situ* (after the membrane formation), by physical (adsorption or absorption), or chemical (oxidation, esterification, etc.) methods. Another drawback regarding bacterial nanocellulose is the high cost of standard culture media during its production, which has been solved with alternative solutions. This review selected 8 papers in the PubMed and Science Direct databases, in which bacterial nanocellulose was obtained by using alternative media of culture, such as (i) kombucha, (ii) agro-industrial wastes, and (iii) fruit/vegetable peel wastes. The aim of this review is to overview how the production of bacterial nanocellulose in alternative media affects its nanostructure and crystallinity index.

Keywords: Nanoscience, biomaterials, fermentation, alternative media, kombucha.

RESUMO

Feridas crônicas são um dos principais problemas de saúde em todo o mundo, principalmente associadas às doenças crônicas e ao envelhecimento, condição essa que diminui a qualidade e expectativa de vida dos pacientes. Biomateriais são uma tendência crescente na indústria biomédica devido à sua composição incluir substâncias/estruturas semelhantes ao corpo humano, isso traz possibilidade de descoberta e utilização de determinados sítios de ligação de proteínas e sinais fisiológicos que podem auxiliar no processo de cicatrização e biointegração. A nanocelulose bacteriana é um biomaterial constituído pelo entrelaçamento de nanofibrilas (cerca de 100 nm de diâmetro), tornando-se um excelente material de base para curativos de feridas crônicas devido às características específicas, como (i) capacidade de absorção de líquidos, (ii) elevada cristalinidade, (iii) pureza, (iv) estrutura tridimensional, (v) permeabilidade a gases e (vi) biocompatibilidade. Para superar

1 Master's work.

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uma de suas limitações - ausência de atividade antimicrobiana - são necessárias modificações estruturais. Estas podem ser *in-situ* (durante a formação da membrana) ou *ex-situ* (após a formação da membrana), por métodos físicos (adsorção ou absorção) ou químicos (oxidação, esterificação, etc.). Outra desvantagem é o alto custo dos meios de cultura padrão durante sua produção, que vem sendo contornado com soluções alternativas. Esta revisão selecionou 8 artigos nas bases de dados PubMed e Science Direct cuja produção utilizou meios de cultura alternativos, como (i) kombucha, (ii) resíduos agroindustriais e (iii) resíduos de cascas de frutas/vegetais. O objetivo desta revisão é apresentar uma visão geral da influência de meios alternativos sobre a nanoestrutura e o índice de cristalinidade.

Palavras-chave: Nanociências, biomateriais, fermentação, meios alternativos, kombucha.

INTRODUCTION

The skin is the largest organ of the human body, and it is composed of two distinct layers: the epidermis (external part) and the dermis (internal part). Its major function is the protection of adjacent tissues, in which the skin acts as a mechanical barrier against impacts and humidity loss, besides serving as a chemical barrier that promotes an acidic layer to suppress bacterial growth (BARANOSKI *et al.*, 2016; SUSSMAN; BATES-JENSEN, 2012).

When a lesion occurs, a series of physiological, biochemical, and cellular events happen in order to reestablish both the structural and functional integrity of the target area (KEVIN; VAN DEN KERKHOF; JIMENEZ, 2016; SANTOS *et al.*, 2014). The healing process is a continuous series of events that impose biological changes to the cells to facilitate hemostasis, combat infections, deposit a new extracellular matrix, and promote angiogenesis (HOLLOWAY *et al.*, 2016). The exact mechanisms that lead to an improper wound healing process are not well defined nowadays, however, the two main factors are chronic diseases and aging (KEVIN; VAN DEN KERKHOF; JIMENEZ, 2016). When it takes more than three months for the wound to heal, and the healing process is not ordered, it is defined as a chronic wound (KORTING; SCHÖLLMANN; WHITE, 2011).

Chronic wounds are a worldwide health problem that leads to life quality decrease, to deaths, and expensive costs in healthcare systems (OLSSON *et al.*, 2019). Chronic wounds demand the use of complex wound dressings with a high capacity of exudate retention (UZUN, 2018). Another important characteristic of wound dressings designed for chronic wounds is the antimicrobial activity, once the chronic wounds are very susceptible to bacterial infections, and biofilm formation, two major causes of healing problems (VERBANIC *et al.*, 2020).

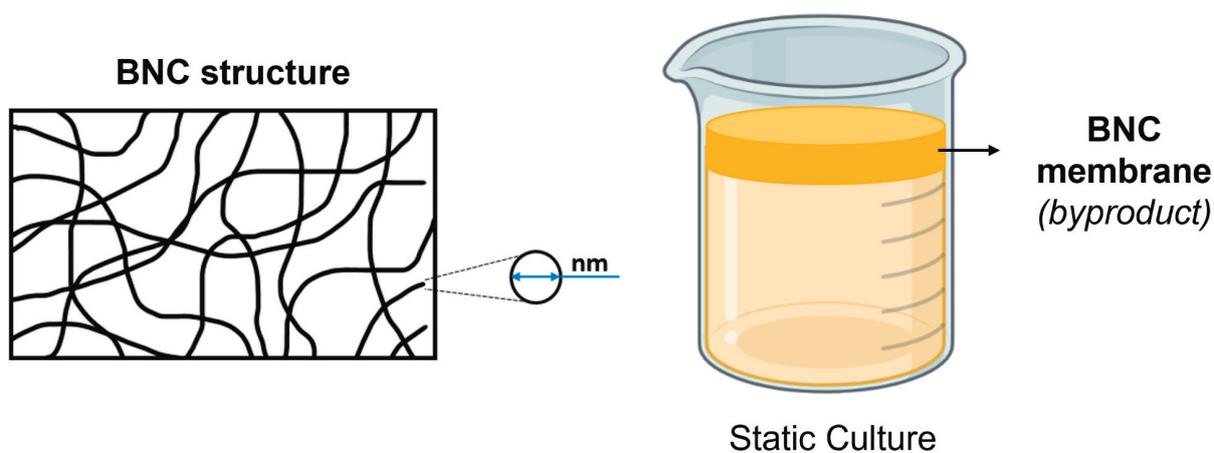
Thus, the main roles of wound dressings are: (i) to promote hemostasis, and (ii) to serve as a physical barrier that protects the wound area in a mechanical way. The most common example of traditional wound dressing is cotton gauze (SHERIDAN, 1999). Nevertheless, traditional dressings, in general, show problems when applied to chronic wound treatments, such as: (i) they can damage the epithelium when removed; (ii) they promote superficial dehydration; and (iii) they are not able to

handle exudate leaking, what increases the probability of infections and bacterial biofilm formation (NAIMER; CHEMLA, 2000; SIRITIENTONG *et al.*, 2014; WEI *et al.*, 2019).

Based on the aforementioned, complex wound dressings should be engineered to promote the following characteristics: (i) humidity control; (ii) low adherence; (iii) protection to mechanical trauma; (iv) low management and simple handling; (v) thermal isolation; (vi) high exudate/blood absorption; (vii) antimicrobial and anti-inflammatory activity; (viii) gaseous exchange promotion; (ix) not be toxic; and (x) be a low-cost product (BROWN-ETRIS; CUTSHALL; HILES, 2002). Moreover, complex wound dressings can be classified into three categories, based on the material characteristic: (i) traditional; (ii) biomaterials-based; and (iii) artificial wound dressings (FREYMAN; YANNAS; GIBSON, 2001; KUS; RUIZ, 2020).

Along with the advances in biomaterials science and nanotechnology, nanostructured wound dressings have been investigated to treat chronic wounds (RATNER *et al.*, 2020; STOICA; CHIRCOV; GRUMEZESCU, 2020). In this sense, a natural biomaterial known as bacterial nanocellulose (BNC) has been explored and used as an alternative dressing for chronic wounds and burns of all degrees of severity (PANG *et al.*, 2020). Also named bacterial cellulose (BC), this exopolysaccharide is chemically composed of cellulose, produced by acetic and non-pathogenic bacteria from a fermentation process that requires oxygen and carbon/nitrogen sources (ABOL-FOTOUH *et al.*, 2020; PORTELA *et al.*, 2019). As these bacteria ferment, a gelatinous biomembrane (located on top) is formed on the culture medium when this culture is static, and suspensions (spherical, pellets, or fibers) when the culture is dynamic (AZEREDO *et al.*, 2019) - the NCB structure and static culture productions are illustrated in Figure 1.

Figure 1 - BNC structure and static culture.



Source: the authors.

It is worthy mentioning that BNC is composed of D-glucose units, linked by β -1,4 glycosidic bonds. Its structure is formed by a network of random fibrils with about 100 nm of diameter, what

results in unique properties, such as: (i) high capacity of exudate absorption; (ii) high-purity (due to the absence of lignin, pectin and hemicellulose phases presented on plant cellulose); (iii) biocompatibility; (iv) tridimensional structure able to mimic the extracellular matrix of native tissues; and (v) permeability to gases (GORGIEVA; TRČEK, 2019). All these properties turn BNC into a promising dressing material for chronic wounds treatment.

Despite the interesting properties of BNC-based wound dressings intended for chronic wounds, it presents two disadvantages. The first one is that it lacks antimicrobial properties in the pristine form, what can be fixed by the addition of antimicrobial agents into its structure (ZHENG *et al.*, 2020). The impregnation methods to solve this problem can be made by *in-situ* modification (during the culture) or *ex-situ* modification (after the culture) (STUMPF *et al.*, 2018). The second disadvantage is the scaling-up production, in which the cost of culture media represents 30% of the total production cost when using standard culture media (JOZALA *et al.*, 2016). The commonly used standard culture medium for BNC production is the Hestrin-Schramm (HS) (COSTA *et al.*, 2017).

In order to overcome problems concerning large-scale BNC production, several approaches have been studied in the literature, such as the use of alternative culture media during static production. Some of these approaches include the use of agroindustrial residues (e.g., sugar cane molasse, beer bagasse, fruit, and plant peel wastes, etc.) as carbon and nitrogen sources (HUSSAIN *et al.*, 2019), while others involve kombucha-like culture media and kombucha fermentation by-products usage (ZHU *et al.*, 2014).

Kombucha-like culture media has been attracting attention of the scientific community (OLIVER-ORTEGA *et al.*, 2021). Kombucha is a fresh and naturally carbonated drink obtained by the fermentation of acetic bacteria and yeasts by using green or black tea (*Camellia sinensis*) infusions and a sugar source as substrates (VILLARREAL-SOTO *et al.*, 2018). The fermentation process of kombucha occurs through a symbiosis between bacteria and yeast, what also results in a cellulose biomembrane (named SCOBY) as a byproduct on the top of the culture medium (LAAVANYA; SHIRKOLE; BALASUBRAMANIAN, 2021). Several bacteria and yeast were already identified during the fermentation of kombucha and *Acetobacter xylinum* was found to be the main responsible for kombucha's BNC production, which is also essentially composed of cellulose nanofibers (GORGIEVA; TRČEK, 2019).

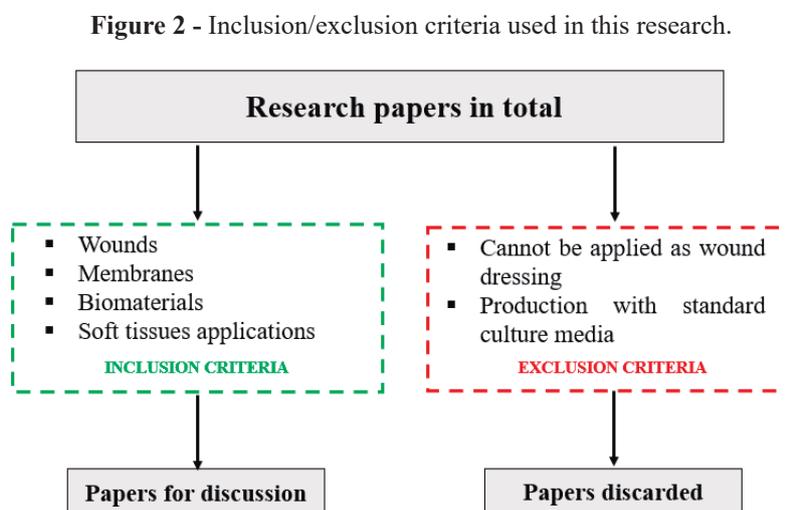
Regarding the BNC production by using fruit and agroindustrial wastes as substrates, the process is also based on the fermentation of acetic bacteria, which results in a cellulosic membrane with a protective role on top of the culture medium (MARESTONI *et al.*, 2021). In this sense, the high carbohydrate content of fruit and agroindustrial wastes serves as an important carbon source and leads to a low-cost fermentation media (GÜZEL; AKPINAR, 2020; KADIER *et al.*, 2021).

Despite the alternative approaches for BNC production before mentioned, their influence on the fiber diameter in BNC fibrous network should be addressed to ensure it is at the nanoscale.

The crystallinity index (CrI), another important and commonly measured property after the purification of BNC, should also be considered as it influences directly into the BNC properties. Then, this review aims at overviewing the influence of alternative culture media during BNC production on nanofiber diameters and crystallinity index.

METHODOLOGY

The research was carried out in the Science Direct and PubMed databases. Also, the following descriptors were used: “*bacterial cellulose*”, “*nano**”, “*wound*”, “*tea*”, “*fermentation*”, “*fiber*”. Based on that, the research papers were selected according to the inclusion and exclusion criteria shown in Figure 2.

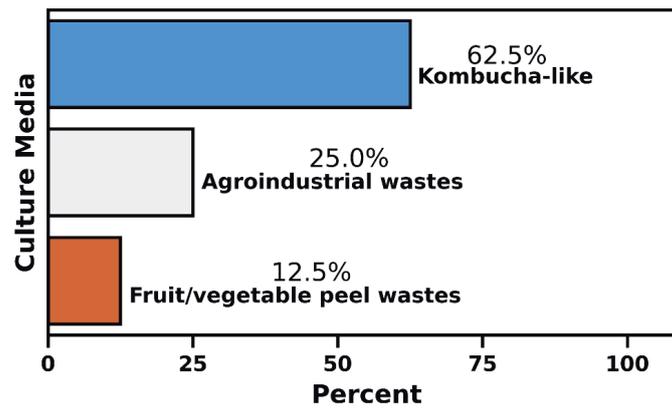


Source: the authors.

RESULTS AND DISCUSSION

In total, 20 research papers were found, from which 8 were selected based on the inclusion and exclusion criteria. Additionally, all these papers used alternative culture media to produce BNC. Figure 3 shows the alternative culture media used for BNC production. It is possible to note the predominance of kombucha-like culture media (5 papers, 62.5%), which 40% were supplemented with corn syrup (DIMA *et al.*, 2017) or calcium carbonate and yeast extracts (BODEA *et al.*, 2021). Likewise, 25% (2 papers) of the investigations used agro-industrial wastes, and 12.5% (1 paper) used fruit and vegetable peel wastes as carbon and nitrogen sources for culture media. The predominance of kombucha-like can be associated with the popularity of the drink and the simplicity of the process, what can be compared to a static production of BNC.

Figure 3 - Alternative culture media used in the selected studies.



Source: the authors.

The parameters used for BNC production such as culture medium, bacteria strain, inoculum concentration, temperature, and fermentation time are shown in Table 1. As most of the papers did not present the sugar and tea concentration and not all of them included pH control, this information was omitted from culture parameters. Table 2 shows the results obtained in terms of BNC nanofiber diameters and CrI.

Regarding the bacteria used during BNC production, the most used microorganisms were those included in kombucha SCOBY, as this was the main alternative media used in the investigations. It is known that kombucha SCOBY is usually composed of *Acetobacter* and *Gluconobacter* (now renamed as *Komagataeibacter*) bacteria genus, as well as osmophilic yeasts (LAAVANYA; SHIRKOLE; BALASUBRAMANIAN, 2021; PILLAI *et al.*, 2021). For the other alternative media, the *Komagataeibacter* genus was the most used due to its wide association with BNC production (REVIN *et al.*, 2021).

Concerning agroindustrial wastes used as fermentation substrates, side-way byproducts from sugar industries, such as sugar beet molasses, can be a low-cost carbon source for BNC production, as its dry matter is formed by about 45-48% of sucrose (REVIN *et al.*, 2021). In the study by Revin and colleagues (2021), this kind of molasses, which also contain aminoacids, vitamins, minerals, and organic acids, almost doubled the BNC production yield by decreasing the cost of culture medium by about 20% when compared to HS-derived BNC production (REVIN *et al.*, 2021). In this case, the authors reported NCB production in 5 days, with a higher CrI than HS-derived BNC and a nanofiber diameter between 60-90 nm.

Table 1 - BNC production parameters using alternative culture media.

Medium	Bacteria	Inoculum % (v/v)	Temperature (°C)	Culture time (days)	Reference
Kombucha-like	SCOBY	10	-	14	Pillai <i>et al.</i> , 2021
Citrus peel and pomace enzymolysis	<i>Komagataeibacter xylinus</i>	10	30	8	Fan <i>et al.</i> , 2016
Wood hot water extracts (WHWE)	<i>Acetobacter xylinum</i>	5	26, 28, 30	10	Kiziltas; Kiziltas; Gardner, 2015
Sugar beet molasses	<i>Komagataeibacter sucrofermentan</i>	10	28	10	Revin <i>et al.</i> , 2021
Kombucha-like	SCOBY	6	25	35	Xiang; Acevedo, 2017
Kombucha-like	SCOBY	-	28	15	Pal <i>et al.</i> , 2017
Kombucha-like supplemented with corn syrup	SCOBY	10	23	30	Dima <i>et al.</i> , 2017
Kombucha-like supplemented with CaCO ₃ and yeast extract	<i>Komagataeibacter xylinus</i>	1- 5	26	3, 6, 9, 12, 18	Bodea <i>et al.</i> , 2021

Source: the authors.

Table 2 - Influence of culture medium on fiber diameter and crystallinity index.

Medium	Fiber diameter (nm)	CrI (%)	Reference	Comment
Kombucha-like	210	67.3	Pillai <i>et al.</i> , 2021	The authors used a kombucha-like culture medium to decrease the costs of BNC production, focusing on its processing to be applied as a bioink intended for 3D printing and tissue engineering. They also used a SCOBY, weighing 200 g.
Citrus peel and pomace enzymolysis	50	63.0	Fan <i>et al.</i> , 2016	The alternative medium served as the carbon and nitrogen source. Also, it was compared to HS-derived BNC. It presented lower crystallinity, but higher production yield.
Wood hot water extracts (WHWE)	15-70	79.0	Kiziltas; Kiziltas; Gardner, 2015	Low-cost and good yield of BNC production. The resulting membrane showed slightly lower crystallinity compared to HS-derived BC. Glucose and xylose were the nutrients provided by the WHWE.
Sugar beet molasses	60-90	83.0	Revin <i>et al.</i> , 2021	The cost of culture media used for production was reduced to 20%. Two-fold BNC production yield (compared to HS-derived BNC) was obtained.
Kombucha-like	59	75.5	Xiang; Acevedo, 2017	Fermentation occurred at room temperature and started with 100 g of SCOBY. The authors produced BNC and BNC/PLA nanocomposites, leading to mechanical toughness increasing compared to pristine BNC.
Kombucha-like	20-40	86.8	Pal <i>et al.</i> , 2017	The authors did not mention the content of <i>starter</i> , sugar, and tea used during the synthesis. The fibrous structure was obtained, and BNC presented a great crystallinity.
Kombucha-like supplemented with corn syrup	5-100	87%	Dima <i>et al.</i> , 2017	The researchers also impregnated BNC with Ag nanoparticles, resulting in an antimicrobial wound dressing. The sugar source was represented by 50% of fructose, 44% of glucose, and 6% of oligosaccharides. CrI of 37% without purification and 87% after purification was achieved.
Kombucha-like supplemented with CaCO ₃ and yeast extract	40.6-51.33	-	Bodea <i>et al.</i> , 2021	The authors used a Box-Behnken design to optimize the BNC production. The CaCO ₃ addition into the culture media was not justified.

Source: the authors.

Other agroindustrial wastes that can be used during BNC production are wood hot water extracts (WHWE), derived from lignocellulosic industries (ERBAS KIZILTAS; KIZILTAS; GARDNER, 2015). Although WHWE shows a low-composition of sugars, it is a waste material that does not need treatment or supplementation to be applied into BNC production, turning it into a low-cost alternative that results in a slight lesser CrI when compared to BNC produced by using HS medium (ERBAS KIZILTAS; KIZILTAS; GARDNER, 2015). The study of Kiziltas and colleagues (2015) confirmed similarities between structures of HS- and WHWE-derived BNC, with nanofiber diameter (ranging 15-70 nm) slightly lesser than HS-derived BNC.

Similarly, fruit/vegetable peel wastes were also used as carbon/nitrogen sources during the BNC production. Citrus peel and pomace enzymolysis were used as alternative culture media in the Fan and collaborators' work and this resulted in a BNC yield 1.46 higher than HS-derived BNC (FAN *et al.*, 2016). The methodology implicated in CrI decreasing (CrI = 63% against 65% of HS culture medium) and in a smaller average diameter of the BNC nanofibers (50 nm against 60 nm of control BNC) (FAN *et al.*, 2016). Furthermore, kombucha-like media or media that reuses kombucha byproducts can also be used for BNC production. The kombucha fermentation process is relatively simple as it only needs green or black tea, a solution containing bacteria and yeast from a previous process (commonly called *starter*), and the BNC membrane is naturally formed during fermentation (PAL *et al.*, 2017). In the study of Pal and collaborators (2017), it was possible to obtain the BNC membrane in 15 days and the fermentation broth could be used as the new *starter* solution. The authors achieved a CrI of 86.8% after purification of the obtained membranes, which presented outstanding nanofiber diameters (20-40 nm).

In addition, when kombucha is used as the culture medium for BNC production, a SCOBY can also be used and this trends to assist the fermentation (XIANG; ACEVEDO, 2017). In the work of Xiang and colleagues, a larger and unusual time of fermentation of 5 weeks was evaluated, what leads to a 59 ± 17 nm average nanofiber diameter. Also, the CrI was found to be $75.5\% \pm 2.5\%$ (XIANG; ACEVEDO, 2017). In this sense, Pillai and collaborators also used a SCOBY during the fermentation process and noted different swelling properties for wet and dry NCB membranes, which is an important property for wound dressings (PILLAI *et al.*, 2021).

As previously mentioned, supplemented kombucha-like culture media was also investigated in the literature. Dima and colleagues supplemented the culture media with corn syrup due to its composition of fructose (50% of dry matter), glucose (44% of dry matter), and oligosaccharides (6% of dry matter), what makes it an interesting source for carbon during a longer fermentation time to obtain a kombucha vinegar (DIMA *et al.*, 2017). The authors obtained CrI up to 87.0% and nanofiber diameters in the range of 5-100 nm, respectively. Similarly, Bodea and collaborators (2021) supplemented the kombucha-like medium with calcium carbonate, despite the reason was not informed in their paper. It was found that the inoculum and fermentation time did not influence the homogeneity

of obtained BNC membranes, as well as a two-step effective purification process for BNC (BODEA *et al.*, 2021). Also, nanofibers' average diameter was between 40.6-51.33 nm and the CrI was, unfortunately, not measured.

Despite the possibility of obtaining a BNC membrane in 8 days (FAN *et al.*, 2016), most of the studies focused on larger fermentation times, relying on 10-30 days (fermentation parameters are shown in Table 1). Concerning temperature, the range of 23-30 °C seemed to be suitable for BNC production.

According to Table 2, it can be seen that CrI values were high overall, as expected for BNC. It is interesting to point out that the CrI is often calculated by X-ray diffraction (XRD) by using Equation (1) and it is directly related to BNC properties (REVIN *et al.*, 2021). Additionally, the culture medium and fermentation parameters such as those listed in Table 1 can influence the CrI of the produced BNC membranes.

$$CrI (\%) = \frac{I_{(002)} - I_{amorphous}}{I_{(002)}} \times 100 \quad (1)$$

Where:

$I_{(002)}$: maximum intensity of the peak related to the (002) diffraction plane;

$I_{amorphous}$: minimum intensity of the amorphous area between the two characteristic peaks of NCB diffractogram.

It is also important to mention that the nanofiber diameters of BNC were mainly determined by microscopic images, and they were commonly represented as a range - as can be seen in Table 2. It is also worthy pointing out that the nanofiber diameter was generally less than 100 nm, with the study of Pillai and colleagues as the exception (PILLAI *et al.*, 2021). In this study, larger nanofiber diameters were obtained (up to 290 nm) and such values were assigned to the culture of BNC by a planar geometry, which results in anisotropy of the resulting material during static cultivation (PILLAI *et al.*, 2021).

Moreover, to optimize the BNC production, some statistical methods such as Design of Experiments (DOE) can also be used, and these methods can positively affect BNC properties, resulting in reproducible nanofiber diameters and CrI (BODEA *et al.*, 2021; ERBAS KIZILTAS; KIZILTAS; GARDNER, 2015). Based on that, CrI and nanofiber diameter might be used as response variables in addition to BNC production yield.

CONCLUSION

On account of the economic and social impact of chronic wounds worldwide, aligning nanoscience and biomaterials can lead to alternatives to this issue. This said, BNC is a biopolymer

that displays unique properties due to its nanosized structure. The tridimensional and nanofibrillar morphology of NCB turned it into an interesting and potential dressing intended for chronic wounds. However, the high cost of standard culture media, such as HS medium, is a drawback for BNC scale-up production. To overcome this, several alternative culture media have been investigated by using kombucha byproducts, agroindustrial residues, and fruit/vegetable peel wastes. Despite the advances in alternative BNC production, it is important to confirm the nanosized fiber diameter and high CrI, which ensures the unique properties of BNC. It was concluded that the use of alternative culture media maintained the nanosized fiber diameters of BNC and these diameters were majorly found to be less than 100 nm. Nevertheless, the use of alternative culture media led to variations in BNC nanofiber diameters, while the CrI continued high when compared to BNC produced by conventional methods. Thus, as the fibrous network of BNC remained at the nanoscale, the unique properties of this kind of cellulose are maintained. In addition, these results justify the use of alternative culture media as an economic way to obtain nanofibrous BNC membranes. Yet, further studies involving robust statistical methods, such as DOE, could be done to decrease the variability of the resulting nanofiber diameters when using alternative culture media for BNC production.

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