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REVIEW ARTICLE

Opportunities of Bacterial Cellulose to Treat Epithelial Tissues

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Abstract: In this mini-review, we highlight the potential of the biopolymer bacterial cellulose to treat damaged epithelial tissues. Epithelial tissues are cell sheets that delimitate both the external body surfaces and the internal cavities and organs. Epithelia serve as physical protection to underlying organs, regulate the diffusion of molecules and ions, secrete substances and filtrate body fluids, among other vital functions. Because of their continuous exposure to environmental stressors, damage to epithelial tissues is highly prevalent. Here, we first compare the properties of bacterial cellulose to the current gold standard, collagen, and then we examine the use of bacterial cellulose patches to heal specific epithelial tissues; the outer skin, the ocular surface, the oral mucosa and other epithelial surfaces. Special emphasis is made on the dermis since, to date, this is the most widespread medical use of bacterial cellulose. It is important to note that some epithelial tissues represent only the outermost layer of more complex structures such as the skin or the cornea. In these situations, depending on the penetration of the lesion, bacterial cellulose might also be involved in the regeneration of, for instance, inner connective tissue.

Keywords: Biomaterials, bacterial cellulose, epithelial tissues, wound dressing, cell carrier, drug delivery, epithelial regeneration.

1. INTRODUCTION

Epithelial tissues are, essentially, continuous cell sheets that delimitate both the external body surfaces and the internal cavities. Epithelia have a reduced content of extracellular matrix and exhibit strong cell-to-cell adhesions known as tight junctions. Epithelial tissues are not vascularized and receive support from the underlying basement membrane formed by connective tissue. Examples of epithelial tissues are the external linings of the skin, cornea and mouth but also those from the hollow internal organs such as lungs, digestive system, urogenital conducts and spinal cord. Depending on its location in the body, epithelia can be found as single (*e.g.*, intestines, lungs) or multiple cell layers (*e.g.*, skin, cornea, esophagus). The glandular epithelium that surrounds the glands in our body is a highly specialized epithelium that will not be addressed here. In this manuscript, we have used "epithelial tissue" as an umbrella term to refer to diverse body surfaces and barriers.

Epithelial structures physically protect the underlying tissues, regulate the diffusion of molecules and ions, secrete substances and filtrate body fluids among other vital functions. Because of their surface location, epithelia are constantly exposed to environmental stressors ranging from infections caused by microorganisms and mechanical injuries to the exposure to toxic chemicals. Moreover, epithelial tissues are also greatly affected by inflammatory diseases and cancers. Despite the extraordinary regenerative capacity of epithelial tissues, they can be overwhelmed by large-area injuries, surgical scissions, burns or ulcers which might result in chronic lesions [1]. Additionally, diabetes, infectious processes, systemic and chronic treatments or other pathological conditions can make epithelial regeneration less efficient [2]. In these specific cases, the use of biomaterials to assist the regeneration of sensitive epithelia becomes vital.

Biomaterials represent a core element of regenerative therapies and are used in multiple ways to treat epithelial defects. Biomaterials are designed to interface with biological systems to evaluate, treat, increase or replace tissues, organs or functions in the body (European Society for Biomaterials, 2nd Consensus Conference on Definition, 1991). The palette of available biomaterials is extensive being polymers, ceramics and metals the main categories. Ceramics and metals are indicated for bioengineering load-bearing structures and are out of the focus of this minireview. Polymeric biomaterials are often classified into synthetic and natural polymers according to its origin. Because of its superior biocompatibility and bioactivity, naturally-occurring polymers (*e.g.*, collagen, fibrin, chitosan, keratin, silk, alginate, cellulose) are frequently used for repairing epithelial tissues. Biomaterials based on natural polymers can serve as transitory

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treatments like wound coverages [3], temporary skin substitutes [4], carriers for cell therapy [5, 6] and drug delivery platforms [7, 8] as well as long-term replacements for damaged epithelial tissues [9, 10].

Despite the broad spectrum of natural polymers and natural-natural [11] or natural-synthetic [12] composites that are being investigated for epithelial regeneration, currently, the main clinical procedures rely on collagen-based solutions [13]. Collagen is a fibrous structural protein that forms triple helix assemblies; it is a major constituent of the extracellular matrix and inherently bioactive and biocompatible. It is therefore understandable that collagen has long been considered the gold standard to repair organs and tissues (skin, cornea, oral mucosa *etc*.) exposed to the environment. Collagen is primarily obtained from livestock sources like cow, pig, rat and more recently also from fish [14] and typically needs extensive manipulation prior to attaining the final product. One of the main drawbacks of animal collagen is its moderate immunogenicity [15] and its high batch-to-batch variability. On the other hand, religious constraints against animal derived medical products also have played a role [16]. Recombinant collagen from bacteria or plants [17] can help to overcome these issues but the production is still far from meeting the worldwide increasing collagen demand [18]. Last but not least, the mechanical properties and degradation kinetics of collagen do not always meet clinical requirements. Thus, novel biomaterials able to fulfill the enormous diversity of conditions and patients' needs are required.

Third generation natural biomaterials are expected to be biocompatible as well as to foster the regeneration of damaged tissues. To achieve this, researchers are screening not only alternative biopolymers [19] but also novel architectures of already well-known natural materials [20]. In line with this, nanostructured biomaterials, typically in the form of nanofibrous hydrogels, have recently attracted much attention [21-23]. Nanostructuration can endow biomaterials with high surface area to volume ratios, enhanced cell attachment and proliferation; mechanical stability and adequate porosity [24]. Such nanostructured substrates can be fabricated for instance by electrospinning [25]. Electrospinning has already allowed forming gelatin and gelatin-alginate nanofibers with improved mechanical properties compared to unstructured hydrogels [26]. Silk fibroin electrospun nanomatrices showed reduced inflammation and faster re-epithelization in a rat burn model compared to conventional treatments [27]. These authors partially ascribed the over-performance of the nanostructured wound dressing to the nanoscale dimensions of the fibers that accurately mimic the properties of soft tissues and retain certain amounts of liquid.

A lesser explored family of natural biopolymers with potential applicability in epithelial regeneration are nanocelluloses [28]. The term "nanocellulose" refers to cellulose-based materials with at least one dimension in the nanoscale. Nanocelluloses can be subdivided into bacterial cellulose (BC), cellulose nanofibrils (CNF) and cellulose nanocrystals (CNC). CNF and CNC are commonly obtained from plant/wood cellulose after mechanical and/or chemical treatments while BC is biotechnologically produced by microorganisms using different carbon sources [29]. The three types of nanocellulose have been proposed for a diversity of medical and/or pharmaceutical applications. Regarding plant-derived nanocellulose hydrogels, recent encouraging applications include renewable and xeno-free wound dressings for skin graft donor sites [30] as well as controlled drug release platforms for both low and high molecular weight substances [31]. As an alternative to CNC and CNF, cellulose produced by microorganisms is emerging as a promising natural source of ready-to-use nanocellulose for medical and pharmaceutical applications.

2. BACTERIAL CELLULOSE

BC is produced extracellularly by Gram-negative bacterial cultures such as Gluconacetobacter, Acetobacter, Agrobacterium, Achromobacter, Aerobacter, Sarcina, Azobacter, Rhizobium, Pseudomonas, Salmonella and Alcaligenes. Among them, the most efficient BC producer belongs to the *Komagataeibacter genus*, specifically called *Komagataeibacter xylinus* (*K. xylinus*) [32, 33]. The observation that *Acetobacter xylinus* produces a gelatinous mass on liquid/air interfaces has been known since 1886 by the work of A.J. Brown [34]. This gelatinous mass was later identified as BC. The bacterium uses the nanofibrous film to protect itself from environmental stresses such as dehydration, nutrient deficiency and UV radiation. In addition, the BC allows the bacteria to float and to remain at the interface between medium and air thus increasing oxygen supply.

BC can conveniently be produced in laboratories following the process summarized in (Fig. **1**). The bio-synthesis starts with the inoculation of a culture medium with a BC-producing bacteria strain (Fig. **1A**). A typical culture medium contains the following compounds: 2% (w/v) glucose, 0.5% (w/v) yeast extract, 0.5% (w/v) peptone, 0.3% (w/v) sodium hydrogen phosphate and 0.1% (w/v) citric acid (Hestrin-Schramm (HS) culture medium) [35]. At molecular level, the biosynthesis of BC in the microorganism can be divided into four sub steps (Fig. **1B**). First, phosphorylation of glucose by a glucokinase occurs (a) in the nucleus, followed by isomerization of glucose-6-phosphate to glucose-1-phosphate (b). Finally, it reacts with UDPG-pyrophosphorylase to form uranyl diphosphate-glucose (UDPG) (c), followed by the synthesis of BC by a cellulose synthase (d). The last step in the cytoplasm is a chain growth at the reduced end of the β-1,4-glucan chains by UDPG to form cellulose fibers [36].

In the extracellular space, the unassembled cellulose chains aggregate into fibrils. These fibrils usually consist of 10-15 fibers, have an approximate width of 15 nm and form microfibrils, which are arranged in cellulose bands with a width of approximately 80 nm [37]. This mechanism explains the three-dimensional cross-linked BC microstructure depicted in (Fig. **1D**). The structure of the cellulose network can be affected by variation of bacteria strain, culture medium, pH value, temperature and mechanical stresses. With static cultivation, BC in form of fleeces or thin films is obtained, whereas agitated cultivation results in irregular aggregated, fibrous structures or spheroidal particles (Fig. **1C**) [38].

The as-synthetized BC membranes exhibit unique properties proving its adequacy for epithelial regeneration pur-

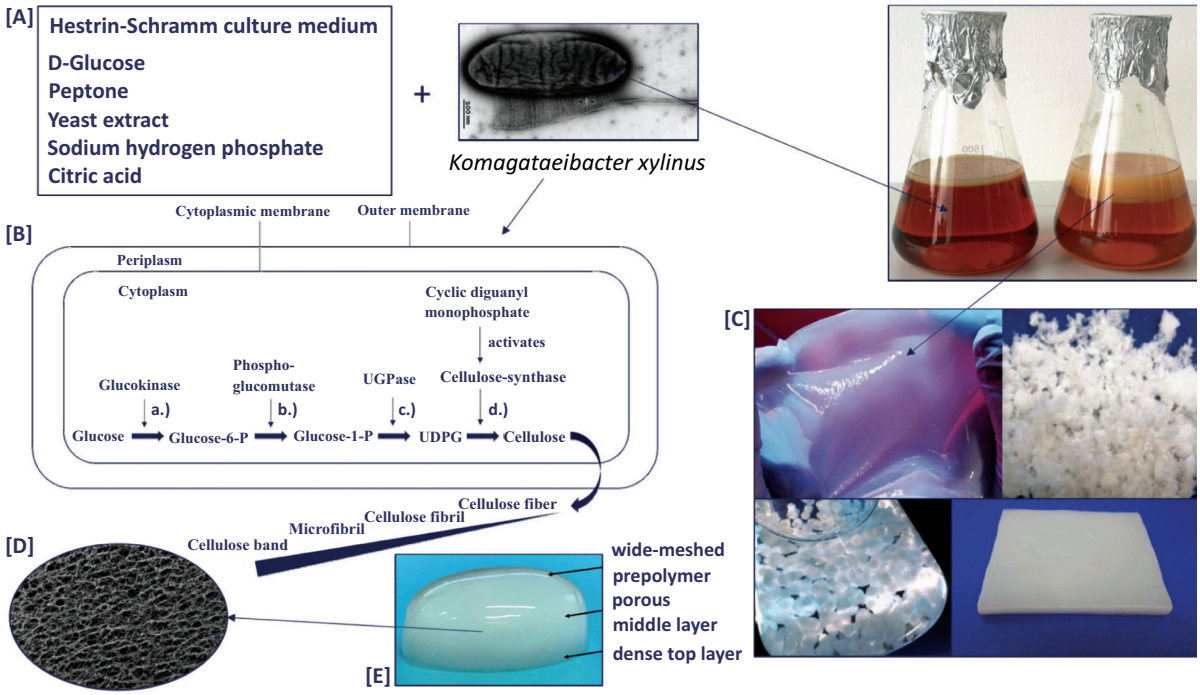


Fig. (1). Schematic representation of the basic BC generation process steps. (**A**) Formation process of BC fleece during cultivation of *K. xylinus* in HS medium in Erlenmeyer flasks. (**B**) Metabolic pathway of cellulose formation. (**C**) BC produced in different shapes. (**D**) Scanning electron microscopy (SEM) picture of BC porous middle layer depicting its three-dimensional fiber network. (**E**) Layered structure of a BC pellicle. (*The color version of the figure is available in the electronic copy of the article*).

poses such a high degree of polymerization (4,000 - 10,000) [28] and crystallization (up to 90%) [39]. For medical applications, the high mechanical stability, the lack of immunogenicity and the high purity are of particular relevance [38, 40]. The biocompatibility of BC cannot solely be attributed to the high purity of the material but also to its similar organization of the fibers as in native collagen [41]. Despite the identical chemical structure of BC and plant-based cellulose [42], BC clearly defines itself by its structure and material properties. The three-dimensional interwoven network of BC is characterized by a high surface area of 35 – 40 m^2/g (measured in freeze-dried form) [43, 44] and a water content of about 99% [45]. The latter characteristic is the reason why BC is also called a "hydropolymer" or "hydrogel" [39]. Moreover, BC exhibits high temperature stability which allows temperature sterilization processes [46].

Last but not least, the attractiveness of this innovative biofabricated material has further increased due to its animal and human-free origin [47]. Its biosynthesis opens up the opportunity to develop biotechnological production to significantly influence and control the final BC shape and material features. Shapes, especially designed to come into contact with epithelial tissue, range from thin foils and fleeces used as covering, patch or dressing, tubes for artificial blood vessels [48] to preformed structures for implantation (*e.g.*, artificial meniscus [46] and ear cartilage replacement [49]). In recent years, enormous progress in BC cultivation techniques has been made to provide tailored-made and high-quality BC based materials. In parallel, the possibility to scale up BC production may broaden BC applicability in the near future [28].

To facilitate contextualization, a comparison between the hallmarks of BC and collagen, can be found in Table **1**.

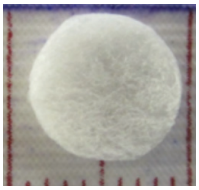
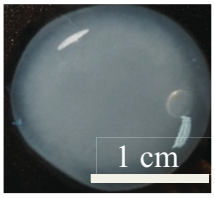
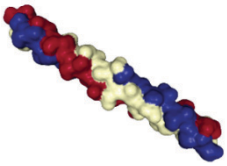
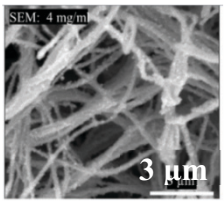
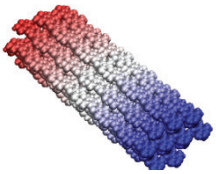
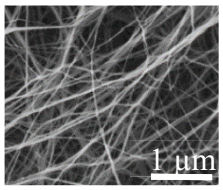
3. APPLICATIONS OF BC IN EPITHELIAL REGENERATION

In this section, several applications of BC in epithelial regeneration are summarized. Special emphasis is made on dermal treatments since, to date, this is the most widespread medical use of BC. Afterward, less studied applications of BC in epithelial regeneration identified as the most promising current research directions are compiled.

3.1. Dermal Applications

Skin is the largest and outermost human organ and covers the entire external body surface. Therefore, above all, the skin's primary function is to protect the underlying muscles, bones, ligaments and internal organs from external biological and chemical agents as well as physical influences [70, 71]. Furthermore, skin is also involved in sensation, temperature regulation, immunological surveillance, prevention of dehydration and synthesis of vitamin D3 [72]. The large epithelium of the skin, which is responsible for the barrier function against infection and waterproofing, is called epidermis. This outermost layer of the skin is a stratified squamous epithelium, composed of proliferating basal and differentiated suprabasal keratinocytes. The epidermis contains no blood vessels, and cells in the deepest layers are nourished by diffusion from blood capillaries extending to the upper layers of the dermis [73]. The integrity of this organ can be affected by cuts, burns, ulcers, surgical incisions or illnesses,

Table 1. Comparison between collagen (as a benchmark material) and bacterial cellulose regarding relevant properties of biomaterials for epithelial regeneration.

Property	Collagen	Bacterial Cellulose
Macrostructure	Sponges, hydrogels Image: Collagen sponge from: [50] 	Hydrogels, aerogels or films mainly with planar forms [51] 
Micro/nano structure	Triple helix protein fibers organized in 3D a network. SEM image of collagen image from [52]  	3D network of pure cellulose nanofibers  
Building blocks	Amino acids, mainly glycine, proline and hydroxyproline	β-1,4-linked D-glucose units
Origin	Mainly, livestock animals (cow, pig). Also plants [53] and fish [14]	Bacterial cultures, mainly *Komagataeibacter xylinus* strains
Purity	Variable	Very high
Fiber cross-section	≈ 100 nm [54]	20-100 nm [28]
Fiber length	≈ 1 µm [54]	> 1 µm, hard to determine precisely
Interwoven fibers	Yes	Yes
Degree of polymerization	> 1400	4,000-10,000 [28]
Molecular weight	High	High
Options for structuration	Fiber alignment [55, 56] Sacrificial templates [57]	Fiber alignment [58] Templates during biosynthesis [59]
Fiber Crystallinity	Non consensus	High (≈ up to 90% [60]), mix between Iα and Iβ cellulose structures
Porosity	Very variable depending on collagen source and fabrication method 35-99% [50, 61, 62]	Very variable depending on the drying method and posterior treatments 60% -95 % [51, 61, 63]
Pore type and size	Interconnected pores with variable size: 26 [61] - 200 µm (SpongeCol®)	Multi-size Native BC ≈5 µm. Can be modified with porogens (40 µm in [64]) and by *in situ* modifications [65]
Water content	98% [50]	99%

(Table 1) contd….

Property	Collagen	Bacterial Cellulose
Temperature stability	200 ºC [66]	Up to 300 ºC
Biodegradability	High, ≈ 1 month *in vitro* [62]	Low/none in the body, biodegradable by cellulases
Biocompatibility	High	High
Immunogenicity	Low/moderate	Low
Bioactivity	High, supports cell attachment and proliferation	Tunable Moderate as-synthetized, increases after modification [63, 67, 68]
Mechanical stability	Very variable: low in native collagen [13], increases after crosslinking [5]	High in general. Reported to be higher than collagen [61], to be improved after surface modification [69] and to recapitulate native cartilage [49]
Price	Variable, high for pure forms	Variable, depends on area of application
Commercial availability/scalability	High	High in the food form *nata de coco* (500-1500 tons per year per producer) and cosmetics but still low for high quality/purity (medical-pharmaceutical grade)

such as diabetes [74]. When the skin integrity is compromised, its structure and functions must be re-established as soon as possible to recover tissue homeostasis. To accomplish that, the wound healing process should begin almost immediately after a skin injury occurs, in order to avoid bacterial infection and dehydration [75, 76]. Due to the properties described above, BC is a promising biomaterial for healing skin injuries. In fact, BC has already been used as a natural polymeric wound care material since the 80s [77, 78]. BC meets many of the requirements of an ideal wound dressing: it acts as a physical barrier against bacterial infections, allows gas exchange, absorbs exudates, keeps a moist environment that enhances reepithelization, and is easy to remove without pain. [79, 80] Furthermore, BC is non-toxic and non-allergenic as described [36].

Today, several types of BC based wound dressings provided by different companies are on the market. The first BC-based medical product on the market was Biofill®, a thin BC film with a water content of 8.5% used as temporary skin substitute and biological wound dressing. It has been successfully applied for the treatment of several skin injuries such as basal cell carcinoma, severe burns, dermabrasions, chronic ulcers as well as at donor and receptor sites in skin grafts. Among other benefits, immediate pain relief, close adhesion to the wound bed, spontaneous detachment following reepithelization and reduced treatment times as well as costs have been reported for this product. The only flaw discussed in some reports was the limited elasticity, when applied in areas of great mobility [77]. Along with the rising trend for modern moist wound management, clinical investigations of wet, never-dried BC for both, chronic wounds and burns, followed [81, 82]. Moist BC-based dressings such as XCell® were described as more effective than conventional wound dressing materials in promoting autolytic debridement, accelerating granulation and simultaneously donating and absorbing moisture from the wound [82].

Some recent studies on dermal BC applications focused on the understanding of the accelerated healing observed for both, dry and wet BC wound dressings, and thus contributed to a better understanding of the effects. Kwak and colleagues [83] performed an *in vivo* study on rats and reported on distinct improvements in thickness of both, epidermis and dermis, as well as the number of blood vessels and an inhibition of the infiltration of mast cells at indicated time points in case of BC treated burns compared to gauze. The authors hypothesized that BC may accelerate the process of wound healing in burn injuries through regulation of angiogenesis and connective tissue formation.

Li and colleagues [84] evaluated the effect of the structure of BC on full-thickness skin wound repair. The hierarchical structure of BC films and their different effects on skin wound healing were studied both *in vitro* (in a wound healing model placed on a microfluidic chip) and *in vivo* (Wistar rats). The results indicated clear benefits of BC in the healing of full-thickness wounds compared to gauze in terms of inflammatory reaction and healing time. The *in vivo* and *ex vivo* experiments on rats also demonstrated a certain difference in performance of both sides of the BC pellicle. The bottom side of the BC film promoted blood vessel regeneration and collagen production of the wounds more than the top side. The authors argued that a looser BC network also promotes cell migration and proliferation and suggested heterogeneous BC-based biomaterials for complex tissue engineering. However, they did not investigate yet, whether a higher porosity and surface roughness may compromise the easy and pain-free detachment after reepithelization reported for BC wound dressings.

Cavalcanti *et al.* recently published the outcome of a randomized and controlled trial investigating the efficacy of perforated dry BC membranes for the treatment of lower limbs chronic varicose ulcers [79]. In the BC group, ulcers were more superficial at the end of the observation period (120 days) in more than 80% of the patients (*versus* 60% in the control group treated with triglyceride oil and gauze). The authors suggested that BC dressings could act as an inducer of tissue remodeling, stimulating the granulation process. They stressed the fact that the ulcer healing depends not only on the epidermal proliferation at the margins of the

lesion but also on the growth of the granulation tissue from the central area.

Several modifications allow to further increase the functionality of BC as wound care device while keeping the essential BC properties of biocompatibility and nanofibrillar structuration. Modifications of the cellulose can be obtained during the biofabrication process (*in situ*) *e.g.* using additives and by *post*-modification such as drying, chemical functionalization or loading of the BC network with active ingredients. An excellent overview of BC in various modifications developed for wound healing applications can be found by Sulaeva *et al.* [33]. However, some recent findings are highlighted in (Table **2**) and discussed below.

3.1.1. Material Modifications

Modifications of the BC such as control the water content, surface topography and nanocomposites have been applied to improve wound healing. Rebelo *et al.* recently investigated the effects of varying water content on BC material properties. They demonstrated that the dehydration effects on BCs viscoelastic and electrochemical properties. Lower water contents as 80% and 50% caused increased stiffness and BC resistance to electron transfer became higher with lower electron capacity [96]. Those findings have implications for BC wound dressings with different moisture content. They may range from practical aspects such as handling and draping of the dressing to electrolyte exchange through the dressing. However, this should be investigated in further studies. Another group focused on modifications of the surface topography of BC dressings in order to improve wound healing. Bottan and colleagues introduced a new approach called guided assembly-based biolithography (GAB) technology [85]. They developed PDMS molds with different surface patterns allowing a controlled *in situ* modification of the BC surface topography. The structured surface was shown to influence migratory patterns and alignment of human dermal fibroblasts and keratinocytes. A full-thickness wound model tested on mice confirmed the promotion of fibroblast infiltration and new collagen deposition in the wound bed by the modified dressing compared to flat BC.

3.1.2. Combination of BC with Other Biomaterials

In many studies, BC has been combined with other biomaterials known for their beneficial effects on wound healing. To give an example, Moraes and colleagues [97] investigated a self-prepared wound gel made from disintegrated bacterial cellulose and collagen type I (BC/COL). In an animal study, healing of surgical skin wounds in rat dorsum with BC/COL gel was compared with those from animals treated with commercial collagenase ointment and an untreated group. BC/COL hydrogel was found to be more efficient than the collagenase ointment. Wound closure and fully repaired epithelium and dermis with organized collagen fibers and tissue rich in blood vessels were observed at day 15. At the same time, the dermis was thinner in case of the collagenase ointment treatment and still under repair with the presence of numerous inflammatory cells for the untreated group. Especially, the adhesion of the hydrogel on the wound bed was found to be advantageous for the treatment.

Other groups reported the combination of BC with silk-sericin [98], chitosan [99] and dextrane [100]. Silk-sericin was selected due to its cytoprotective and mitogenic effects, whereas chitosan and dextrane were selected based on their antibacterial efficiency and positive effects on fibroblast cell proliferation, respectively. In all cases, positive effects of the combination compared to native BC were reported.

H. Wu *et al.* used bacterial cellulose nanocrystals (BCNCs) to reinforce regenerated chitin (RC) fibers to form BCNC/RC filaments for surgical sutures. Mechanical measurements demonstrated that the strength of the BCNC/RC filament increased dramatically over the RC analogue. A yarn made of 30 BCNC-loaded fibers also achieved satisfactory mechanical performance, with a knot-pull tensile strength of 9.8 ± 0.6 N compared to 6.8 ± 0.6 N of RC yarn without BCNC. While obtaining biocompatibility of the surgical suture, enzymatic degradation rate can be tuned by varying the concentration of BCNCs in the yarn. It has been proven that BCNC/RC promotes cell proliferation (*in vivo*) murine skin wound closure experiments, without any adverse effects. The combination of strength-enhanced fiber and promising *in vivo* experiments qualify BCNC/RC to be a new candidate for application as BC-based medical suture [86].

3.1.3. Drug-delivery Systems

Furthermore, an increasing number of studies report on drug delivery systems based on BC for dermal applications [47]. To avoid the risk of bacterial infections, *e.g.* Amoxicillin loaded BC sponges were examined [101]. The functionalized sponges displayed good porosity and swelling, which are beneficial for absorbing wound exudates. Moreover, a wound infection model proved enhanced wound healing ability *in vivo*. In another study, antimicrobial peptides such as ε-poly-L-Lysine (ε-PLL) were investigated [94]. This peptide is a non-toxic biopolymer with broad-spectrum antimicrobial activity. Fürsatz *et al.* cross-linked low molecular weight ε-PLL in pristine BC membranes and to carboxymethyl cellulose functionalized BC using carbodiimide chemistry. The functionalization of BC with ε-PLL inhibited growth of *S. epidermidis* on the membranes but did not affect the cytocompatibility to cultured human fibroblasts as compared to native BC. The functionalization had no significant effects neither on the nanofibrous structure nor on the mechanical properties of the BC. Furthermore, there are recently published studies taking advantage of some classical approaches in cellulose chemistry applied to BC. *e.g.* Wu *et al.* used the 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) oxidation to obtain superficially oxidized bacterial cellulose pellicles (TOBCP) and subsequently loaded them with silver nanoparticles (TOBCP/AgNP) [87]. Through this modification, they established antimicrobial activity by a silver ion release with a rate of 12.2% per day at 37 °C in three days while retaining the biocompatibility of TOBCP.

Following the same purpose, other groups reported about the incorporation of zinc oxide nanoparticles into BC. The nanocomposites exhibited high antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Citrobacter freundii*. In a burn wound model, animals treated with the BC/ZnO nanocomposite further showed a significant healing of 66% after 15 days related to day 0 compared to BC, which showed a healing of 50.5%

Table 2. Modifications of BC and properties resulting from the modifications.

Material	Title of Paper	Results Obtained by BC Modification
BC with structured topography [85]	Surface-structured bacterial cellulose with Guided Assembly-Based Biolithography (GAB)	Improved cell alignment Promotion of fibroblast infiltration and new collagen deposition in the wound bed
BCNC/RC [86]	Regenerated chitin fibers reinforced with bacterial cellulose nanocrystals as suture biomaterials	Biocompatible surgical sutures increasing strength of BCNC/RC filaments Enzymatic degradation possible Degradation rate can be tuned by varying concentration of BCNCs in the yarn Chitin can promote cell proliferation (*in vivo*)
TOBCP/AgNP [87]	TEMPO-Oxidized Bacterial Cellulose Pellicle with Silver Nanoparticles for Wound Dressing	Antimicrobial activity Ag^{+} release with a rate of 12,2%/day at 37°C in 3 days Biocompatible wound dressing
BC/ZnO [88]	Bacterial cellulose-zinc oxide nanocomposites as a novel dressing system for burn wounds	Antimicrobial activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Citrobacter freundii* Significant healing of 66% after 15 days related to day 0
BC/TiO_2 [89]	Bacterial cellulose-TiO_2 nanocomposites promote healing and tissue regeneration in burn mice model	Antimicrobial activity against *Escherichia coli* (81.0 ± 0.4%) and *Staphylococcus aureus* (83.0 ± 0%)
BC/SMN-Zein [90]	Drug release and antioxidant/antibacterial activities of silymarin-zein nanoparticle/Bacterial cellulose nanofiber composite films	Flavonoid silymarin (SMN) and zein loading through nanoparticle adsorbing onto BC nanofibers Change of wettability and swelling Antioxidant and antibacterial activity air-dried SMN-Zein/BC nanocomposite slow down the lipid oxidation
BC/Octenidin [91]	Controlled extended octenidine release from a bacterial nanocellulose/Poloxamer hybrid system	Long term controlled release of octenidine up to one-week improved mechanical and antimicrobial properties. Ready-to-use system with Poloxamer loaded BC for advanced treatment of infected wounds Toxicity test performed with shell-less hen's egg model
BC/CMC/MTX [92]	Effect of *in situ* modification of bacterial cellulose with carboxy-methylcellulose on its nano/microstructure and methotrexate release properties	Impact of DS-CMC on methotrexate loading Topical treatment of psoriasis Decrease of the elastic modulus as the DS of CMC increased
BC/PHEMA [93]	Embedding of Bacterial Cellulose Nanofibers within PHEMA Hydrogel Matrices: Tunable Stiffness Composites with Potential for Biomedical Applications	New modification: *in situ* UV radical polymerization of HEMA monomer impregnated into wet BC nanofibrous structure Significant improvement in mechanical properties Tensile strength increased Non toxic rMSCs (rat mesenchymal stem cells) proliferation tissue replacement and wound healing
BC/ ε-poly-L-Lysine [94]	Functionalization of bacterial cellulose wound dressings with the antimicrobial peptide ε -poly-L-Lysine	Antimicrobial activity (broad-spectrum) without affecting the beneficial structural and mechanical properties Modification with non-toxic biopolymer ε-PLL inhibited growth of *S. epidermidis* on the membranes but did not affect the cytocompatibility to cultured human fibroblast

(Table 2) contd….

Material	Title of Paper	Results Obtained by BC Modification
BC/PVA [95]	Preparation and *in vitro* characterization of BC/PVA hydrogel composite for its potential use as artificial cornea biomaterial	Higher visible light transmittance than plain BC
BC/HA [60]	Bacterial cellulose/hyaluronic acid composite hydrogels with improved viscoelastic properties and good thermodynamic stability	Higher visible light transmittance than plain BC
ABC/urinary bladder matrix [67]	Acetylated bacterial cellulose coated with urinary bladder matrix as a substrate for retinal pigment epithelium	Higher adhesion and proliferation of retinal pigment epithelium cells than uncoated BC Closer recapitulation of the *in vivo* cell phenotype than uncoated BC
BC/varying porosity [64]	Bacterial cellulose-based biomimetic nanofibrous scaffold with muscle cells for hollow organ tissue engineering	Higher pore size than native BC to allow muscle cell ingrowth Higher porosity Small decrease in mechanical strength

after the same treatment [88]. The incorporation of titanium dioxide nanoparticles (TiO_2) in BC has also given encouraging results [89]. Khalid *et al.* depicted *in vivo* burn wound healing potential of BC and TiO_2 nanocomposites (BC/TiO_2). Antimicrobial activity of the nanocomposite was against *Escherichia coli* ($81.0 \pm 0.4\%$) and *Staphylococcus aureus* ($83.0 \pm 0.0\%$) was confirmed through agar disc diffusion protocol.

The combination of BC with natural substances or natural derived Active Pharmaceutical Ingredients (APIs) is becoming more and more notable. Tsai *et al.* investigated a composite film with silymarin-zein nanoparticles and BC nanofibers. They applied adsorption of flavonoid silymarin (SMN) and zein nanoparticles to load them onto the fibers for improving higher antioxidant and antibacterial activity. The authors could also show that air-dried SMN-Zein/BC nanocomposites slowed down lipid oxidation [90].

Lima Fontes *et al.* have shown the effect of CMC *in situ*-modifications on BC nano/microstructure and methotrexate (MTX) release properties. The degree of substitution of CMC (DS-CMC) has a massive impact on API loading; since carboxymethylcellulose (CMC) is a well-known candidate to change *e.g.* pore-sizes of the three-dimensional network of BC. For topical skin application, MTX is used as disease-modifying anti-rheumatic drug for *e.g.* treatment of psoriasis. However, besides the impact of loading capacity, increasing DS-CMC causes a decrease of the elastic modulus of BC [92].

Remarkable is also the new *in situ*-modification by UV radical polymerization of HEMA monomer impregnated into wet BC nanofibers. The combination of BC with poly(2-hydroxyethyl methacrylate) depicted a significant improvement in the mechanical properties (*e.g.* tensile strength) and the rat mesenchymal stem cells proliferation which qualifies this modification for tissue replacement and wound healing applications [93].

Considering all these wound dressings loaded with an API as drug-delivery systems, most of the studies show initial bursts of the API release. Up to now, long-term controlled release systems are still very rare. Nevertheless, Alkhatib *et al.* designed a new delivery system consisting of BC and Poloxamer developed for the antiseptic API octenidine as a long-term ready-to-use system for dermal wound treatment (Fig. **2**). This delivery system provides a prolonged retention time for octenidine, up to one week, with improved mechanical and antimicrobial properties as well as a high biocompatibility [91].

3.1.4. BC as Cell Carrier

Because of the possibility to support mammalian cell attachment and proliferation, BC films are also investigated as cell carriers in cell transplantation [102]. For instance, bacterial cellulose/acrylic acid (BC/AA) wound dressing hydrogels (without cells) enhanced wound healing capacity in nude mice. Interestingly, when the BC/AA hydrogels were loaded with human epidermal keratinocytes and human dermal fibroblasts, the positive effects of the BC/AA in burn recovery were accentuated. The *in vivo* results showed that the cell-loaded hydrogel produces the greatest acceleration on burn wound healing, followed by treatment with the hydrogel alone in comparison to the untreated group. The percentage wound reduction on day 13 in the mice treated with BC/AA hydrogel loaded with cells ($77.3 \pm 6.2\%$) was significantly higher than that in the control-treated mice ($64.8 \pm 6.8\%$) or the hydrogel-treated ones alone (71.5 ± 2.3), respectively. Histological analysis for the expression of collagen type I *via* immunohistochemistry and transmission electron microscopy indicated a greater deposition of collagen in the mice treated with the hydrogel loaded with cells than in the mice administered with other treatments. Therefore, the BC/AA hydrogel proved promising applicability as a wound dressing and as a cell carrier.

In summary, very promising experimental investigations and preclinical studies have been performed suggesting the future application of modified, drug-loaded and/or native BC in an increasing number of dermal applications. The increasing number of BC-based wound dressings on the market follow the same trend and confirm the high commercialization potential of innovative BC based medical products. Other fields of BC application in damaged epithelial tissues regeneration are still in its infancies, as described below, but show the same promise.

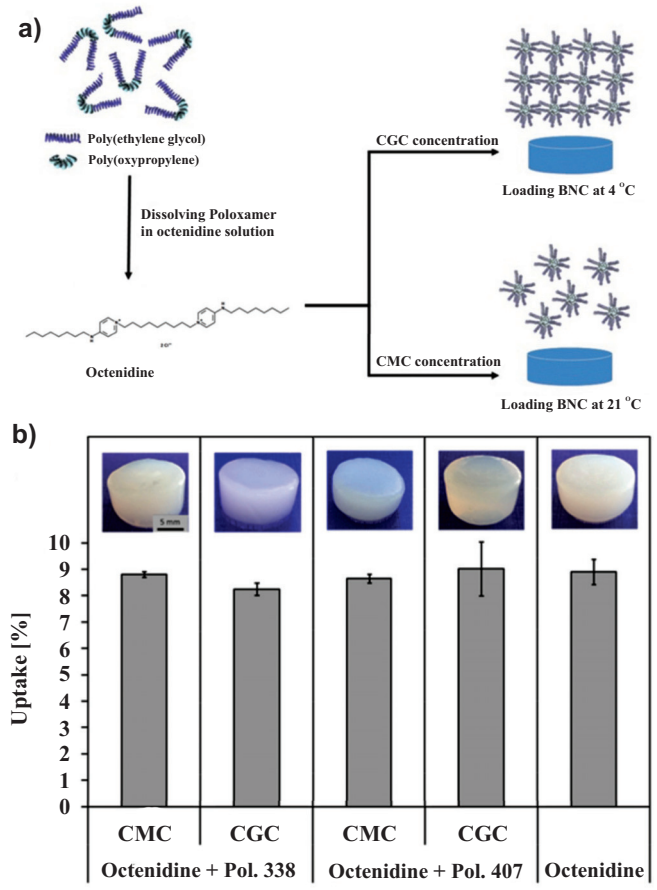


Fig. (2). (**a**) Schematic overview of the loading of BC with Poloxamers forming critical micelle concentration (CMC) and critical gelation concentration (CGC) samples. (**b**) Photographs of octenidine and octenidine/Poloxamer loaded CMC and CGC BC samples and percentage uptake of octenidine (mean ± SD, n = 3) after incubation of fleeces for 48 h by Alkathib *et al.* reproduced with permission from Elsevier [91]. (*The color version of the figure is available in the electronic copy of the article*).

3.2. Ophthalmology

Ophthalmology is a branch of medicine historically linked with the use of biomaterials, exemplified by contact and intraocular lenses. The application of biologically derived materials in regenerative ophthalmology predominantly concentrates on the ocular surface and, to a lesser extent, on the retina. [103] (Fig. **3**) localizes these two tissues in a 3D human eye anatomy representation. To date, for ocular surface wound healing, amniotic membrane patches are regularly applied [104] and the most common clinical approach for ocular surface reconstruction relies on corneal transplantation, whereas innovative regenerative medicine approaches are gradually gaining acceptance [105].

The outermost part of eye comprises two epithelia: The corneal and the conjunctival epithelium. Recently, collagen based materials have been designed to reconstruct these two structures [106-109], while other authors developed silk or keratin-based membranes [110]. Some previous reviews already pointed out that the innate hydrophilicity, flexibility and mechanical stability of BC suggest a potential application on corneal regeneration [111, 112]. One more strength of BC for this specific application is its conformability, which might facilitate the adaptation of the biomaterial to the dome shape of the ocular surface. BC has been shaped into a contact lens-like form by culturing *K. xylinus* on top of hydrophilic surfaces [113] and, in parallel, BC has proven to support the growth of human corneal stromal cells [114]. However, research papers on this topic are scarce and describe preliminary findings, indicating that the application of BC in ocular surface regeneration is still a field in its infancy that deserves to be explored in more depth.

Native-state BC has a visible light transmittance around 70% due to the dispersive character of the fibers bundles and pores. In order to increase the transparency of BC for long-term applications in corneal regeneration, BC has been combined with other components such polyvinyl alcohol (PVA) [95]. BC/PVA composites, prepared by a freeze-thaw method, were satisfactorily evaluated in terms of water holding capacity, light transmittance, mechanical properties and thermal stability; important characteristics for a corneal substitute. However, no biological characterization of those materials have been published at the time of this review. Similarly, BC/Hyaluronic acid composites (BC/HA) were prepared by a physical gelation method with the resulting material displaying 90% of visible light transmittance [60]. Interestingly, this feature was maintained after a drying-rewetting cycle. According to the authors, biocompatibility tests for the BC/HA composites are in progress.

To our knowledge, the only *in vivo* assessment of BC as a corneal replacement was carried out by R. V. Sepúlveda *et al.* [115]. In this study, dry BC and BC/polycaprolactone (PCL) hydrogels were implanted into rabbit's eyes to replace the corneas. Both BC and BC/PCL implants remained stable over the 45 days of the study and delayed the manifestation of corneal edema with respect to the control group that received no treatment. Nevertheless, the authors report chronic inflammation and incomplete re-epithelization in the long term for the rabbits receiving the BC and BC/PCL implants. These results hint that the use of BC as a permanent corneal substitution will be challenging.

Another research direction regarding ophthalmological applications of BC is the repair of retinal pigment epithelium (RPE). The function of this highly specialized epithelium is impaired in patients suffering from age related macular degeneration, the most common cause of vision loss in Europe [116]. Gonçalves *et al.* described that acetylated BC supported the attachment and proliferation of RPE cells and envisioned a potential application of BC as a carrier for RPE cell transplantation to the retina [117]. More recently, the same group reported a further functionalization of acetylated-BC (ABC) with urinary bladder matrix [67]. It is encouraging to read that when RPE cells were seeded on these substrates, they recapitulated closer the *in vivo* phenotype than on uncoated ABC.

Taken together, these studies set the basis for future research on BC-based biomaterials specifically targeting eye epithelia. The above-summarized results are still immature and, due to the lack of *in vivo* experiments, conclusions must be drawn with caution. Nevertheless, the field of regenerative ophthalmology appears as an opportunity for the BC-based biomaterials to find a potential niche in the health market, which appears as less competitive than *i.e.* the skin.

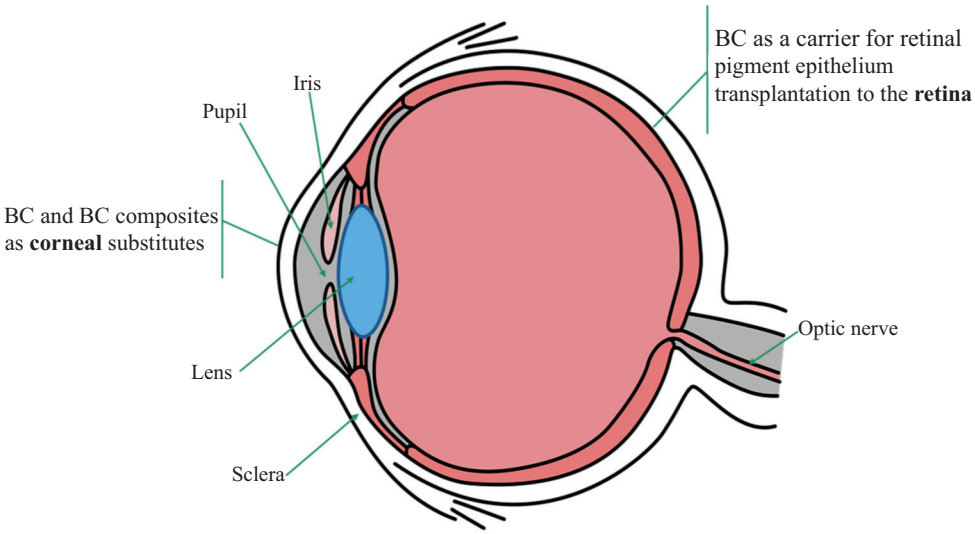


Fig. (3). Schematic representation of the human eye anatomy and the targeted tissues treated with BC-based therapies. Image modified from [106]. (*The color version of the figure is available in the electronic copy of the article*).

3.3. Stomatology

Deliberations for potential applications of BC, *e.g.* temporal implants in dental extraction alveoli or wound dressing after mucosal transplantation recently came up, but the testing of BC and specific product developments are still rare. However, the softness of the hydropolymer plus its flexibility and self-attachment to surfaces strongly suggest a broader scope of application in dentistry. Studies of Weyell *et al.* depicted the benefits of doxycycline-loaded hydrated and freeze-dried BC in dental therapies such as dental extraction or mucosal transplantation [118]. Both applications would benefit on the one hand from a material, which degrades under physiological conditions and on the other hand from an antibiotic environment. Consequently, periodate-oxidation of BC was performed to modify its degradation kinetics. In addition, native and oxidized BC loaded with doxycycline were tested for prophylaxis against infection. An *in vitro* toxicity test ensured biocompatibility of oxidized BC, whereas agar diffusion tests of samples loaded with doxycycline against pathogenic oral bacteria proved high antibiotic efficiency. Release studies of the drug from native and oxidized BC confirmed a comparable release behavior showing an initial burst of 50-60% within the first hour and a total release of about 90% after 3-5 h [119].

Chiaoprakobbkij *et al.* developed freeze-dried composite sponges made from BC fibers and alginate, crosslinked with $CaCl_2$. This recent *in vitro* study also showed a supported proliferation of human keratinocytes and gingival fibroblasts caused by this composite material [120]. In conclusion, there is still an unmet potential for BC-based products (*e.g.* periodontal dressings, sponges, tamponades, sutures or even drug delivery systems) in dentistry.

3.4. Other Epithelial Surfaces

Epithelial tissues form part of a myriad of membranes and barriers inside the human body. Some of these structures such as the eardrum, the meninges or the linings of hollow organs are difficult to rebuild after disease or trauma and would largely benefit from new repair approaches based on natural biomaterials. In this last section, we have grouped further applications of BC regarding the regeneration of diverse body surfaces.

The tympanic membrane (TM) separates the external ear form the middle ear and its key function is to amplify airborne vibrations and transduce them to the middle ear. TM perforation is a common clinical situation and implies a risk of prolonged damage and hearing reduction, especially if bacterial infection occurs. BC patches have been evaluated as wound healing devices in eardrum perforations to substitute the muscle, fat or cartilage autografts that are conventionally used in TM reconstruction. F. Coelho Alves Silveira *et al.* performed a randomized controlled trial with 40 patients and reported a higher success rate (90 *vs* 80%) when BC films were used as wound dressings respect to autologous temporal fascia (muscle) patches. Notably, the BC treatment reduced the operation time in more than one hour and the total hospitalization costs were 13 times lower. Another study tested the efficiency of BC to solve small but long-lasting TM perforations in 16 ears [121]. The authors conclude that the high rate of recovery of these patients treated with BC (81.3% of the cases) encourages for further investigations of BC in otology. Interestingly, this publication highlights, from a clinical point of view, some advantages of BC respect to other grafting materials for TM reconstruction: no need of general anesthesia for the surgical procedure, easy shaping of the material to match the defect size, enhancement of cell growth in the damaged area, easy sterilization and short operating time.

Because its limited endogenous regenerative potential, the nervous system is another area where BC patches could be of great interest. In particular, dura mater, the outermost of the three meninges that surround the brain and the spinal cord, is frequently disrupted after neurosurgical interventions or trauma and thus can be regarded as a potential target for BC-based treatments. *In vitro*, patterned BC substrates proved to support and guide the growth of neural stem cells [59]. In line with this, Goldschmidt and coworkers reported the proliferation of human dural fibroblasts (primary cul-

tures) on BC films [122]. These authors propose BC as a conceivable option for dural implants principally because of its mechanical stability and its capability to support the growth and migration of native dural cells. *In vivo*, damage to dura mater has been experimentally treated with BC patches [123]. In this study, sutureless BC implants were inserted in 40 rats and examined after 120 days without noticing any complication such as infection, cerebrospinal fluid leakage, hemorrhages or behavior disturbance in the animals during the study time. The levels of inflammation were similar between the group that received BC patches and the group implanted with a polytetrafluoroethylene-based material (positive control). The authors claim a satisfactory level of BC graft acceptance and highlight the potential application of BC in dura mater repair. Actually, in 2014 the commercial product SYNTHECEL Dura Repair was launched for this specific application after showing an equivalent effectiveness compared to other commercially available products for dura replacement [124].

BC native structure in the form of a fibrous hydrogel and some reported BC film thickness [51] are comparable to those of the mucus layers covering the body's internal cavities [125, 126]. Thus, BC has also been proposed for reconstruction of hollow organs [112] that is, urinary, reproductive, respiratory and intestinal tracks, which contain a mucosa on its inner side. To this end, asymmetric BC structures exhibiting one site with densely packed BC fibers and another side with loose BC fibers were generated mimicking the architecture of tubular organs [64]. These scaffolds achieved higher porosity than native BC and after being seeded with muscle cells, were implanted in dog urinary systems yielding better outcomes than unmodified BC.

The findings summarized in this section collectively underline the versatility BC and its potential to take part in the regeneration of diverse body surfaces. Likewise, the adaptability of BC in terms of size, shape and porosity will be crucial in the future to conceive tissue-specific biomaterials based on BC.

CONCLUSION

The outstanding properties of BC, in conjunction with its natural origin and sustainable manufacturing call for many diverse applications in epithelial regeneration. Here, we provide a compact but detailed synopsis about the opportunities for BC-based alternatives to conventional treatments in this field.

Huge progress has been made in the development of novel BC-based materials for dermal applications and in the understanding of their positive effects on wound healing. Approaches ranging from modifications of topography, water content and pore structure to combinations with other biopolymers, active ingredients and/or cells have shown that BC is not only an excellent wound dressing material in its native form but also a versatile platform material to tailor-made product design. Along with the increasing comprehension of the reasons for accelerated wound healing observed for native as well as modified BC, new BC-based medical products, designed for the treatment of specific skin lesions, can be expected to enter the market within the next couple of years.

Besides the well-known example of the outer skin, we pinpointed other epithelial surfaces that could benefit from innovative treatments based on BC. In the field of ophthalmology, the preliminary findings reviewed here should encourage future research on BC-based biomaterials specifically targeting eye epithelia since the field of regenerative ophthalmology appears as an opportunity for BC to find a niche in the competitive health market. Similarly, the softness of the BC hydrogels together with its flexibility and self-attachment to body surfaces strongly suggest a broader scope of potential application in dentistry, a field that definitely deserves more research efforts. Worth noting are the reports on tympanic membrane reconstruction highlighting important advantages of BC compared to other grafting materials from a clinical perspective: no need of general anesthesia for the surgical procedure, easy shaping of the material to match the defect size, enhancement of cell growth in the damaged area, easy sterilization and short operating time.

The potential of BC as cell carrier should not be underestimated. In this manuscript we gathered abundant examples of cell types that can effectively attach and proliferate on BC substrates. These cell types include diverse human cells; epidermal keratinocytes, dermal fibroblasts, corneal stromal cells, retinal pigment epithelium and other mammalian cells like neural stem cells (mouse) and muscle cells (dog). On top of that, BC exhibits potentiality as a substrate for stem cell transplantation as it proved to maintain stemness of mouse mesenchymal stem cells for a longer period of time than traditional culture methods [127].

Naturally, there are some difficulties that BC-based biomaterials will need to overcome to effectively contribute to epithelial regeneration. When permanent replacement for epithelial tissue is targeted, BC should allow cell ingrowth to provide a proper integration of the biomaterial into the surrounding tissue. So far, this can only be achieved when BC is specifically modified to increase porosity. Moreover, BC based (implant) materials need to degrade after fulfilling the intended medical purpose. Degradability of BC under physiological conditions can only be achieved after chemical modification or enzymatic treatment and the verification of total degradation and metabolization in *in vivo* studies is still open. Likewise, for the specific application of long-term corneal replacement, BC will also need to be adapted to improve visible light transmittance.

However, these limitations in some specific fields of medical application are already addressed in current research and will probably be overcome in the next years. The significant progress in controlled production and the successful design of bioreactors suited for industrial scale production of medical grade BC [38] already paved the way for faster commercialization. Together with the profound knowledge gained by young companies world-wide about the production of BC based products according to current quality management and medical device regulations, this progress will significantly accelerate the market entrance of further BC based products including an increasing number of implant materials designed for epithelial regeneration.

LIST OF ABBREVIATIONS

API	=	Active Pharmaceutical Ingredient
BC	=	Bacterial Cellulose

BC/AA	=	Bacterial Cellulose/Acrylic acid
BC/COL	=	Bacterial Cellulose/Collagen
BC/HA	=	Bacterial Cellulose/Hyaluronic Acid
BC/PCL	=	Bacterial Cellulose/ PolyCaproLactone
BCNC	=	Bacterial Cellulose NanoCrystals
CGC	=	Critical Gelation Concentration
CMC (1)	=	Carboxymethylcellulose
CMC (2)	=	Critical Micelle Concentration
DMARD	=	Disease-Modifying Anti-Rheumatic Drug
DS	=	Degree of Substitution
HA	=	Hyaluronic Acid
HEMA	=	2-HydroxyEthyl MethAcrylate
K. xylinus	=	Komagataeibacter xylinus
MTX	=	Methotrexate
PCL	=	PolyCaproLactone
PHEMA	=	Poly (2-HydroxyEthyl MethAcrylate)
PVA	=	Poly Vinyl Alcohol
RC	=	Regenerated Chitin
RPE	=	Retinal Pigment Epithelium
SEM	=	Scanning Electron Microscope
SMN	=	Flavonoid Silymarin
TEMPO	=	2,2,6,6-Tetramethylpiperidine 1-oxyl radical
TM	=	Tympanic Membrane
TOBCP	=	TEMPO-Oxidized Bacterial Cellulose Pellicle
UDPG	=	Uranyl Diphosphate-Glucose
ε-PLL	=	ε-Poly-L-Lysine

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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