Recent Developments of the Agroindustry Byproducts Utilization in Bacterial Cellulose Production and Its Medical Devices Applications

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Abstract Bacterial cellulose (BC) is a renewable material which is currently playing a central role in medical device applications due to its biocompatibility and capability to be structurally, chemically, and morphologically modified at macro, micro, and nano scales. In addition, BC also has high water content, mechanical strength, and purity which are also excellent properties for use in biomedical applications. Despite the numerous advantages of BC properties for biomedical applications, its use for commercialization is still a challenge due to the high expense of the carbon and nitrogen sources required for BC synthesis. This study will provide an overview of numerous alternate sources of carbon and nitrogen from agricultural byproducts for BC synthesis that have been investigated and the potential of BC to be used for medical devices.

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1 Introduction

In the biomedical field, synthetic or natural polymers are used for different purposes (Sionkowska 2011; Tian et al. 2012). Although the application of synthetic polymers in medical devices has advanced significantly, it is known that using these polymer products in biomedicine poses irritation risk issues for tissue due to their low biocompatibility (Gunatillake et al. 2003; Bilgi et al. 2016). The higher biocompatibility properties of natural polymers make these polymers the most widely recommended alternatives as synthetic polymers substitutes in medical applications (Aravamudhan et al. 2014). Currently, plant-derived cellulose is the most abundant natural polymer produced on earth and is used extensively in the textile and food industries. However, its use in the medical and cosmetic fields is limited due to its impurities such as lignin, hemicellulose, and pectin (Klemm et al. 2005; Moran-Mirabal and Cranston 2015).

Apart from being sourced from plants, there is cellulose which is sourced from microbial synthesis called bacterial cellulose (BC). In contrast to plant-derived cellulose, BC is a cellulose with a high purity, thus it has found extensive use in the biomedical sector, including as polymer scaffolding for bone and cartilage repair, wound dressings to restore burned skin, a membrane for skin drug delivery, artificial blood vessels for microsurgery, and wound dressings to treat burned skin (Trovatti et al. 2011; Gomes et al. 2013). Bacterial cellulose is a natural extracellular polymer with the molecular formula of $(C_6H_{10}O_5)_n$ which is synthesized extensively by *Gluconacetobacter* strains via linear coupling of glucopyranose sugar monomers (Shoda and Sugano 2005). The strain that was employed to synthesize this polymer is non-pathogenic, extensively distributed in fruits and their products, and simple to grow in a lab (Klemm et al. 2009; Moosavi-Nasab and Yousefi 2011). This polymer is a biomaterial with superior properties due to its nanofibrous network structure (50–120 nm), 100% purity, high surface area, high crystallinity, high degree of polymerization, high capacity to absorb and hold water, high wet tensile strength, biocompatible, and easily degradable (Chen et al. 2013; Dhar et al. 2019).

However, the use of BC for industrial-scale applications for medical devices is constrained by its high production costs. For industrial-scale application, production parameters including temperature, pH, surface area to volume ratio of culture medium air–liquid interface (S/V), inoculum ratio and incubation time should be optimized for high quality, cost-effective, and high-yield BC production (Bilgi et al. 2016; Gea et al. 2018). Among the factors that affect the production costs, the sources of carbon and nitrogen used in the BC production are one of the factors that significantly determine the manufacturing costs, which can amount to 65% of the total cost (Chen et al. 2013; Sudying et al. 2019). The traditional source of carbon for BC fermentation is sugars such as glucose, fructose, and sucrose. Coconut water is currently the most affordable and sustainable raw material utilized in BC industrial production. However, coconuts are only grown in the tropics countries such as the Philippines, Indonesia, and other South and Southeast Asian (Cao et al. 2018). In most countries in the world, coconut production is extremely low and import-dependent. Thus, the use of this alternative substrate cannot be a solution for reducing BC production costs in many countries.

Meanwhile, the demand for BC, especially in the food and renewable material industry, continues to increase and it is predicted that demand for BC will eventually outpace supply in the future (Çakar et al. 2014; Padmanaban et al. 2015; Gea et al. 2022). Adding to this, in 2016, BC market was valued at US$207 million, and it is anticipated to reach US$700 million in 2026 (Calderón-Toledo et al. 2022).

In recent years, many researchers have focused on efforts to produce BC by developing cost-effective carbon and nitrogen feedstocks from local agroindustry product residues (Hong et al. 2011, 2012). Agricultural waste is known to contain high amounts of lipids, carbohydrates, including mono-, oligo- and polysaccharides, and proteins which can be converted into renewable energy sources with high added value (Calderón-Toledo et al. 2022). The advantage of using agricultural residues as raw materials in BC production is to reduce the cost of raw materials so that they can be mass-produced and commercialized and can be used as a basis for developing advanced materials, especially in their applications as biomedical devices (Chen et al. 2013). In addition, effective utilization of agricultural byproducts will be a good mode of recycling biomass which will simultaneously reduce the burden of waste treatment (Cao et al. 2018).

2 Bacterial Cellulose

Bacterial Cellulose is an extracellular polymer produced by bacteria from the genera *Sarcina*, *Gluconacetobacter*, and *Agrobacterium* through oxidative fermentation in non-synthetic and synthetic media (Esa et al. 2014; Huang et al. 2014). Among the various types of bacteria, *Gluconacetobacter xylinus* is the producer that receives the most attention for commercial-level production because it can digest a variety of carbohydrates in liquid media to produce BC in larger quantities (El-Gendi et al. 2022). In the BC synthesis, the bacterial body will releases glucose chains through the tiny holes in their cell envelopes, and the hydroxyl groups in the polymer chains form microfibrils, which subsequently group to form random nanofibers, will create 3D nanopore networks (Calderón-Toledo et al. 2022). The main structure of this fibril is formed of β-1,4-glycosidic linear polysaccharide structure that is connected by hydrogen bonds (Ul-Islam et al. 2012). Because it is secreted in the form of 2–4 nm fibrils, which are 100 times smaller than plant cellulose fibrils, this fiber is categorized as a nanoscale network (Gayathry and Gopalaswamy 2014; Costa et al. 2017).

In its natural state, BC possesses good hydration and high water holding capacity which is up to 100 times of its initial weight (Rani and Appaiah 2013). In addition, BC has a high degree of polymerization, crystallinity, and biological adaptability. BC also offers biocompatibility, biodegradability, and renewable capabilities (Costa et al. 2017). Therefore, BC is a desirable material for future use in a variety of industries, including electronics, paper, and food as well as the biomedical industry (bone and cartilage reconstruction, tissue engineering, wound dressings, implants, corneal restorations, orthodontics, artificial blood vessels), pharmaceuticals, veterinary medicine, and the leather industry (Andritsou et al. 2018; Popa et al. 2022).

3 Nutritional Requirements for Bacterial Cellulose Production

Currently, the use of bacteria to produce high-purity cellulose is in great demand because this cellulose has good nanometric, thermal, and mechanical properties. Moreover, it does not require aggressive treatment for purification and is environmentally friendly (Lin et al. 2013; Shi et al. 2014). Since this sort of cellulose is produced by bacteria, the availability of nutrient-rich elements in the growth media is a key factor for the production process as illustrated in Fig. 1 although there are also several things that need to be considered, such as, culture type (static vs. dynamic, surface vs. submerged), pH, shear force, and level of oxygenation support (Fernandes et al. 2020; Popa et al. 2022). Therefore, carbon sources include sugars such as fructose, glucose, sucrose; polysaccharides such as amylose or starch; nitrogen such as peptones, yeast extract, and casein hydrolyzates; inorganic salts such as ammonium sulfate; organic acids such as citric acid; some low molecular weight hydroxylated compounds such as glycerol, mannitol, and ethanol; are among the most important in the production of BC.

Currently, synthetic media, such as Hestrin-Schramm (HS) media, are utilized extensively in laboratory-scale BC production. However, the use of this medium in a large-scale BC production is not recommended due to its high cost, low yield, time consumption, and intensive labor required (Calderón-Toledo et al. 2022; Popa et al. 2022). These facts present a significant barrier and restrict the commercial use of BC products. Consequently, finding inexpensive substrates becomes crucial (Cavka et al. 2013; Huang et al. 2014). According to estimations, fermented media consumes up to 65% of the whole production budget (Chen et al. 2013; Sudying et al. 2019). Thus, the main challenge in bacterial cellulose production is to find an abundant, suitable, inexpensive, and non-competitive carbon source with food production (Dórame-Miranda et al. 2019). In recent years, agroindustrial wastes have emerged as a potential affordable substitute medium for BC production (El-Gendi et al. 2022). This method is advantageous because it is able to produce high-quality

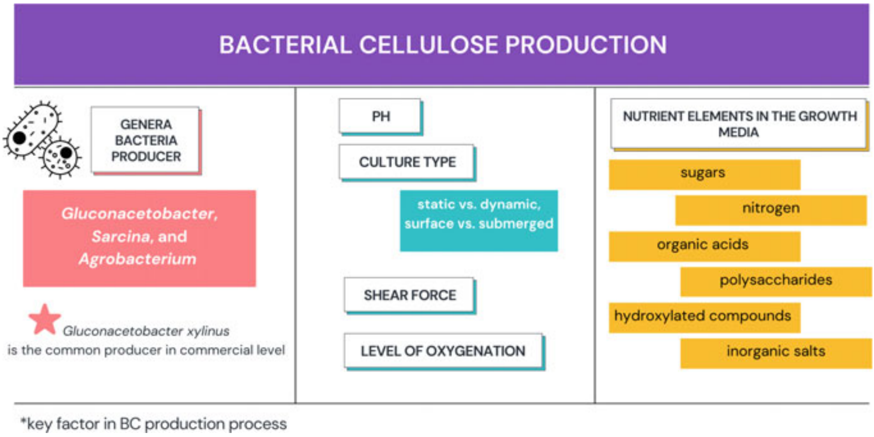

Fig. 1 Key factor in BC production process

BC and reduces waste disposal by converting waste water into a cheap fermentation promoter (Popa et al. 2022).

4 Agroindustry Byproducts that Used as Bacterial Cellulose Medium Culture

Given that BC has demonstrated excellent potential as a useful biopolymer in many applications, numerous studies have been conducted to identify an efficient method for generating BC at a reasonable price. The most notable is the utilization of agricultural byproducts as a replacement of carbon and protein for BC production. Each of the agroindustry byproducts and the bacterial strain that have been studied in BC production is shown in Table 1. This table also includes information of BC yields and highlights of BC produced from each agro-industrial byproduct used.

4.1 Wine Pomace

Pomace grapes are the main solid byproduct of the wine industry consisting of grape skins and seeds. These byproducts contain lignified fiber and soluble compounds such as sugars, phenolics, and a number of alcohols (Muhlack et al. 2018; Troncozo et al. 2019). As a result, grape pomace and its hydrolyzate have the potential to be used as a low-cost bioactive substrate to produce BC which has antioxidant and antibacterial activity. The pomace substrate pretreatment process was carried out by hydrolysis using commercial enzymes, namely pectinase and cellulase (Li et al. 2021).

Table 1 The utilization of agroindustry byproducts as a carbon and nitrogen source replacement in BC synthesis

Byproduct source	Bacterial strain	Yield	Highlight	References
Wine pomace	*Komagataeibacter rhaeticus*	4.28 ± 0.21 g/L in 10 day	Possess antioxidant and antibacterial activity	Li et al. (2021)
Carob-haricot bean extract	*Gluconacetobacter xylinus*	1.8 g/L in 9 days	Predict and optimize BC production yield	Bilgi et al. (2016)
Mango (*Mangifera indica*) waste extract	*Komagataeibacter rhaeticus*	25.34 g/L in 21 days	Provide a high yield with a reasonable price	Calderón-Toledo et al. (2022)
Citrus pulp	*Gluconacetobacter hansenii* and *Gluconacetobacter xylinum*	8.77 g/L in 10 days	Almost achieve industrial level	Cao et al. (2018)
Corn stalk	*Acetobacter xylinum*	2.86 g/L in 10 days	Matched with the idea of a biorefinery because it is affordable, green, and sustainable	Chen et al. (2013)
Sugarcane straw	*Komagataeibacter xylinus*	2.96 g/L in 12 days	Provides a different strategy to meet the commercial demand	Dhar et al. (2019)
Pecan nutshell (*Carya illinoinensis*)	*Gluconacetobacter entanii*	2.816 g/L in 28 days	Chemical functionalization of BC becomes methylcellulose and reduces its crystallinity	Dórame-Miranda et al. (2019)
Dry olive mill residue	*Gluconacetobacter sacchari*	0.85 g/L in 4 days	Demonstrate positive outcomes to combat high production costs in BC	Gomes et al. (2013)
Cashew tree residue	*Komagataeibacter rhaeticus*	2.8 g L^{-1} in 7 days	Up to a 33% of cost reduction	Pacheco et al. (2017)

(continued)

Table 1 (continued)

Byproduct source	Bacterial strain	Yield	Highlight	References
Coffee cherry husk	*Gluconacetobacter hansenii*	8.2 g/L in 14 days	Provides a more affordable alternative substrate and offers solution for toxic agricultural waste disposal	Rani and Appaiah (2013)
Rice washing drainage	*Komagataeibacter nataicola*	0.20 g/L in 13 days	A potential alternate carbon source that does not require any pretreatment	Sudying et al. (2019)
Tobacco waste extract (TWE)	*Acetobacter xylinum*	5.2 g/L in 7 days	Nicotine in TWE, which is known to inhibit BC production, can be removed by steam distillation treatment	Ye et al. (2019)

4.2 Carob and Haricot Bean Extracts

Carob (*Ceratonia siliqua* L.) production in Turkey is known to reach 15 × 10^3 tons/year with a total production of more than 400 × 10^3 tons/year in the world. Carob contains about 50% sugar (75% of sucrose and the rest is fructose, maltose, and glucose), 8% protein, and a number of important minerals (AYAZ et al. 2007; Bilgi et al. 2016). Meanwhile, haricot beans (*Phaseolus vulgaris*) are known to contain protein of 18.5–22%, a number of minerals (such as magnesium and calcium) and carbohydrates (de Almeida Costa et al. 2006; Shimelis et al. 2006). Therefore, the mixture of haricot nuts and carob has the potential to be employed in BC production as sources of carbon and nitrogen, respectively. According to the studies that have been published, Plackett-Burman and Central Composite Design techniques were used to prepare carob and haricot bean extracts as alternative growth media for *G. xylinus* in the development of cost-effective BC production methods. While, the pretreatment process used in this medium is by hydrolyzation process of the extract with distilled water using an autoclave (Bilgi et al. 2016).

4.3 Mango Variety (Mangifera Indica)

The Food and Agriculture Organization estimates that around 55% of mango produced globally, equivalent to 1.1 million tons, is wasted due to rotting during the transport, packaging, and storage (García-Sánchez et al. 2020). Mango extract (*Mangifera indica*) is known to contain 13.7–15.0% of sugar in the form of glucose, fructose, and sucrose and 1.5–5.5% of protein, making mango waste potentially can be used as an alternative low-cost substrate source for BC production (Prasanna et al. 2003; Maldonado-Celis et al. 2019). Moreover, mango fermentation with yeast and bacteria has been widely used in producing probiotic juice, wine, vinegar, yeast lipase, etc. (Li et al. 2012; da Pereira et al. 2019). Previous studies stated that it is necessary to use mangoes as a medium for BC production by first applying a pretreatment in the form of a hydrolysis process followed by a sugars reversion reaction with acid hydrolysis in 1 M HCl (Calderón-Toledo et al. 2022).

4.4 Citrus Pulp Waste

Oranges are one of the fruits that are produced in very big quantities worldwide, with an annual production reaching 27.1 million tons where 40–60% of its total weight is a byproduct in the form of peels and pulp (Fan et al. 2016). Currently, oranges have been used as vitamins by ingesting their active constituents or as a beverage ingredient in ethanol, vinegar, liquor, lactic acid beverages, mushrooms, and high-protein feed (Shan 2016). In China, peel of the orange has been used to produce traditional medicine by extracting its pectin, refined oil, and flavonoids content. However, orange pulp manufacturing has not yet been optimized, resulting in an accumulation of this byproduct. While it is known that citrus pulp is used as a production medium in BC by first being pretreated with enzymatic hydrolysis using cellulase and pectinase enzymes to reduce the viscosity of citrus pulp-based medium and reduce sugar so that mono/disaccharides could be used by the microorganism to synthesize BC (Cao et al. 2018).

4.5 Corn Stalk

Corn stalks are a byproduct of the annual production of corn agriculture, which is widely available worldwide (Luo et al. 2017). Thus far, this byproduct has only been treated inefficiently as compost (Boufi and Chaker 2016). Recently, the utilization of this biomass has been developed to produce bioethanol with biorefinery process (Shen and Wyman 2011; Cheng et al. 2017). Furthermore, according to a number of research, corn stalk prehydrolyzate contains high sugar content that can be employed in the fermentation process, offering another option for maximizing the use of these agricultural byproducts (Boufi and Chaker 2016; Esteves Costa et al. 2016). However, it is known that the utilization of the prehydrolyzate content in corncobs does not optimally support the production of BC. Therefore, its utilization as a carbon source to cultivate *Acetobacter xylinum* required a pretreatment using acetic acid and followed by pre-hydrolysis liquor (PHL) detoxification using activated carbon and ion exchange resin (Cai et al. 2016; Jiang et al. 2016).

4.6 Sugarcane Straw

Sugarcane is an agricultural commodity that is produced in large quantities every year. Brazil, is one of the largest sugarcane producing countries in the world, estimated to produce 93.3×10^6 tons of sugarcane waste each year in the form of bagasse and straw (dos Santos Rocha et al. 2017). It is estimated that every 1000 kg of sugar cane that processed in agroindustrial, will result in residues of 176 kg and 231 kg in the form of straw and dregs respectively. However, this residue is still not managed adequately, and as a result, the primary method of this waste treatment is burning. Recently, bagasse has been utilized as a component in bioethanol, biobutanol, or for bioenergy production for power plants, however the utilization of straw as waste is still rare (Dhar et al. 2019). It is known that sugarcane straw contains cellulose, hemicellulose, and lignin fraction ranging from 35–45%, 25–35%, to 10–25% respectively, which can be used as a medium for BC synthesis. Several pretreatment techniques such as enzymatic hydrolysis, acid hydrolysis, or hydrothermal treatment can be used to optimize the ultilization of this byproduct as a medium for BC production. Interestingly, the utilization of biomass as the carbon source was reported to produce BC with higher yield compared to pure glucose (Costa et al. 2017).

4.7 Pecan Nutshell

Pecan nut (*Carya illinoinensis*) is an agricultural product in which its seed is the part that is most widely used. The Food and Agriculture Organization (FAOSTAT) estimates that 460×10^3 tons of Pecan nut are produced annually while 40–50% is hazelnut shells which is a byproduct of this agroindustry (do Prado et al. 2014; Hilbig et al. 2018; Dórame-Miranda et al. 2019). Pecan nut shells are recognized to have the potential to be used as a source of nutrition for bacteria that specialize in producing BC because they contain significant levels of crude fiber (particularly lignin and cellulose) and carbohydrates (~90%) (Flores-Córdova et al. 2016). The utilization of hazelnut shells as a substrate in the production of BC is also reported does not require special pretreatment (Dórame-Miranda et al. 2019).

4.8 Dry Olive Mill Residue

Olive oil industry is one of the significant economic activity in several nations, including Portugal (Trichopoulou and Critselis 2004; Sieri et al. 2004). An estimated

40 × 103 tons of two-phase olive pomace (OP), which is made up of the pulp, skin, and stone fragments of the olives, are produced in Portugal each year as a result of the industrial extraction of olive oil (Fernández-Bolaños et al. 2006). OP has been used to make OP oil with a yield of 9.2%, therefore this method creates a byproduct known as dry olive mill residue (DOR), which can reach up to 35% of the mass of the original dry OP (Vlyssides et al. 2004; Sánchez Moral and Ruiz Méndez 2006). Currently, DOR has been utilized to produce electricity, organic fertilizers, and additives for animal feed (Martín García et al. 2003; López-Piñeiro et al. 2007). The utilization development of DOR continues to be studied and it is reported that DOR contains a substrate rich in sugars monomer as a source of carbon and nutrients for BC production after pretreatment in the form of mild acid hydrolysis (Gomes et al. 2013).

4.9 Cashew Tree Residues

Cashew (*Anacardium occidentale*) is an agricultural product whose main product is cashew nuts and cashew juice and has byproducts in the form of cashew pulp and exudate. Since cashew nuts are the most valuable output of the cashew tree, the exudate from this tree trunk must regularly be removed in order to stimulate the production of cashew nuts. Each of these trees produces approximately 700 g of exudate each year, which becomes a waste (Pacheco et al. 2017). Cashew tree exudate contains of arabinogalactan proteins, mono- and oligosaccharides, mineral salts, and 70% of branched heteropolysaccharides, called as cashew gum (Pereira-Netto et al. 2007; Silva et al. 2010). The polymer chains are mainly composed of D-galactopyranose units, as the primary building block, which are joined by β-(1 → 4) glycosidic bonds. Glucose, rhamnose, glucuronic acid, and arabinose are additional sugars that can incorporate branched cashew gum chemical structures (Pacheco et al. 2017). At least 68×10^3 and 48×10^3 tons of cashew gum and tree exudate respectively, are produced annually (Pacheco et al. 2017). Large quantities of this byproduct made an opportunity to carry out a research in efforts to treat this waste for the benefit of the economy and environmental sustainability. This residue has been extensively utilized in the food, biotechnology, and pharmaceutical industries (Kumar et al. 2012). The usage of cashew tree exudate and cashew gum as an alternative carbon source in BC production has been examined and claimed to exhibit good chances to be used in lowering the production cost (Pacheco et al. 2017).

4.10 Coffee Cherry Husk

Coffee cherry husk is one of the most prevalent byproduct that is produced in coffee cherries agroindustrial. The amount of this byproduct is almost 18% of the total coffee cherries that are processed (Rani and Appaiah 2013). This husk is rich in polyphenols, minerals, proteins, and carbohydrates. However, their use in agriculture has been restricted leading to a significant pollution issue at coffee cherries processing due to the existence of undesirable compounds like tannins, caffeine, and other polyphenols. While, according to studies, coffee cherry husk has the potential to be utilized in bioprocesses as an alternative substrate which is affordable. Coffee cherry husk can be added straight to the medium without going through any extra processing as a carbon source (Rani and Appaiah 2013).

4.11 Rice Washing Drainage

The global average of rice consumption per year in 2016 was 478.38 $\times$ 10^6 tons (Sudying et al. 2019). According to this data, almost all industries that are engaged in rice processing washed the rice with clean water before being cooked for consumption. In this rice washing drainage, numerous amino acids, saccharides, vitamins, and other nutrients are contained. Previous study reported the utilization of rice washing drainage as a source of carbon for BC synthesis can be used as cost reduction alternative because does not need special pretreatment (Sudying et al. 2019).

4.12 Tobacco Waste Extract

Tobacco (*Nicotiana*) is a plant with high economic value that is cultivated worldwide because it is the main ingredient in the cigarette production industry (Wang et al. 2015). Every year, it is estimated that about half (50%) of the tobacco used in cigarette production ends up as waste (Liu et al. 2015). This waste is found in the form of tobacco stems, tobacco leaves, and unwanted waste (Zhong et al. 2010; Wang et al. 2013). This waste has a high toxic nicotine content so it tends not to be managed but only thrown away or burned (Zhang et al. 2013; Okunola et al. 2014). This certainly endangers human health and contributes to environmental pollution. Recently, tobacco waste has been widely studied for its use as a substrate for producing fertilizers, pectinases, and some drug precursors (Wang et al. 2015; Zheng et al. 2017). Furthermore, the potential of tobacco waste as a substrate for BC production was also studied because it has a high sugar content in the form of glucose, sucrose, fructose, and other polysaccharides. In its utilization as a substrate for BC pretreatment production in the form of a steam distillation process used to remove nicotine which can inhibit microorganisms in producing BC. TWE is reported to be an ideal substrate for lower cost BC production (Ye et al. 2019).

5 Bacterial Cellulose in Medical Application

The unique physico-mechanical properties of BC, especially its biocompatibility properties make it widely used for direct applications in biomedical fields such as tissue engineering, wound healing, and drug delivery (Choi et al. 2022; El-Gendi et al. 2022). In this section, the superior qualities of BC will be described, along with the rationale for its use and research development in medical device.

5.1 Wound Dressings

In the biomedical sector to date, BC has played a significant role in the development of dressings for various types of skin trauma such as chronic skin ulcers, burns, surgical incisions, and other trauma (Popa et al. 2022). In general, the wound healing process is a complex process which is divided into four stages, namely: hemostasis, inflammation, proliferation, and maturation. The type of dressing material used to treat the wound is known to affect how quickly and effectively each of these stages progresses (Kushwaha et al. 2022). According to the scientific method of wound care, a bandage must have a number of qualities in order to support and hasten the wound healing process. These qualities include the ability to maintain moisture, absorb exudate, support angiogenesis, enable gas exchange, create thermal insulation in the wound area, prevent microbial infection, and be non-toxic, non-sticky, and non-allergenic (Niculescu and Grumezescu 2022).

In this case, BC is one of the greatest materials for creating a good wound dressing because BC has a high water holding capacity which enables it to absorb wound exudate, maintain a moist environment at the injury site, and stimulate the acceleration of the re-epithelialization process (Hajmohammadi et al. 2020; Pasaribu et al. 2020a, b). Additionally, the high water content of BC can also prevent pain and secondary trauma in patients during dressing removal (Weyell et al. 2019). Numerous hydroxyl groups in BC can form hydrogen bonds with water to produce flexibility, which makes it flexible enough, especially for contoured skin surface, to act as wound physical barrier from the outside environment (Swingler et al. 2021). However, from a biofunctional perspective, BC lacks the antibacterial and antimicrobial properties which are helpful in preventing infection throughout wound healing phase. In order to maximize the contribution of BC wound dressings to expedite the wound healing process, a combination with other substances is required (Choi et al. 2022). Numerous studies show that BC works well for wound healing when mixed with other compounds or materials such nanoparticles, benzalkonium chloride, hydroxyapatite, Aloe vera, and vaccarin (Picheth et al. 2017; Hasibuan et al. 2021). The effectiveness of BC as a wound dressing is also proven by the availability of several BC commercial wound dressing products such as BioFillTM (Curitiba, Brazil) and DermafillTM (Londrina, Brazil) which are used to treat burns and boils, Membracel® (Curitiba, Brazil) for ulcers and leg vein lacerations, xCell® (New York, NY, USA) for venous leg ulcers, and EpiProtect® (Royal Wootton Bassett, UK) for burns (Cielecka et al. 2019).

5.2 Bone Tissue Engineering

Tissue engineering has recently emerged as a viable solution for the replacement of damaged tissue (Swetha et al. 2010; Zhou et al. 2014). Therefore, research engaged in the manufacture of extracellular matrix (ECM) scaffolds that imitate the composition and architecture of natural ECM of target tissues is widely carried out, especially in bone tissue engineering (Mano et al. 2007; Stevens 2008; Swetha et al. 2010). Bone, which is a component of the skeletal system, is produced through a formation process known as osteogenesis that developed during the prenatal until adulthood phase of each individual. Thus bone has the capacity for restoration and regeneration to repair minor injuries and mechanical damage caused by normal trauma as long as it is not a birth defect. Bone tissue engineering using scaffolds is currently widely recommended in the treatment of bone repair by stimulating bone regeneration through a complementary combination of cells, biomaterials, and factor therapy (Li et al. 2013; Vadaye Kheiry et al. 2018).

The selection of biomaterial for scaffolding in bone tissue engineering is crucial because in this approach the biomaterial acts as a structural and/or functional supporting template for the cell regeneration process (Sill and von Recum 2008). Bone tissue engineering requires unique biomaterials with characteristics such as strong mechanical stress resistance and tunable biodegradability (Atila et al. 2019). Bacterial cellulose (BC), is one of the biomaterials that have received extensive study for Bone tissue engineering scaffolding production due to its high compatibility, although on the other hand, these polymers do not have the appropriate mechanical properties (Sell et al. 2010; Huang et al. 2014). Due to its superior purity, tensile strength, modulus, and elasticity, BC is used in regenerative medicine more frequently than plant cellulose. Moreover, BC also has biofunctionality and is biocompatible (Khan et al. 2015). BC-based scaffolds also have porosity and 3D network structures that support cell growth (Wan et al. 2007). BC was also reported to have a structure similar to bone collagen and increase cell proliferation in-vitro (Chen et al. 2009; García-Gareta et al. 2015). When compared to animal-derived biomaterials like collagen, the usage of BC scaffolds has also been shown to enhance tissue and bone regeneration and decrease the potential danger of cross-infection (Kong et al. 2004; Popa et al. 2022).

5.3 Dental Implants

In dental clinical practice, dental implants are a common operation, however this practice is frequently constrained because the maxillary region lacks the necessary bone height for the treatment (de Oliveira Barud et al. 2021). The integration of dental implants into the surrounding tissue is a significant concern. Additionally, for bone regeneration, osseointegration between the implant and bone must be complete (Choi et al. 2022). Despite their excellent application in tissue engineering and biomedical devices, BC-based materials are still under-explored in dentistry. Whereas the use of BC for commercial purposes in dental applications is very profitable because of its good absorption capacity, volume retention, and mechanical strength (Mensah et al. 2022). In addition, research suggest that BC can preserve graft space, enhance bone structure, and be used for dental implant insertion when applied to guided tissue regeneration techniques for the treatment of periodontal disease (de Oliveira Barud et al. 2021).

5.4 Vascular Grafts and Artificial Blood Vessels

Vascular Grafts and Artificial Blood Vessels is a method used in replacing blood vessels by cutting damaged or diseased blood vessels. In this treatment, the development of intimal hyperplasia is severely hampered by the material incompatibility of artificial blood vessels (Choi et al. 2022). Currently, ePTFE, Dacron, and polyurethane are the most commonly utilized materials for artificial blood vessels. Comparative studies have shown that BC is superior to PET and ePTFE products for usage as a vascular graft material (Picheth et al. 2017). BC is a promising new material for application in artificial blood vessels because BC nanofiber may avoid blood clots by displaying delayed thrombin production on the surface (Fink et al. 2010). In general, the use of pure BC nanofibrous scaffold for tissue regeneration does have limitations due to the presence of nanopores which can inhibit cell infiltration and vascularization of the 3D scaffold. However, several modifications made to the BC reported the potential for the BC to adapt to mechanical properties similar to those of small diameter vessels (<5 mm) (Picheth et al. 2017). Development of BC tubes also shows better resemblance to the human saphenous vein ($4.27 \times 10–2\%$ per mmHg for 30–120 mmHg) than commercially available Dacron saphenous vein products and ePTFE (Choi et al. 2022).

5.5 Delivery of Drug and Bioactive Agents

In recent years, numerous natural biopolymer-based hydrogels have been extensively researched for drug delivery applications (Dasari et al. 2022). Drugs are manufactured into drug delivery dosage forms because they are typically administered in numerous doses, possess fluctuating plasma concentrations, and have shorter half-lives. BC-based hydrogel scaffolds have recently been employed in drug delivery applications due to their potential in terms of high reactive surface, fine tissue structure, and high porosity (Swingler et al. 2021). Moreover, BC can be easily modified, blended, and impregnated with nanoparticles to change how receptive it is to drug release (Choi et al. 2022). Lyophilization followed by immersion is the most typical technique used to load the drug into the membrane of BC (Swingler et al. 2019). The drugs most commonly incorporated into bacterial cellulose are anti-inflammatory drugs, such as diclofenac and ibuprofen, and antimicrobial drugs (Ao et al. 2020; Bernardelli de Mattos et al. 2020; Junka et al. 2020). The effectiveness of BC as a drug delivery material can be boosted by utilizing the tensile strength and water absorption of BC to load it with antimicrobial substances such as antibiotics, to provide new features and functionalities (Gupta et al. 2019, 2020; Swingler et al. 2021). Researchers also frequently use BC-based as controlled-release drug delivery agents, for instance, the application of BC powder as paracetamol tablets coat via a spray-coating approach, demonstrates that the thickness of the BC film is used to affect the *in-vitro* drug release rate (Amin et al. 2012). Due to the lack of barrier interference and erythema, BC has also been widely researched as a transdermal medication delivery agent. It has been discovered that the skin is well-tolerated and moisturized because BC porosity can manage hydrophilicity of environment and also alter the release rate of the drug (Almeida et al. 2014; Ullah et al. 2016).

6 Conclusion and Future Perspective

This study focuses on the review of alternative substrates that sourced from the agroindustry byproducts in order to replace carbon and nitrogen and the advantages of the basic properties of bacterial cellulose for application as medical devices. Bacterial cellulose is a polysaccharide synthesized by various non-pathogenic bacteria under specific cultivation conditions. This appealing biopolymer has a number of physicochemical, mechanical, and biological qualities, including: environmental friendliness, biodegradability, biocompatibility, non-toxicity, optimal viscoelasticity, a 3D porous structure, high tensile strength, easy to modify, sufficient capacity to retain large amounts of water, and higher crystallinity and purity than plant cellulose. Either by itself or in combination with other biopolymers and bioactive substances BC has been reported to have therapeutic effects on various body areas of humans when used as medical devices. However, the development of BC as the main component in commercial medical device applications is still constrained due to the high-cost production of BC. Therefore, further research to find alternative synthesis media to reduce the BC production costs will continue to develop in the future.

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