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2**Current progress on the production, modification, and applications of bacterial cellulose**

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6**Institute of Food Science** and **Technology, National Taiwan University, Taipei, Taiwan**; hDepartment **of Medical Research, China Medical University Hospital, Taichung, Taiwan** **ABSTRACT**

1**Adoption of biomass for the development of biobased products has become a routine agenda in evolutionary metabolic engineering. Cellulose produced by bacteria is a “rising star” for this sustainable development. Unlike plant cellulose, bacterial cellulose (BC) shows several unique properties like a high degree of crystallinity, high purity, high water retention, high** mechanical **strength, and enhanced biocompatibility. Favored with those extraordinary properties, BC could serve as ideal biomass for the**

development of various industrial products. However, a low yield and the requirement for large growth media have been a persistent challenge in mass produc- tion **of BC. A significant** number **of techniques has been developed in achieving efficient BC** pro- duction. **This includes the modification of bioreactors**, fermentation **parameters, and growth media. In this article**, we **summarize progress in metabolic engineering in order to solve BC growth limitation. This article emphasizes current engineered BC** production **by using various bioreactors, as well as highlighting the structure of BC fermented by different types of** engi- neered-**bioreactors. The comprehensive overview of the future applications of BC, aims to** pro- vide **readers with insight into new economic opportunities of BC and their modifiable properties for various industrial applications. Modifications in** chemical composition, **structure, and genetic regulation, which preceded the advancement of BC applications, were also emphasized**

. ARTICLE HISTORY Received 21 February 2019 Accepted 29 October 2019 KEYWORDS Bacterial cellulose; BC production; BC application; BC modification; Bioreactor design Introduction

12**Bacterial cellulose (BC) is a structural carbohydrate** that is **produced from microorganisms** [1,2]. **BC has the same chemical structure as plant cellulose**, (C6H10O5)n, **but with** nano-size **polymer fibers**

. The name suggests, that BC is produced by bacteria as an extracellular metabolic product. Some common cellu- lose-producing bacterial strains that have been identi- fied are Gluconacetobacter, Sarcina, Agrobacterium, Rhizobium, Rhodobacter, and Agrobacterium [3–7]. The species Gluconacetobacter xylinus (identified initially as Acetobacter xylinum and later reclassified to be Komagataeibacter xylinus) is famous for its ability to produce BC on a commercial scale. BC from

2**this strain has been used in many industries such as food**, packaging materials, **and**

recently, with more advanced materials in biomedical and tissue engin- eering [4,8–10]. BC was first discovered in 1886 by A. J. Brown as the extracellular gelatinous fiber produced by Acetobacter xylinum. The earliest application, BC was widely used in the manufacture of coconut gel, popu- larly known as nata (also called as nata de coco). This translucent jelly-like food was produced from the fer- mentation of coconut water by bacteria, and the fer- mentation technique was initially popularized in the Philippines in 1973. The popularity of BC as a food continues to spread in many Asian countries, including Vietnam, Indonesia, Japan, etc. In 1993, the market history in Philippine recorded that 90% of nata, CONTACT Kuan-Chen Cheng kccheng@ntu.edu.tw Graduate Institute of Food Science and Technology, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei, Taiwan FG Blanco Parte and SP Santoso contributed equally to this work.

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produced in Philippine was exported to Japan [11]. Nata from BC was popularized as a food with many health benefits, and this statement played a crucial role in its breakthrough in the market. Moreover, the ease of BC (as nata) production causes the growth of many small industries in many rural households in Southeast Asia. In modern applications, BC has started to penetrate commercial and medical applications, such as a paper binding agent, a clothing base, and wound dressing material. The extensive use of BC is expected to arouse market interest with BC. Extensive cultivation times, low production yields, and the limited thickness of cellulose layers are major obstacles in the conventional production of BC, which limited its commercial application. Moreover, BC pro- duction in conventional culture requires a substantial amount of culture medium, which costs approxi- mately 30% of the total production costs [12]. The latest research trends in BC production are focused on efforts to increase production efficiency by modi- fying BC in terms of fermentation parameters and bioreactor design. Current methods of BC production that being improved, instead of a static method, sub- merged fermentation methods with aeration or agita- tion, and reactor-based production systems are being developed. This review covers important aspects to achieve efficient BC production and fermentation designs that leading to an innovation breakthrough of BC production in both economic and industrial aspects. The new emerging application of BC in bio- technology and non-biotechnology is also summar- ized in this review. Production of BC Fermentation techniques Almost all of the acetic acid bacteria (AAB) species are Gram-negative, and to date, only the Gluconacetobacter genus with a species name of hansenii has been identi- fied as Gram-positive bacteria. Amongst the common AAB species, Gluconacetobacter xylinus is popularly used as a model organism to study BC biosynthesis because of its ability to justify BC production on a com- mercial scale [13]. BC fermented by AAB has an ultrafine three dimensional (3 D) nanofibril structure with super- ior crystallinity and purity. The cellulose content of BC is a combination of cellulose I and II [14,15]. More than 95% of the mass of BC is the result of the enormous amount of water held between its nanofibril network [16,17]. BC can be produced through a static or sub- merged fermentation in a sugar-rich medium (including glucose or sucrose; while fructose, lactose, and maltose do not support BC production) [7]. Static fermentation Static (or surface) culture is a type of fermentation that is widely carried out for extracellular based products. Static culture has been widely adopted for BC produc- tion due to the simplicity by comparison of its utiliza- tion. This technique embraces bacterial culture in shallow bottles or trays containing the liquid growth medium, as shown in Figure 1(A). The cultivation of BC can be conducted several days after inoculation and fermentation at 25–30 C and a pH of 3–7. During a cul- tivation time of 5 to 20 days, the surface of the medium is gradually covered with a floating layer of a gelatinous Figure 1. Schematic diagram of BC culture. (A) Conventional static culture: (i) substantial amounts of medium are being fed all at once, (ii) only one layer of a BC sheet can be obtained. (B) Intermittent fed-batch culture: (i) a certain amount of medium being fed gradually, (ii) fresh batch of the medium being fed after 1st BC layer is formed, (iii) another layer of BC is formed and another fresh medium will, subsequently, be fed (Redrawn from ref. [18]). BC pellicle. The bacteria themselves will eventually be entrapped in the BC pellicle. Although widely adopted in BC production, static culture has certain limitations, mainly because of its extensive cultivation time and its low productivity. In addition, bacteria during cultivation exposed to unequal conditions (both in terms of nutrients, oxy- gen, and population distribution) during their growth cycle so that the thickness of the BC layer is produced unevenly. These drawbacks lead to the development of a newly modified static and sub- merged culture. An intermittent feeding strategy, or fed-batch fer- mentation, has been developed to enhance the prod- uctivity during static culture. This technique involves a periodic addition of media; i.e. in conventional cul- ture 200 ml of media which is added directly for fer- mentation. Whereas in intermittent culture, the addition is segmented for instance into 40 ml 4- times/10 days. Figure 1(B) shows a schematic diagram of the intermittent feeding process. Briefly, a new batch of the fresh medium should be fed directly from the top of the formed BC pellicles (1st layer) and new pellicles will form on the air/liquid surface in a critical depth of over 1 mm. Subsequently, a new batch of fresh medium is fed on the top of newly formed pellicles. This process is continuously con- ducted until several layers of pellicles are obtained. As shown in Figure 1(B), the growth medium was used efficiently in intermittent feeding process com- pared to the conventional process. The intermittent feeding could also maintain a constant BC production rate (0.02 g/day) for 30 days cultivation, while for the conventional process, the production rate is almost close to zero [19]. Metabolic engineers have shown that modifica-

tions to the growth medium may be applied in order to boost BC production in the fed-batch technique. Bae and Shoda [20] show the optimization of this technique by adding H2SO4 heat-treated molasses as a carbon source for A. xylinum; up to 7.82 g/L of BC can be cultivated using a fed-batch fermentation while only 5.3 g/L of BC can be cultivated using con- ventional batch fermentation techniques [20]. Shezad et al. showed that liquid waste from beer combined with the fed-batch technique could boost the pro- duction of BC from G. hansenii PJK to 3-fold in 30 days of cultivation [21]. Dubey et al. reported that K. europaeus SGP37 could produce BC at 1.47 times higher in fed-batch fermentation using an HS media modified with a hot water extract of sweet lime pulp [22]. Submerged fermentation Due to the shortcomings of static culture, submerged fermentation has been adopted. The advantages of submerged fermentation compared to static culture have been shown in several studies, and it is essentially higher productivity. However, submerged fermentation also has several issues to overcome, including the development of cellulose non-producing strains [23], production of irregular shaped BC granules and the modification of BC's physical properties [24]. Furthermore, the bacteria favor gluconic acid synthesis over cellulose production during high rotation speeds, and the hydrostatic stresses leading to the accumula- tion of self-protection metabolites [25]. For the production of BC, many types of submerged fermentation have been conducted including: stirred tank, rotating disk and airlift bioreactors. In a recent study, BC production in a stirred tank bioreactor was investigated and the results show that the production of BC was 1.13 and 0.54 g/L with 700 rpm and 500 rpm agitation respectively. This suggests that higher agita- tion rates do increase the total productivity of BC yields. However, this BC has lower crystallinity compared to the BC produced through a static culture [26]. A plastic composite support (PCS) has been incorpo- rated to enhance the advantages of submerged fer- mentation, further. PCS, a compost of polypropylene and nutritious compounds, allows biofilm adhesion for higher BC production, as shown in Figure 2 [17]. With the success of the PCS biofilm reactor, further experi- ments based on this PCS biofilm reactor will have been conducted that involved a PCS rotating disk bioreactor Figure 2. (A) Side view of the bioreactor with plastic compos- ite supports (PCS). (B) Top view of the bioreactor shows the arrangement of PCS crossing each other. (C) Formed BC sheets attached onto the support, BC is described as a trans- parent sketch with color gradations (Redrawn from ref. [22]). (PCS-RDB). This semi-continuous method yielded satis- factory

15**0.24 g/L/day** production of BC **in** 5 consecutive **5-day**

runs [27]. Despite higher yields, submerged fer- mentation could not produce a membrane-type BC pel- licle. Under agitated culture, bacteria tend to form irregular spherical granules of BC, with lower crystallin- ity and a looser, more porous microfibril network [24]. This would limit the application of an agitated culture since most applications require BC pellicles. Efforts have been made to modify the submerged culture method in order to produce a BC pellicle with similar film-like qualities. Wu et al. [28] developed a new airlift bioreactor that was able to produce a mem- brane-type BC,

2**with a series of net plates** placed verti- cally **in the**

reactor and an air distributor at the bottom. This bioreactor design produced a membrane-type BC film in an agitated way. Modifiable parameter in BC fermentation Culture media From an economic standpoint, low productivity could be tolerated if culture media is derived from signifi- cantly less expensive sources. For instance, citrus peel and pomace from beverage industry waste have been proven to be potential as a BC culture medium. Moreover, the used waste medium

9**resulted in a BC yield of** 5.7 **g/l**, higher than **the**

conventional HS medium that only

9**resulted in a BC yield of** 3.9 **g/l**

[29]. Waste beer yeast (WBY) alone has proved to be fully capable of growth of Gluconacetobacter hansenii CGMCC 3917, and subsequent BC production. WBY hydrolysates treated by ultrasonication gave a 6 times higher BC yield when compared to untreated WBY; and more importantly, 2 times higher than BC with the con- ventional chemical media [30]. In another study, chem- ically treated molasses were used as fermentation media and it gave higher BC yields compares to HS and Zhou medium in batch mode operation [31]. These studies demonstrate that alternative media, with a com- plex natural composition, is more productive and is as cost-effective as the traditional chemically defined syn- thetic medium. Since BC production uses fermentable sugars as a carbon source, it is no surprise that cellulosic materials are trailed for their potential as a feedstock for BC pro- duction. For example, fiber sludge from sulfate (SAFS) and sulfite (SIFS) processes were used as a feedstock to produce BC after enzymatic treatment; and it yielded 11 g/L and 10 g/L, respectively [32]. The utilization of low-value waste to produce high-value materials cer- tainly has a significantly higher market value. Algal biomass can also be used as an alternative car- bon source. In one of the studies, starch from the algae Chlorella vulgaris was hydrolyzed into glucose for BC production. Initially, in order to increase its starch con- tent, the algae was starved of nitrogen. Then the hydrolysate was added to the fermentation medium under static condition to produce BC. This process yielded 1.104 g/L of BC, which is higher compared to 1.202 g/L of BC with regular glucose as a carbon source [33]. Fruits and related byproducts have also been widely investigated in this field. Fruit peels [2], rotten fruit [34] and fruit juice production waste [29] have been studied for their potential as a BC feedstock. Considering the large amount of fruit that is damaged during transport and the occasional bumper harvests that result in fruits are left to rot in the field. Farmers and BC producers could both benefit from this practice if this fruit attri- tion can be converted into high-value BC. The wine industry produces a large amount of by- products that have potential in BC production. Supplementing thin stillage into traditional an HS medium has a record of 2.5 times BC produced com- pared to HS medium without supplementation [35]. Wastewater of candied jujube is rich in organic nutrients and therefore if discarded directly, the high organic substances are liable to cause significant dam- age to the environment. However, if this wastewater is treated with heat and acid and then diluted into differ- ent concentrations, it can yield 2.25 g/l of BC [36]. Even, lipid fermentation wastewater when inoculated with G. xylinus CH001 could produce 0.659 g/L of BC by day 5 and a reduced 30% of COD from the waste water [37]. Carbon and nitrogen sources Each strain of cellulose-producing bacteria needs differ- ent carbon sources. Komagataeibacter genus bacteria, for instance, are highly diverse in terms of optimized carbon sources, such as glucose, sucrose, and fructose [38,39]. In the case of Komagataeibacter sucrofermen- tans DSM 15973, glycerol and sucrose were the two best performing carbon sources [40]. As for nitrogen sources, similar experiments have been conducted in search of a low- cost, high-productiv- ity nitrogen source. For instance, the utilization of milk whey

7**as a nitrogen source and** rotten fruits **as carbon source**

yielded more BC than the reference HS medium [34]. Magnitude of pH The importance of pH during the synthesis of BC has been extensively studied. pH below 7 is considered to be optimal pH for the genus of Komagataeibacter. Yet during fermentation, the pH value decreases gradually and often falls below the optimal pH for BC synthesis. This is because of multiple existing metabolic pathways such as

22**the conversion of glucose to gluconic acid and**

oxidation of ethanol to acetic acid [41]. For the Gluconacetobacter medellinensis strain ID13488, the effect of pH was studied with colonies forming units (CFUs) on HS-agar plates under pH of 4 and 7, and the result

demonstrates that acidic environ- ment exhibits better cell viability than neutral pH [42]. Although most strains are generally more productive under slightly acidic environments, at least one strain (K. intermedius FST213-1) showed better BC production under basic condition. The highest BC production was at pH 8 and cellulose producing ability has been dem- onstrated until pH 9, the first study to report BC pro- duction at this pH value [43]. Even though most strains favor an acidic condition, the accumulation of gluconic acid seems to have adverse effects on the bacteria's productivity. The add- ition of acetate buffer to the medium results in better production rates and the conversion yield of BC.

> 4**BC produced from 200 mM**, and **pH 4.75 acetate buffered medium was 3.56 g/L, higher than that** produced **from** the **YPD medium (0.66 g/L) and HS medium (1.23 g/ L**

) [44]. Oxygen level The genus of a BC producing bacteria, namely Komagataeibacter is known to be an obligate aerobic microorganisms [45]. This is implying that they compul- sorily require oxygen for growth as well as for BC pro- duction. Oxygen acts as a precursor that activates adenosine triphosphate (ATP) in the bacteria cells. Parameters such as the surface area are directly linked to the availability of oxygen in the growth medium in the form of dissolved oxygen (DO). DO was thought to be the limiting factor in an airlift bioreactor, and it was suspected that cellulose formation is more related to oxygen uptake than to medium nutrients [28]. In another experiment conducted on various media including the HS medium and apple residue/ sugar cane medium with static culture, depletion of DO was not observed during the cultivation period of 13 days; suggesting that in this case, DO might not be the limiting factor [42]. To further

> 18**investigate the** effects **of oxygen tension on cell growth and BC production**

, Vitreoscilla hemoglo- bin (VHb) encoding gene vgb was transformed into

> 18**G. xylinus via pBla-VHb-122 plasmid**

. VHb is a homodimer oxygen-binding protein widely use to overcome hypoxia for microorganism cultures. The results suggest that G. xylinus favors cell growth rather than BC produc- tion under high oxygen tension conditions. On the con- trary, lower oxygen tension supports BC production, and under low oxygen tension, VHb positive G. xylinus produces significantly higher BC compared to G. xylinus with no VHb [46]. Long- term fermentation During the batch fermentation process, a waiting period (lag phase) for the starting time is inevitable and this waiting period is unproductive in the sense of eco- nomic viability. One study conducted with molasses employing fed-batch culturing method suggested that not only diluted molasses are a better culture media compared to HS and Zhou medium, but the semi-continuous process used in the experiment gave a longer production period of BC, up to 28 days [31]. Also, considerable research conducted on PCS-RDB shows the potential of long-term fermentation in a semi-continuous manner, as previously described [27]. Other additives for efficient BC production Additives were incorporated into the media to either increase the productivity or

> 15**improve the mechanical properties of BC**

or both. Water-soluble PVA

15**was added to the culture medium**

to test for its in situ modification effect. This PVA reinforced BC showed better mechan- ical properties compared to the native BC. Addition of 0.6, 6 and 14 wt% of PVA elevated

11**Young's modulus and tensile strength** at **the** break **by** 15, 165, 680% **and**

1, 12, 40%, respectively [47]. The PCS-RDB method is combined with different additives for in situ modification. The addition of car- boxymethylcellulose (CMC), avicel, agar, and sodium alginate into the medium showed 80% and 113% increases in the BC production, respectively. However, a further examination showed that these additives decreased the total crystallinity of the final BC pro- duced; since they are incorporated into BC fibrils during the fermentation [48]. Ethanol and acetic acid have been trailed for their potential to promote BC productivity [49]. In a recent study, ethanol and acetic acid were added to the modi- fied HS medium as alternative energy sources. The results demonstrated that BC production is stimulated by the addition of ethanol and acetic acid. 0.1 wt% of ethanol and acetic acid can increase BC production up to 279% and 222%, compared to a medium without these two compounds [50]. Vitamin C, also known as ascorbic acid, is considered to be an effective anti-oxidant. It has been discovered to promote BC production by 188%, and reduce glu- conic acid synthesis when present in the medium at 0.5% w/w [51]. Ethylene, a well-known phytohormone that regulates plant development, is also studied for its effect on BC production. The presence of ethylene (in situ) produced by ethephon does increase BC produc- tion and up-regulates bcsA and bcsB directly; and cmcAx, ccpAx, bglAx, another set of genes known for their role in BC synthesis, indirectly. As for other phyto- hormones, indole-3-acetic acid (IAA) decreases BC pro- duction via down-regulation of bcsA expression [52]. Bioreactor design Static and submerged culture has been considered not feasible for industrial-scale production of BC due to major drawbacks. It exhibits long culture time, and high production costs. An engineered method that is reactor-based BC, production has been developed to overcome this drawback. As mentioned before, BC is produced at the air-medium interface, and one of the challenges in designing better reactors is to increase this air-medium surface. However, an optimal reactor should also address the main drawback of agitated cul- tures, which mainly consists of: (i) mutations into non- cellulose producing phenotypes, which are accelerated in agitation due to shear forces [23] (ii) oxygen transfer rates, as dissolved oxygen has been reported to be one of the factors affecting BC synthesis [53] and iii) shape of the final BC, as agitated cultures mostly produce pel- let-shaped BC, which has fewer applications due to its low mechanical strength and crystallinity [53]. Here we would discuss recent advancements in various bioreac- tor design for BC production that have tried to focus on these constraints. Stirred tank Stirred tanks offer distinct advantages for bioprocess- ing; the schematic diagram of the tank is shown in Figure 3(A). They display high volumetric mass-transfer coefficients, and the technology is already being widely used. Recently, fermentation parameters of K. xylinus in stirred tank reactors have been analyzed [26]. The study indicated that higher agitation rates produced increased cell densities as well as high BC production. The study reported that a BC with 0.59 g L?1 yield and 0.01 g L?1 h?1 productivity was obtained with an agitation speed of 500 rpm; 1.13 g L?1 BC yield and 0.02 g L?1 ?1 productivity obtained with an agitation h speed of 700 rpm. Volumetric oxygen transfer coeffi- cients, strongly related to BC production, is dependent on the agitation speed. Together with non-Newtonian behavior, will demand high mixing rates, which would reflect a high power demand. Figure 3. Bioreactor designs (top figure) and shape of BC cultivated from fermentation using the specific bioreactor (bottom fig- ure). (A) Stirred tank bioreactors and grain-like BC pellets with size 5–3 mm, (B) rotating disk bioreactors and BC sheets, (C) airlift bioreactors and thin layer BC pellets (Redrawn from ref [21,54,55]). Airlift bioreactor Airlift, Figure 3(C), the reactor has been extensively researched for BC production [56]. This type of reactor produces less shear stress than stirred tank bioreactors, as well as is reduced energy demand. However, it dis- plays a lower oxygen transfer rate, which is an essential parameter for BC production. Recently, Wu et al. [28] modified a wire-mesh tube airlift reactor with net plates to produce BC membranes, more adequate for

biomed- ical applications than BC pellets. The BC concentration after 96 h of culture reached 2.6 g L?1, with 0.027 g L?1 productivity rate. It was found that the number of plates correlated with the dissolved oxygen, further increasing the number of plates increased the oxygen transfer rate. This study was also the first to report cellulose production in the medium instead of the air-medium interface. Rotating disk bioreactor General drawbacks of the stirred tank and airlift bio- reactors are the

16**adhesion of BC to different parts of the**

reactor, which cause a reduction inhomogeneity and the production of pellet-shaped BC. Rotating disk bio- reactor (RDB), that consists of a central shaft to which circular disks are coupled have been reported as a way of producing BC pellicles [57]. Latest reports in RDB-BC production include a semi- continuous method of BC production based on a plastic composite support (PCS) rotating disk bioreactor, as shown in Figure 3(B) [27]. The productivity of 0.24 g L?1 was achieved per day for 5-day cultures, utilizing a sys- tem that was able to operate for at least 5 times with- out reinoculation. BC had the same water content and thermostability but displayed lower mechanical proper- ties (such as Young modulus and crystallinity). More recently, the same reactor has

7**been used to incorporate** different components **into the BC matrix**

to produce BC-composites [48]. The utilization of microcrystalline cellulose, carboxymethylcellulose, and sodium alginate as additives in ratios

20**as low as 0**.2%–0.8% (**w/v**

), has improved the productivity up to 113% when

3**compared to the control** group. **The** properties **analysis showed** that **the**

resulting composites displayed similar strains and the water content as that of native BC, but with lower stresses. RDB can also be applied to the material coating. Zhang [58] used a roller-equipped horizontal bioreactor for in situ coating of cotton gauzes with BC, which also allowed cotton to act as an adequate material for K. xylinus culture, as porous matrices are more suitable for bacteria immobilization in RDB. Faster and higher prod- uctivity was observed when compared to static culture, with RDB-BC showing 2.61 mm sheets of BC and 1.62 g L?1 of BC in 3 days against 2.34 mm and 1.49 g L?1 of BC in 10 days in static culture. Other bioreactors Trickling bed reactors (Figure 4(A)) can also be a suit- able option since it helps to increase oxygen supply, provides a higher surface to volume ratio, and decreases the shear forces. Up to now, only the

13**physical properties of the BC** produced on **this**

kind of reactor have been reported, therefore making it tough to comment on the productivity of BC. BC extrudes by the bacteria will gradually attach to the packing as fer- mentation proceeds. BC produced in trickling bed reac- tors displayed a better polymerization degree, purity, Figure 4. A schematic diagram of (A) trickling bed reactor, (B) bioreactor with two oxygen-permeable silicone (Si) tubes as sup- ports, (C) roller/O2 duct-mounted bioreactor with ENM membrane, and (D) Si tube-supported reactor with paraffin wax

packing (Inspired and redrawn from ref. [59–61]). porosity, water holding capacity as well as thermal stability in comparison with BC produced by conventional static or shaking cultures [59]. Other reactors have been designed to shape BC amongst its synthesis. A new bioreactor with two oxy- gen-permeable silicone tubes as supports to form BC tubes among culture have been designed, Figure 4(B) [62]. BC cylinders of 3 mm internal diameter, 2.5 mm wall thickness and 45 mm length were obtained after 7 days fermentation with Kombucha, instead of the 25 days needed for the same product with K. xylinum. The final structures displayed the same mechanical properties as those obtained from other procedures in the literature, thereby pitching it as a fast and cost- effective method for BC tubes synthesis. Similar silicone tubing bioreactors, filled with paraffin wax microsphere packing (300–500 micrometer), was used to produce microporous BC that is a potential as a scaffold for tis- sue engineering application [60]. The schematic of the bioreactor is shown in Figure 4(C). Naeem et al. also demonstrated the used of a roller/ O2 duct-mounted bioreactor for producing a three- dimension BC/electrospun membrane (ENM), Figure 4(D). The 3 D composite was synthesized as the BC formed on the ENM surface, and consequently binding the ENM to form a three-dimensional hybrid network [61]. Studies concerning BC production in reactors are summarized in Table 1. Modification of bacterial cellulose Although BC presents many favorable properties for dif- ferent uses, modification, and incorporation of other molecules still need to broaden its range of applica- tions. Different physical treatments can be employed

11**to enhance the mechanical properties of** BC. Exposing **the** growing **polymer**

chain to a rotating magnetic field has demonstrated an increase in water absorption and a density of BC [66]. The rheology of BC under ultrasound treatments has been analyzed, it is shown that short treatments of polymer suspensions for 1 min resulted in the break down of the fibers into half of the original width, thus increasing water holding capacity as well as its stability [67]. Such modifications could boost BC properties for

16**its applications in the biomedical field**

16**as a material for** highly exudating **wound dressing**

or for the use as a food additive. Chemical modifications of BC have recently been exhaustively reviewed [68]. In the following, we will only highlight the latest trends in BC chemical modifica- tion. The oxidation of hydroxyl groups of cellulose is a very common modification, commonly using 2,2,6,6-tet- ramethyl-1-piperidinyloxyl (TEMPO), which specifically targets primary hydroxyls, turning it into carboxylated cellulose (CBC). This carboxyl groups can be used for covalently anchoring the functional molecules, for example, the binding of photoluminescent particles after the amine activation of CBC [69], or for altering surface charge for enhanced ionic interactions during the Agþ assembly on CBC surfaces [70]. Other chemical modifications of BC include aminoalkyl grafted BC [71], or acetylated-BC [72]. Nevertheless, one of the mostly used chemical modifications involves acid hydrolysis of BC for nanocrystal formation [73]. BC has also been used for various composite formu- lations. BC can be mixed with other polymers with in situ procedures. This is by adding the composite poly- mer directly into the culture media. In this way, hyaluronic acid-BC composite with a rougher structure and more hydrophobic BC chains can be produced [74]. Also, CaCO3 has been incorporated, resulting in higher O/C ratios that gives the composite an amphoteric sur- face characteristic [75]. BC-polymer composites can also be achieved by ex situ synthesis. Some examples of this practice are the chitosan(CS)-BC composite, formed by simple solvent dissolution and casting [76], or CS/PVP/ BC synthesized by salt leaching methods [77]. BC com- posites with oxide and metal-oxide nanoparticles (NPs) have also recently been reviewed [78], and usually involve vigorous mixing

of BC and the metallic nano- particles (NPs). However, the primary practice to date of introducing active molecules into BC matrices remains immersion into a water solution containing the desirable ingredi- ent. Studies concerning BC modification are summar- ized in Table 2.

5**Table 1. Comparison of different types of bioreactor** employed **for BC production. Reactor type Advantage Disadvantage Productivity** Stirred tank **reactor**

High cell concentration High power demand, high shear stress 0.02 g L?1 h?1

21**Airlift reactor High cell concentration; Relatively low High energy requirement**

0.027 g L?1 h?1 shear stress

21**Rotating disk reactor High cell concentration**

; Ease on Semi-continuous production; 0.01 g L?1 h?1 ingredients incorporation Trickling bed reactor Higher oxygen supply; Better Semi-continuous physical properties production;Recovery issue Production Reference 2.6 g L?1 1.13 g L?1 [63] [64] 1.2 g L?1 [14,65] Table 2.

5**Summary of BC modification and composites** developed **in the past 5 years**. Modification **Application**

Reference Physical modifications Rotating magnetic field exposure Increases water holding capacity and density of growing BC. Ultrasound treatment Break down of fivers to half of the width enhancing WHC. Chemical modifications TEMPO Oxidation to carboxyl Changes surface charge and allow to bind other components chemically or by ionic interaction. Aminoalkylation Displays antibacterial activity. Acetylation Increases hydrophobicity. Composites Hyaluronic acid Rougher composites and increases hydrophobicity. CaCO3 Higher O/C ratio and raises amphoteric character. Chitosan Displays antibacterial activity. Polihexanide Displays antibacterial activity. Alginate Enhanced chondrocytes growth. Hydroxyapatite Enhanced osteoblasts growth. Keratin Enhanced fibroblasts growth. Ag NPs Displays antibacterial activity; gives plasmonic properties for sensing; SERS. Au NPs SERS. Si NPs Conductive BC-based materials. Cobalt ferrite NPs Conductive BC-based materials. Fe3O4 Displays antibacterial activity. Graphene oxide Selective ion permeation. Graphene oxide/TiO2 Displays antibacterial activity. Drugs Drugs incorporated into BC can

19**be used for wound healing** purposes **or** as a **drug delivery**

platform. [79] [19] [21,22,37] [23] [24] [25] [26] [27,80–82] [62] [50] [51,52] [53] [21,22,36,37] [83,84] [77] [78] [38] [39,40] [74,75] [32,33,41–47] Bacterial cellulose applications

5**Pharmaceutical applications Wound healing** Wound healing **is a dynamic process that involves** a col- laboration **of** different **cell types**

2**and their products, such as extracellular matrix** components, **mainly** colla- gen, **and secreted soluble compounds** like **growth** fac- tors **for cell proliferation**

[85]. The practice in modern medicine demands wound healing to go beyond moisturizing and mechanical protection. This has led the development of materials with advanced character- istics, such as excess exudate removal, appropriate gas diffusion, thermal and pH control, painless removal of the dressing, infection prevention, and cost-effective- ness. All of these procedures can be achieved from BC or different BC composites [86,87]. In the last few years, many efforts have been executed concerning BC and its modification to improve its display as a wound-healing material. Lamboni et al. [83] developed silk sericin-BC by solution impregnation that enhanced fibroblast pro- liferation, and enhanced extracellular matrix production that shortened wound healing time. In addition to seri- cin, polyhexamethylene as an antimicrobial agent was included in BC membranes, resulting in not only facili- tated cell migration and collagen production, but also demonstrated the absence of irritation, infection pre- vention and rapid reduction of wound size [84]. Antimicrobial material Recent research on BC applications has focused strongly on its modification for antimicrobial purposes, closely related to wound infection prevention, as an innovative way of addressing the increasing issues of antibiotic-resistant bacterial infections. Different approaches have been followed, consisting mainly of antimicrobial agents functionalized-BC, biocidal poly- mers-BC composites or metal/metal oxide NPs impreg- nated BC. A fusion protein consisting of the T4 phage lysozyme and a cellulose-binding module has been designed, dis- playing bactericidal effects against both Gram-negative and Gram-positive bacteria when immobilized in BC gauzes [88]. Other antimicrobial molecules have been added to BC, such as combinations of RGDC ? gentamicin against Streptococcus mutans [89] or bromelain, with effectiveness against the Leishmania genus [90]. BC-polymer composites usually maintain or improve the physical

2**properties of BC, such as high** tensile strength and **water holding**

at the same time; while incorporating others, such as its antimicrobial activity. In situ synthesized CS/BC resulted in a composite dis- playing antibacterial

20**activity against Escherichia coli and Staphylococcus aureus due to the** presence **of**

CS [91]. The antiseptic polymer polihexanide (PHMB) has been used to make PHMB-BC composites that displayed anti- bacterial activity against S. aureus and entirely sup- pressed bacterial growth [92]. In regard to combination with metal/metal oxide NPs, silver NPs-BC, either synthesized by physical immersion [93] or chemically bound [70,94], has proven to be

3**effective against both Gram-positive and Gram- negative bacteria**

. Composites have been developed where BC was incorporated with Fe3O4,

19**which showed antibacterial activity against** S. **aureus**, Staphylococcus epidermidis **and Pseudomonas aeruginosa**

[95], and with Graphene oxide/TiO2/BC, that had antibacterial activity against S. aureus [96]. Drug delivery system In addition

2**to its** favorable **characteristics for wound healing**

, intimate contact of BC formulations with the diseased area making it an auspicious

2**platform for transdermal drug delivery** [97]. **The** most **common** method **of drug loading** into **BC** membranes **is by** sub- merging **the membrane** in **drug**

suspensions, after total or partial dewatering of the BC membranes. Also, chem- ical modifications

2**or BC composites** formulations **have been** developed to **control** drug **release** from **the**

BC matrix(113). Antimicrobial agents and non-steroidal anti-inflammatory drug (NSAIDs) were the most com- mon compounds to be loaded in BC. A model of amoxicillin (AX) release, from BC-AX loaded membranes, shown that the main factor of

3**drug release** was **the** concentration **of the drug**

itself [98]. More recently,

3**tetracycline hydrochloride (TCH**) immer- sion **loaded BC membranes were** analyzed. **The release**

profile showed an initial burst release followed by a steady release after 2 h, displaying antibacterial effect

22**against E. coli, S. aureus**, Bacillus subtilis, and **Candida albicans**

, as well as excellent biocompatibility tested on HEK293 cell line [99]. Antiseptic octenidine loaded on BC fleeces demon- strating high biocompatibility with human keratino- cytes,

3**resulting in a biphasic release profile** with **the first**

burst in the first initial 8 h and continuous release until the 96th h. Moreover, they determined octenidine loaded BC to be stable and active for 6 months without significant changes [100]. More recently, longer-term octenidine release, up to a week, has been achieved by a different combination of poloxamers/octenidine

dis- persions, with a controlled kinetic release by the type and concentration of poloxamer [101]. NSAIDs Diclofenac (DF), whose side effects at the intestine suggest preferable transdermal delivery, has also been studied for release from BC membranes. Recently, poly-N-methacryolyl-glycine-BC nanocompo- sites have been designed with a pH-sensitive control release of DF, retaining the drug at pH 2.1 and releasing it at the human's skin pH, i.e. around 7.4 [102]. Other drugs, such as the traditional Chinese drug alkaloid ber- berine, has also been analyzed for its drug delivery pro- file from BC membranes [103]. A hollow type spherical BC for a controlled release device for fluorescein isothiocyanate-dextran has Figure 5. Schematic diagram of a hollow spherical BC gel. (A) Cell suspension droplet and (B) cross-section of cell suspen- sion showing the hollow body (Redrawn from ref. [104]). recently been reported by Hoshi et al. The hollow spherical BC is formed by dropping the cell suspension aseptically into mixed silicone oils and incubated at 30 C for 14 days. Eventually, the BC fibril layers formed a shell structure which covering the cell suspension droplets. A hollow body is formed in the center, as shown in Figure 5(A,B). As claimed in the study, the hol- low spherical BC with a thin gel-like membrane is potential as a drug release material [104]. Tissue regeneration BC has also been shown to be an excellent support for mammalian cell cultures. In the

8**recent years, BC has been used as a** scaffold **for different** type **cell growth. The porosity of BC is** a positive characteristic **in**

the facilitation of cartilage tissue engineering. Feldman et al. [105] designed a paraffin bead embedded BC scaf- fold where human chondrocytes were able to migrate, differentiate, and display a chondrogenic phenotype in terms of the cartilaginous matrix secretion. Further BC modification may be able to enhance these properties. Laser perforation of BC formed 3 D channels that improved the seeding of chondrocytes [106]. In vivo studies have been addressed to assess the performance of alginate-BC bilayers seeded with human nasoseptal chondrocytes and human mononuclear cells in mice, demonstrating that after 8 weeks the composites had good stability, and provided a good environment for chondrocytes growth [107]. Other tissues have been grown in BC matrices such as bone, skin, muscle, or neuronal tissue. Human Mesenchymal Stem Cells (hMSCs) cultured in BCN mac- roporous structures with mineralized hydroxyapatite differentiated into functional osteoblasts in an osteo- genic medium for 21 days [108]. Likewise, nanocompo- sites of BC, collagen, apatite, and osteogenic growth peptide showed induction of an osteoblastic phenotype [109]. Keskin et al. [110] incorporated keratin to a BC composite to enhance fibroblasts attachment, achieving better skin keratinocytes, and fibroblasts growth than in non-modified BC. Finally,

14**BC has also been used as a scaffold for** stem **cell**

expansion and differentiation. Krontiras et al. [111] concluded that differentiation of mice Mesenchymal stem cells into adipocytes in 3 D-BC scaffolds was a more efficient model of in vitro growth than current methods. More recently, vasculogenesis in human mel- anoma in a BC-IKAVAV peptide matrix was mimicked, which improved SK-MEL-28 cells adhesion and organ- ization, allowing a better model for melanoma drug screening [112]. Vascular grafts BC mechanical properties such as their water-holding capacity, elasticity, strength as well as biocompatibility or low inflammatory induction have been widely reported [29,35]. These characteristics, together with properly shaped composites [113], make BC a suitable material for vascular grafts. Leitao et al. [114] developed a new simple method of BC graft production, consisting of BC perforation by a needle, followed by a drying pro- cess to shape up, and freeze-dry. A graft of similar sur- face roughness as the porcine femoral artery was achieved, with desirable mechanical properties and was tested in vivo by the homolateral-femoral bypass. Results after a month confirmed patency, blood flow, and CD31 positive cells on the luminal face, which were supposed to be endothelial or endothelial progeni- tor cells. Other than large blood vessels grafts, where several materials are already on the market, BC has been pro- posed as a suitable material for small vascular grafts. Recently, second-generation grafts have

been designed with reduced wall thickness and a smoother inner sur- face and assessed its in vivo display in sheep [115]. Potency rates up to 80% and no inflammation have been found. However, antiplatelets were needed to lower the occlusion phenomena, which was still 67% in antithrombotic drug-treated sheep. Food applications BC has been traditionally used for “Nata de coco” des- sert in Asia, as well as this has been studied before for its applications in the food industry as dietary supple- ments because of its low calories or as a substitute component for vegetarian meat. Moreover, it

14**has been classified as “generally recognized as safe**” (GRAS) **by the FDA**

since 1992 [116]. Recent research on BC utilization for food applica- tions is including BC NPs as oil-in-water Pickering emulsions stabilizers, as only 0.05% (w/v) was enough to stabilize peanut oil emulsions. It is suggested as a promising potential for food-grade emulsifiers[117]. Also, BC has been proposed for gastric condition treat- ments, either on its own as a dietary fiber supplement, which displayed constipation alleviation in rats [118], or as a platform for prebiotics delivery, such as Bacillus coagulans delivery [119]. Immobilization platform Biocatalysis is a central process in many chemistry- related industries. Nevertheless, the main drawbacks of enzyme-biocatalysts used in the industry are connected to long-term stability and the difficulty of recovery, which can be solved by enzyme immobilization [120]. In the context of Green Chemistry,

2**biopolymers have become a** core **matrix for** biocatalyst **immobilization**. Recently, **BC** properties have **been explored**

in this field. Lipases are a group of one of most used industrial enzymes for biocatalysis, as its broad substrate specifi- city and regio- and stereospecificity offers

11**a wide range of applications, such as**

: biofuel synthesis, oils hydrolysis or chemical building blocks synthesis [121]. Kim et al. [122] developed an alginate-BC bead synthesis methods from K. xilinus entrapment in anionic polysaccharide alginates and used to immobilize lipases. BC provides a higher surface area, crystallinity, and water-holding cap- acity. However, alginate provides a 3–8 fold higher spe- cific activity compared to only BC immobilized lipase. Industrial lipases have recently been immobilized in sphere-like, aldehyde modified BC, displaying improved properties as compared to free lipases such as optimal

13**activity under both acidic** (pH 5) **and alkaline** (pH 8) **conditions, as well as higher activity at** temperature **under 30 C**

, which could demand lower energy in industrial practice [121]. Laccases are also commonly used as industrial enzymes

3**for a wide variety of applications such as**

stain- ing and the dye decolorization of textiles, pulp delignifi- cation, and the bleaching of paper, and an antimicrobial for the food industry or for bioremedi- ation [123]. Recently, laccases have been immobilized in BC matrices, resulting in doubled Michaelis-Menten constant values but a similar specific activity to that of

free laccases [124]. Improved immobilization of laccases has been achieved by exposing BC to a rotating mag- netic field, which finally led to upgraded operational parameters such as pH resistance [125]. In addition, environmentally friendly bio-coloration of BC mem- branes based on immobilized laccases was able to obtain yellow, orange and dark brown membranes from flavonoids polymerization with great advantages in comparison to aggressive dyeing treatments in the textile industry [54]. Other enzymes and microorgan- isms such as b-galactosidase [126] and yeast [127] for the food industry have been immobilized in BC. Filtration The application of BC as an eco-friendly filter material has also been proposed. Recently, different compo- nents have been added to BC to enhance its selectivity and molecular weight cutoff. BC membranes were used to provide a porous network, where graphene oxide (GO) could be incorporated. The resulting BC-GO com- posites showed both advance properties, water stabil- ity, good

> 7**mechanical strength, and selective ion permeation** up **to the angstrom scale** coming from **the**

GO component. These advantages make the BC-GO composite a promising material for the water purifica- tion and pharmaceutical industries [128]. Palladium NPs included in BC-GO composites led to outstanding effi- ciency in wastewater filtration of organic dyes, eliminat- ing

> 10**up to 99.3% of methylene orange dye and other contaminants, such as methylene blue or 4-nitrophenol**

[129]. Furthermore, a BC-

> 10**CS composite has** also been **proven to be useful**

for

> 2**heavy metal** removal **from water**, reaching **up to 50% removal of copper from**

50 mg L?1 suspensions [80]. Electrical and sensor applications BC can also be modified and applied for electrical appli- cations. Functionalized BC with silicon NPs and polyani- line produced a conductive BC network that was able to maintain its flexibility and other physical properties. The resulting material could serve as a promising anode material for Li-ion batteries [130]. BC has also been used as a template to synthesize cobalt ferrite nano- tubes that could be used as nanowires for many elec- tronics [65]. Furthermore, BC has recently been modified into a piezoelectric material, which is extensively used in dif- ferent engineering applications [81]. Moreover, biomed- ical engineering and electronics are areas where its BC properties such as flexibility, high porosity, high mech- anical strength, printability, and biocompatibility are all highly valuable. Therefore, BC is can be considered as a promising material for sensor applications. Morales- Narvaez et al. [69] designed metal-NPs nano papers and photoluminescent nano paper with an optic sensitivity capacity in addition to being advantageous for small volume analysis. More recently, a BC nano paper optical sensor array has been developed for heavy metal sens- ing [82]. The same group researchers also designed a nano paper ratiometric sensor for biothiol detection, a group of significant molecules from several medical diagnostics applications [131]. Other BC electronic applications includes surface- enhance Raman spectroscopy (SERS), an analysis method increasingly used for its broad spectrum of analyte detection and low detection limits. BC, with Au and Ag NPs has been proven to display SERS enhance- ment [132,133]. Energy production Sustainable development has continued to be estab-

lished for environment protection. Systems metabolic engineers continue their attempts to integrate biomass in the development of sustainable biobased systems for the production of bioethanol [134,135]. BC has a remarkable potency to fulfill this purpose. The cellulose pellicle produced by BC can be an alternative renew- able and inexpensive source of sugar for sustainable fermentation into bioethanol. Furthermore, because lig- nin and hemicellulose do not exist in BC, the pretreat- ment step in industrial processes can be eliminated in order to reduce production costs. The main limitation for this application is the cost of the growth media required to grow the bacteria. One method suggested by the engineer to cover this limita- tion is by using industrial wastes as growth media. As has been reported by Tsouko et al. that a high concen- tration of BC can be cultivated from waste streams of oilseed based biodiesel plants that contain the K. sucro- fermentans (DSM 15973) strain [40].

2**Other applications The** diverse properties **of BC make it** a suitable **material for** many **other applications**

apart from the ones dis- cussed above. In cosmetics, BC facial masks are a trend, and silk sericin BC has been assessed for enhanced facial treatment (113). Caffeine release from BC has also been studied as a method for cellulite treatment [136]. The paper manufacturing industry also evaluates BC as an additive for high-quality paper sheets that have improved as a tensile index or tear index with reduced porosity and elongation, characteristics that are cur- rently in demand in the marketplace [137–139]. BC aerogel with ultra-lightweight and a high porosity can be a promising material for many biomedical appli- cations. As studied by Pircher et al. BC aerogel can be obtained using a supercritical carbon dioxide Table 3. Summary of BC applications in the past 5 years. Type Description Reference Pharmaceutical application Wound dressing Water holding capacity, biocompatibility, and mechanical properties make BC an [29,31–33] adequate material for wound healing on its own or enhanced with charged molecules. Antimicrobial activity After functionalization with antimicrobial molecules or mixed with other ingredients [29,34–39, 82, 131] in composites can be an infection preventive material. Drug delivery Water holding capacity and drug adsorption capacity, with controlled release profiles, [42–47] arising BC as a potential platform of drug delivery. Tissue regeneration BC is a good scaffold material, improved by further physical or chemical modification, [48–53,55] having

8**been used as a** scaffold **for different** cell **types** in vitro **growth**

. Vascular Grafts Water holding capacity, elasticity, biocompatibility or low inflammatory, makes BC a [57,58] suitable material for artificial blood vessels. Food applications Emulsion stabilizer BC NPs act as an oil-in-water emulsion stabilizer. [62] Gastric conditions BC fibers prevent constipation. [60,61] Immobilization platform Enzyme immobilization After chemical modification for binding or by encapsulation, BC can be used for [66,67,69–73] enzyme immobilization. Filtration Filtration BC can be used as a matrix for coating with other carbon-based or metal materials [74–76] for specific components and high-efficiency contaminants removal. Electrical applications Conductive material After functionalizing with metal NPs or other polymers, it can become a conductive [77,78] material for nanowires or batteries application. Sensors BC nano paper can be used as a sensor platform for chemicals o bioreactions. [21,86,87] SERS BC functionalized with NPs displays good characteristics as a platform for SERS [83,84] spectroscopy. Energy production Bioethanol BC use as an alternative to lignocellulose from plants. BC lacks in hemicellulose and [135] lignin so that acid-catalyzed hydrolysis step in bioethanol production can be eliminated. Other applications Cosmetics BC facial masks are moisturizing, and functionalized BC can address specific [41,113] cosmetic problems. Paper manufacturing BC as an additive increases material strength. [88,89] Aerogels BC as the primary polymer, composited with other biocompatible polymers. [140] anti-solvent precipitation method. Various biocompat- ible polymers also (such as polylactic acid, cellulose acetate, etc.) can be incorporated to form a composite BC aerogel [140]. The same BC structure such as plant cellulose enables it as a promising

feedstock for chem- ical production, such as carboxylic acids. Conversion of cellulose into acetic acid and malic acid, by using palla- dium catalyst, has been reported [141]. By using similar treatments and a reaction for plant cellulose, BC may be used as an alternative cellulose biomass for the pro- duction of various chemicals. Applications of BC have been summarized in Table 3. Conclusions The application field of BC has undergone rapid pro- gress. Initially, BC was widely applied for both food and beverages, but now it has been applied to various aspects of biotechnology. This rapid progress is sup- ported by the development of metabolic engineering that triggers various BC modification techniques. Changes in BC properties allow broader applications including network engineering, biomedical material, paper, electronic, membrane filtration manufacturing, and bioenergy. The large scale production of BC is a challenging issue when discussing its implementation on an indus- trial scale. Designs for new bioreactors and/or the modi- fication of available bioreactors have been conducted prior in increasing the production yield of BC. There are many available modification techniques that can be applied for the design of a suitable bioreactor used in BC production and application. Different supporting materials can also be employed in the bioreactor before designing a specific BC configuration or structure. In conclusion, a strategic move to enable continuous production of BC is crucial before meeting the increas- ing demand for BC. Bioreactor engineering and modifi- cation of specific growth nutrients in BC production are essential strategies to produce BC on an industrial scale without modifying the natural characteristics of BC. Furthermore, genetic engineering is a crucial technique to modify the molecular level of the BC strain prior to the ability to produce a high yield of BC. Modifications on physical or structural properties of BC allow the con- version of BC into other functional materials for a var- iety of suitable applications. Disclosure statement The authors declare that they do not have any conflict of interest. Funding This project was supported by the Ministry of Science and Technology, Taiwan [MOST 106-2628-E-002-009-MY3]. ORCID Suryadi Ismadji http://orcid.org/0000-0002-5005-2824 Kuan-Chen Cheng http://orcid.org/0000-0003-0387-7804 References Rangaswamy BE, Vanitha KP, Hungund BS. Microbial cellulose production from bacteria isolated from rot- ten fruit. Int J Polym Sci. 2015;2015:1–8. [2] Kumbhar JV, Rajwade JM, Paknikar KM. Fruit peels support higher yield and superior quality bacterial cellulose production. Appl Microbiol Biotechnol. 2015;99(16):6677–6691. [3] Aydin YA, Aksoy ND. 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