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Application and Prospect of Modified Bacterial Cellulose in the Biomedical Field

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Abstract:

Bacterial cellulose (BC) is an exopolysaccharide synthesized by certain bacterial strains under controlled conditions, known for its remarkable purity, crystallinity, tensile strength, water-holding capacity, and intrinsic biocompatibility. These unique physicochemical properties make BC a highly promising biomaterial across a wide range of biomedical applications. To tailor BC for specific clinical uses, functionalization is typically carried out via in situ or ex-situ strategies, which leverage its abundant hydroxyl groups for chemical derivatization, surface modification, or incorporation with bioactive agents. Through these approaches, composite BC materials can be engineered with enhanced mechanical properties, biological activity, and drug-loading capabilities. Applications in tissue engineering have shown great potential, especially in wound dressings, drug delivery systems, artificial blood vessels, and bone regeneration scaffolds. This review provides a comprehensive overview of current strategies for BC functionalization, summarizes their biomedical applications, and evaluates their performance in clinical or preclinical settings. Finally, it discusses the remaining challenges—such as large-scale production, biodegradability control, and regulatory hurdles—while highlighting future research directions and emerging opportunities in translating BC composites into advanced therapeutic platforms.

Keywords: Biomaterial; Bacterial cellulose; Biomedical materials; Modified

1. Introduction

As the predominant biopolymer on Earth‘s surface, cellulose is primarily sourced from plants. It finds extensive commercial use in industries such as pulp and paper manufacturing, along with textiles. Cellulose biosynthesis occurs ubiquitously across microorganisms which including fungi, algae, and bacteria—primarily through chemosynthetic and enzymatic pathways utilizing glucose derivatives. Louis Pasteur first described bacterial cellulose (BC) in the 1850s as a ‚slippery, gelatinous substance referencing the tradi-

tional Philippine dessert nata de coco produced through coconut water fermentation. Systematically documented in 1886 by Adrian Brown during acetic acid fermentation studies, BC formation was observed as gelatinous pellicles on static culture media surfaces inoculated with Acetobacter species (then termed Bacterium acetic).

Despite its versatility, BC faces application limitations due to inherent deficiencies in antimicrobial, antioxidant, and conductive properties. To overcome these constraints, functional modifications are essential to expand BC's biomedical utility. Furthermore, BC's unique structural architecture renders it an exceptional polymeric matrix for nanomaterial integration. Scientific publications on BC have grown exponentially in recent decades, prompting consolidated reviews of its biomedical and biotechnological applications[1]. However, existing reviews address only a narrow and specific segment of BC modification. A comprehensive review therefore focuses on modifications to BC and its latest developments in biomedical and biotechnological fields, providing insights into applications.

2. Structure of Bacterial Cellulose

2.1 Structure

As a linear homopolymer, BC contains exclusively β-D-glucopyranose monomers connected by (1→4) glycosidic bonds, achieving polymerization degrees up to several thousand units. It forming a six-membered cyclic structure that contains functionally significant primary and secondary hydroxyl groups. BC's crystalline structure combines Iα/Iβ allomorphs with disordered domains (Fig. 1A), forming a hierarchical core-shell architecture superior to plant cellulose. Its 3D hydroxyl-rich network enables exceptional self-assembly from 1.5 nm subfibrils → 2-4 nm nanofibrils → 40-100 nm nanoribbons (Fig. 1B, C). The resulting interwoven network of these nanoribbons constitutes the BC pellicle.

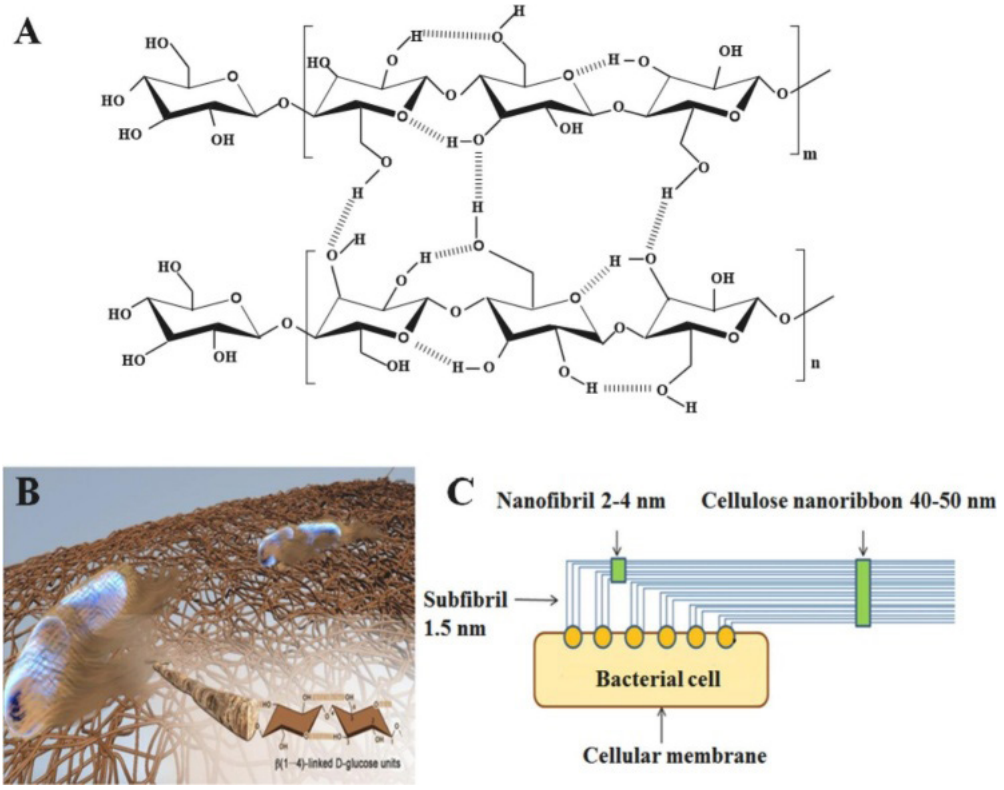

Fig. 1 (A) Chemical structure of BC and (B) the web-like structure of BC membrane [1]. (C) Scheme of the BC fibers [2]

2.2 Biocompatibility

The primary requirement when designing novel biomaterials is biocompatibility and non-toxicity toward living tissues. Conventionally, biocompatibility refers to an appropriate response to the material in its application context, without inducing toxic or allergic effects. BC derives its biocompatibility from its distinctive 3D nanofibrous network structure, which facilitates proliferation. This property has been extensively validated across diverse BC-

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based materials. Specifically, BC implants demonstrate good biocompatibility during initial implantation stages, evidenced by the absence of foreign body reactions. BC serves as an effective scaffold material that sustains optimal microenvironments for diverse cell proliferation. Furthermore, implantable BC devices demonstrate favorable hemocompatibility without inducing hemolytic activity.

2.3 Biodegradability

Biodegradability shows material degradation mediated by biological activity. An ideal biodegradable material must degrade within a timeframe aligned with tissue healing or regeneration, possess adequate shelf-life, exhibit non-toxic degradation products, and maintain biocompatible mechanical properties throughout degradation. While cellulose is primarily degraded by cellulase enzymes, its absence in the human body renders cellulose non-biodegradable. This inherent slow degradation makes BC particularly suitable for applications requiring long-term structural support. Consequently, researchers have pursued strategies to enhance BC's biodegradation rate. BC with improved biodegradability and enzymatic incorporation of cellulase.

3. Modification of Bacterial Cellulose

Although BC's exceptional intrinsic properties, realizing its full potential for targeted biomedical applications often requires modification of its physicochemical and functional characteristics—including porosity, crystallinity, chemical structure, and bioactivity. These modifications are broadly categorized as in situ (incorporating additives into the culture medium during biosynthesis) or ex situ (introducing supplementary components post-synthesis). In this background, diverse synthetic/natural polymers and nanoparticles integrated with BC to engineer advanced functional biomaterials (Fig. 2).

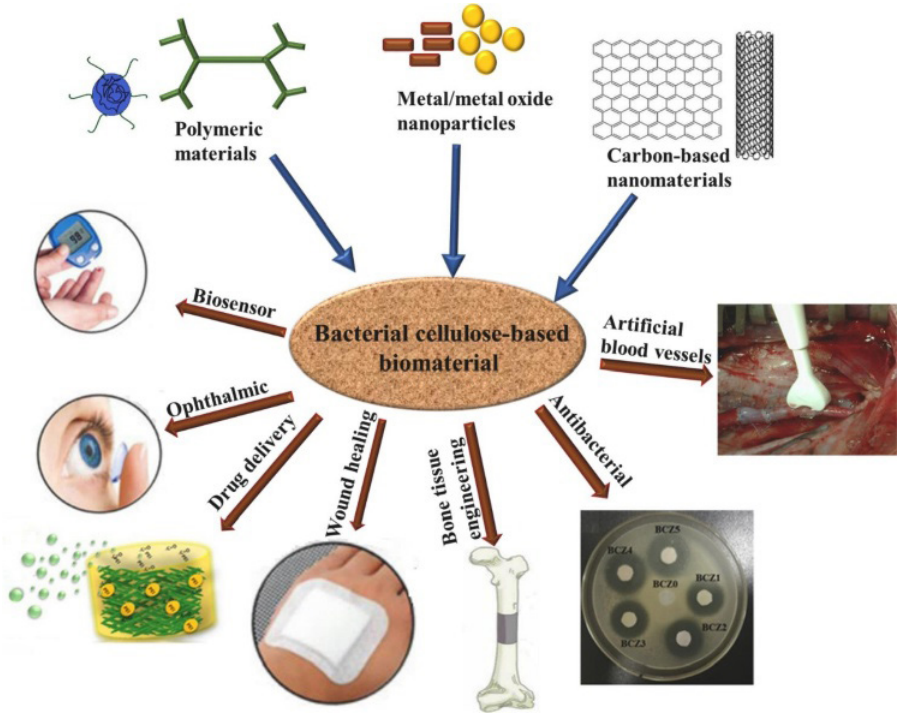

Fig.2. Schematic depiction of diverse material integration within bacterial cellulose (BC) and associated biomedical application potentials [3].

3.1 In-Situ Modification

Recent studies characterize in situ modification as an efficient strategy for functionalizing bacterial cellulose (BC) through direct incorporation of reinforcing agents (e.g., chitosan, poly-3-hydroxybutyrate, nanomaterials) into the culture medium during initial biosynthesis. This approach enables molecular-level integration of additives within BC fibrils, primarily enhancing their physico-mechanical properties through structural reinforcement. The fundamental principle of in situ BC modification entails manipulating the culture medium—either by substituting the carbon source at biosynthesis initiation or introducing additives—to expand the BC fiber network and facilitate interactions between additives and BC's hydroxyl groups, thereby generating new hydrogen bonds.

Exemplifying in situ modification, Park et al. integrated carbon nanotubes into BC to fabricate BC/CNT [4]. To achieve consistent dispersibility, the nanotubes were treated with an amphiphilic comb-like polymer before being added to the culture medium. The resultant nanocomposite scaffolds demonstrated enhanced osteoconductivity and osteoinductivity.

Conversely, Luo et al. incorporated graphene nanosheets into BC, achieving composites, though graphene distribution remained challenging. To address this limitation, Luo et al. developed a novel iterative spray-deposition methodology: BC pellicles were partially grown, sprayed with graphene-supplemented culture medium, and allowed continued growth—repeating this cycle until achieving target thickness. This approach yielded films with 93% higher tensile strength than pure BC, exhibiting uniform dispersion of graphene/GO nanosheets within the 3D BC network and strong interfacial bonding with BC nanofibers [5, 6].

Although in situ modification allows for even distribution of materials within BC for various biomedical uses, the limited conditions of fermentation restrict the inclusion of a wider range of materials. Additionally, fundamental challenges persist regarding additive-BC fiber interactions and precise structural control, requiring further investigation.

3.2 Ex-Situ Modifications

Then subjected to various post-synthesis processes to improve its characteristics. This approach encompasses two primary methodologies: physical and chemical modifications. The chemical modifiability of BC stems from its hydroxyl groups, which facilitate both homogeneous and heterogeneous reactions. Homogeneous modification involves dissolving BC in an appropriate solvent before functionalization with reagents, whereas heterogeneous modification treats solid-phase BC directly with reactive agents. These chemical treatments alter BC's molecular structure to introduce targeted functionalities. Oxidation represents a particularly significant reaction for grafting new functional groups onto cellulose, imparting specialized properties to the material. The physicochemical properties of oxidized cellulose can be precisely tailored by varying reaction conditions (e.g., oxidant type, temperature, pH). Specific reagents selectively convert the hydroxyl groups of BC's glucopyranose units into carbonyl or carboxyl functionalities. Water-soluble 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is commonly employed for cellulose oxidation. This reaction system utilizes TEMPO, NaBr, and NaClO to selectively oxidize the C6 position of glucopyranose units under mild conditions (room temperature, pH 9–11) over several hours.

Sulfation represents a prominent strategy for developing functional BC composites. Cellulose sulfate derivatives—synthesized via sulfuric acid or SO_3–pyridine complex reactions—exhibit bioactive properties including anticoagulant, antiviral, and antibacterial effects. Demonstrating this approach, Sun et al. engineered sulfated BC-gelatin composites as scaffold constituents, achieving enhanced cytocompatibility, hemocompatibility, and anticoagulant performance [7].

Beyond these approaches, BC chemical modification extends to etherification and grafting techniques. Grafting modification plays a critical role in conferring novel properties to BC, with principal methodologies comprising: traditional chemical synthesis, silane coupling agent crosslinking.

Physical modification is extensively employed to impart responsive properties to BC through integration with functional materials, leveraging its operational simplicity. Polymeric or inorganic coatings often protect BC surfaces from environmental degradation. As demonstrated by Beekmann et al., incorporating polyethylene glycol (PEG) into BC converts it into a clear drug delivery system by expanding the pores and boosting water absorption, which greatly enhances its ability to load and release drugs [8].

Another simple method for creating functional BC composites is direct mixing. Wei et al. synthesized dual-crosslinked BC-reinforced hydrogels via freeze-thaw cycles, combining conductive materials' electrical properties with BC's mechanical strength. The resulting composites exhibit superior mechanical resilience and electroresponsive behavior [9].

While it is straightforward to create and precisely manage the structure of materials through physical modifications of BC, the high expense and intricate equipment involved make it challenging to use for large-scale material production.

4. Biomedical Applications

BC exhibits exceptional biocompatibility, mechanical strength, and a 3D nanofibrous structure – attributes that establish its biomedical potential. Furthermore, BC demonstrates minimal immunogenicity. These properties collectively drive extensive research on BC and its functional composites for diverse biomedical applications.

4.1 Drug Delivery

Research methodologies evaluating these systems include the development of single-excipient BC matrices by Khan et al. for oral delivery of model drugs (famotidine, tizanidine). Significantly, all hydrated states (fully hydrated,

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partially hydrated, and lyophilized) of BC formulations exhibited enhanced drug delivery performance relative to traditional tablet systems [10]. Complementing this work, Retegi employed in situ biosynthesis to engineer conformation-controlled BC/graphene oxide spherical hydrogels for oral delivery. Their results established graphene oxide concentration during synthesis as a critical determinant of hydrogel swelling capacity. He et al. developed zwitterionic hydrogels through a one-pot synthesis approach utilizing BC and chitosan as primary constituents for oral drug delivery systems [11]. Their methodology involved partial BC oxidation followed by in situ composite hydrogel formation via Schiff base reaction between oxidized BC and chitosan (BC-AA-CS), yielding materials with significantly improved mechanical strength and pH-responsive behavior. Furthermore, BC incorporation mediates porous structure formation in BC-AA-CS composites, enabling precisely controlled drug release kinetics. This addresses a critical challenge in proteinaceous drug delivery: conventional intravenous administration requires frequent injections due to rapid protein destabilization and degradation, resulting in poor patient adherence. Oral delivery of therapeutic proteins presents both a formidable challenge and transformative opportunity. BC-based carrier systems demonstrate significant potential for enhancing the pharmacodynamic profiles and pharmacokinetic behavior of protein therapeutics.

4.2 Wound Healing

BC serves as an effective wound-healing interface due to its unique property profile. Its biocompatibility minimizes allergic reactions and foreign body rejection—a critical concern for implants where macrophage/giant cell responses represent terminal inflammatory reactions. In vivo studies confirm BC elicits only mild acute inflammation without chronic reactions. Structurally, BC's 3D nanofibrous network manages wound exudates through controlled absorption/evaporation while facilitating oxygen exchange—reducing infection risk. Mechanical stability prevents secondary injury during dressing removal, and high water retention maintains optimal wound moisture. Furthermore, BC scaffolds preserve stem cell functionality, promote keratinocyte differentiation, enhance extracellular matrix deposition, and regulate inflammatory responses—essential mechanisms for epidermal repair. Complementing these properties, BC/GO spheres enable sustained ibuprofen release, demonstrating therapeutic delivery potential [12]. While inherently effective, BC is frequently combined with antibiotics or polymers to enhance antibacterial efficacy against diverse pathogens and optimize dressing performance for accelerated healing.

5. Challenges and Future Perspectives

5.1 Technical Challenges

Specifically synthesize BC nanofibers as a matrix under controlled culture conditions. As an emerging biopolymer, BC demonstrates considerable potential for diverse biomedical applications. However, inherent limitations—notably the absence of intrinsic antibacterial and antioxidant activities—restrict its broader biomedical utility. Consequently, functional enhancement strategies integrate carbon-based nanomaterials, polymers, and metal oxides into BC matrices. Furthermore, tunable biodegradation remains essential; chemical modification offers viable pathways to achieve this property. These research frontiers require focused investigation to fully realize BC's biomedical applicability.

5.2 Prospects in Precision Medicine

BC exhibits distinctive properties—including its 3D nanofibrous architecture, biocompatibility, and support for cellular adhesion/proliferation. Significant biomedical advances have yielded commercial BC-based products (e.g., Biofill®, Bioprocess®, GeliFlex®) for diverse clinical applications. Nevertheless, while existing BC composites demonstrate biocompatibility, non-toxicity, and absence of carcinogenicity, comprehensive long-term in vivo evaluations remain essential for clinical translation. Despite broad application potential, further property optimization is required to advance BC composites toward commercial viability.

6. Conclusion

BC as a remarkably versatile and promising natural biopolymer for advanced biomedical applications due to its structural and physicochemical propertie. However, its inherent limitations—such as the lack of antimicrobial/antioxidant activity, limited biodegradability in vivo, and absence of inherent electrical conductivity—necessitate functionalization to unlock its full potential. This review has comprehensively explored the two primary modification strategies: in situ modificationand ex situ modification. These approaches successfully integrate diverse functionalities (e.g., antimicrobial properties, enhanced biodegradability, electrical conductivity, drug loading/release capabilities) into BC, transforming it into advanced composite materials.

Functionalized BC composites demonstrate significant promise across critical biomedical domains. Their exceptional biocompatibility and nanostructured network make them ideal matrices for tissue engineering scaffolds (bone,

cartilage, skin, vascular grafts), promoting cell adhesion, proliferation, and differentiation. As wound dressings, BC provides a moist, protective barrier, efficiently manages exudate, facilitates oxygen exchange, and, when modified, offers sustained release of antimicrobials or anti-inflammatories to accelerate healing. In drug delivery, modified BC systems (hydrogels, spheres, matrices) exhibit controlled release profiles, stability, and enhanced loading capacity, particularly for challenging payloads like proteinaceous drugs. Furthermore, the integration of conductive materials enables BC‘s application in biosensors and bioelectronics.

Despite substantial progress and the commercialization of some BC-based products (e.g., Biofill®, Bioprocess®), key challenges remain. Scaling up production and modification processes cost-effectively, achieving uniform dispersion of additives (especially in in situ methods), and thoroughly evaluating the long-term biocompatibility, biodistribution, and degradation profiles of novel composites in vivo are crucial hurdles before widespread clinical translation. Future research should focus on developing smarter, stimuli-responsive BC systems, improving biodegradation kinetics to match tissue regeneration timelines, and rigorously validating the safety and efficacy of these advanced materials in targeted therapeutic applications. Overcoming these challenges will solidify BC‘s pivotal role in the next generation of precision biomedicine.

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