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BACTERIAL SYNTHESIS OF CELLULOSE: APPLICATION IN MEDICINE AS A PROMISING BIOMATERIAL

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Abstract. *Komagateibacter xylinus* produces bacterial cellulose (BC), an extracellular polymer that has been demonstrated to have a variety of qualities that make it naturally valuable as a next-generation biopolymer. The structure of BC is made up of glucose monomer units that cellulose synthase polymerizes into β-1-4 glucan chains, which form uniaxially oriented BC fibril bundles with a diameter of 3–8 nm. Chemically, BC and vegetative cellulose are the same. However, BC performs far better in biological applications, potable treatment, nano-filters, and functional applications when compared to other natural or synthetic equivalents. This superiority is primarily caused by the high degree of crystallinity, nano-fibrillar matrix, and chemical purity. When BC is used as a scaffold or carrier with other materials, distinctive and novel traits that are all related to BC's qualities can be seen. These characteristics, along with bacterial cellulose's general physicochemical advantages, make it a prime option for additional scientific investigation into the production of biopolymers. These characteristics include high tensile strength, high water-holding capacity, and microfibrillar matrices. With an emphasis on the use of BC as a next-generation wound dressing, this paper thoroughly examines a number of areas in which BC is being researched, from biological uses to electronic applications. This study aims to summarize and debate the latest developments in the use of bacterial cellulose, mostly in biomedicine but also in biotechnology.

Keywords. Hydrogel, wound dressing, medication delivery, bacterial cellulose, biopolymer, biomedicine

Introduction. With an annual production of over 75 billion tons, cellulose is one of the most abundant and affordable biopolymers on the planet. Plants, microorganisms, and natural and enzymatic chemical reactions have all been found to create cellulose in recent decades. It is one of the main raw materials used in the production of pulp, paper, textiles, and nanofibrous mats, among other marketed materials. Numerous microorganisms, such as bacteria, algae, and fungus, are known to have the capacity to manufacture cellulose; the cellulose that bacterial cells make is known as bacterial cellulose (BC). All plant life contains cellulose, which is one of the most prevalent polymeric compounds in nature and is created by a variety of microbial species. Since wood is now the only dependable supply that can meet the industrial demand for cellulose, it is the main source of cellulose that is exploited. A significant amount of cellulose is also found in a variety of plants, including hemp, cotton, and flax, in addition to trees. Certain materials, such as money, specialty paper, and apparel, are made from these sources.

Additionally, fungi, seaweed, and some bacterial species can produce cellulose [1-5]. However, the most studied species is *Komagateibacter xylinus (K. xylinus),* a non-pathogenic, strictly aerobic, Gram-negative bacterium that was formerly known as *Acetobacter* and *Gluconacetobacter*. *In vivo* and *in vitro* biomedical applications depend on the congruent combination of macromolecular and surface properties, which bacterial cellulose exhibits. Bacterial cellulose has since been demonstrated to be a significant new biomaterial for use in biomedicine. Thus, the purpose of this review is to summarize and explain the latest developments and uses of bacterial cellulose, a bioengineered material, in a biomedical context. At the forefront of regenerative medicine is bacterial cellulose, which boosts cellular adhesion, encourages cell proliferation, migration, and eventual differentiation, improving the rate of re-epithelialization and resulting in faster wound healing. Bacterial cellulose-based biomedical devices have important properties like minimal toxicity and the capacity to keep the wound wet, which permits adequate gaseous exchange, blood and exudate absorption, low tissue adhesion, and thermal insulation [6-12]. The design and production of the bacterial cellulose must have a suitably interactive surface to permit cell contact since all these requirements must be satisfied in order to make a great biomaterial. The effectiveness of in vivo biomaterials, which have been created for implants, drug delivery systems, wound healing, scaffolds, and tissue/organ regeneration, depends critically on the arbitrated interfacial connection between cells and the bacterial cellulose. The way cells react to the biomaterials determines the overall result of novel biomedical devices; these interactions are typically associated with physicochemical and pharmacological properties, such as surface charge, wettability, topography, and the presence of hydrophobic/hydrophilic compounds. These characteristics also affect the material's mechanical properties and inherent biocompatibility. The Science Direct and Google Scholar databases were used as part of the approach for this paper review. The keywords "bacterial cellulose," "medicine," "biomedicine," "wound dressing," and "biomaterials" were used in combination. The publication period began in 2003, which marked the beginning of the subject's importance, and ended in August 2022. These days, the pharmaceutical and biomedical industries have a difficulty in developing new "green" materials using sustainable technology [13-18]. As a result, research has been done recently on the creation and improvement of BC-based polymeric composites and blends for biomedical applications, including the creation of new, customized biomaterials. Numerous evaluations have been published regarding the use of BC in medical applications. New evaluations that summarize the cutting-edge research on the topic are necessary, nevertheless, as the number of publications has increased dramatically. This paper provides an overview of developments in the application of BC in polymeric blends and composites for wound healing and drug delivery systems. Additionally included are BC-producing microbes and BC production techniques. The goal of the review that follows is to compile the most recent abundance of knowledge regarding the modifications and uses of bacterial cellulose in biotechnological and biological applications. While biomedical fields concentrate on the use of bacterial cellulose in wound dressings, biotechnological fields that have been investigated include drug delivery systems, tissue regeneration and surgical materials, immobilization matrices, and electronics [19-23].

The main purpose of the presented manuscript is to provide a brief analysis of the use of bacterial cellulose in medicine as a promising biomaterial based on the results of reputable scientific papers.

Bacterial Cellulose Production. *K. xylinus* manufactures bacterial cellulose extracellularly in four allomorphic forms, I–IV, through the fermentation of carbohydrates; celluloses I and II are the most extensively researched. Although the exact cause of these bacteria's cellulose production is unknown, it is generally acknowledged that the extracellular cellulose, which forms a pellicle at the top of the growth media, keeps the bacterial colony from drying out and maintains adequate oxygenation for the growth of colonies close to the surface. The process of cellulose manufacturing starts when the bacteria passively

take up glucose from their surroundings. This glucose is subsequently isomerized from glucose-6-phosphate to glucose-1-phosphate. Uridine diphosphate glucose, or UDP-glucose, is created when this isomer combines with uridine-5-triphosphate (UTP). Cellulose synthase A then catalyzes the conversion of this UDP-glucose into linear 1,4 glucan chains, which are then triggered by cyclic-di-GMP. The bacterial cell wall's pores allow these cellulose chains to be eliminated. The fructose pathway, which makes use of the pertinent enzymatic processes, will be used if the bacterium runs out of a glucose supply. A particular operon known as bacterial cellulose synthesis ABCD (bcsABCD), which was discovered in K. xylinus in 1999, regulates the metabolic pathways. The catalytic subunit of the enzyme cellulose synthase is encoded by the first gene of the bcsABCD operon, bcsA [5-12]. The second gene, bcsB, produces a regulatory subunit on cellulose synthase that binds to c-di-GMP. This interaction is especially important because it initiates the manufacture of cellulose. Although the roles of bcsC and bcsD are still unclear, it has been hypothesized that bcsC plays a part in the formation of cell membrane holes and that the proteins it encodes for are comparable to those that generate pores. Only cellulose, secondary metabolites, microbial biomass, and leftover nutrients from the growth media are present in the pellicle that results from a successful fermentation; these components may be readily extracted to produce a highly pure crystalline cellulose matrix. The traditional static fermentation method is used to produce the majority of bacterial cellulose. *K. xylinus* can grow in shallow containers of semi-defined growth medium in a static incubator at 30 °C for 7 to 14 days, after which a thick pellicle of cellulose forms at the liquid surface interface and is easily harvested. Despite being the most popular way to produce BC, there are a few drawbacks, including the expense and duration of cultivation. Additionally, the creation of cellulose may be unequal due to the organisms' exposure to varying growth environments, such as anaerobic conditions for some and oxygen for others, as well as variations in carbon supply gradients [14-21].

Bacterial cellulose's inherent characteristics. Linear homopolysaccharides conjugated by β-d-glucose units joined by 1,4-β-glycosidic bonds make up cellulose. This is due to bacterial cellulose's distinct three-dimensional structure, which explains why it has better physical qualities than vegetal cellulose. For instance, extensive aggregate networks with an average diameter of 1.5 nm are formed by bacterial cellulose fibrils, which provide much greater surface area, flexibility, elasticity, and tensile strength. Following the successful synthesis of cellulose exopolysaccharides, the linear chains of cellulose are ordered into 10–15 polymer chains, forming nanofibers. These nanofibers are then arranged to produce microfibrils, which are 100 times smaller than their vegetative counterparts. Microfibril bundles are created by bundling the microfibrils together. The microfibril bundles bind together to produce cellulose ribbons that are 70–80 nm wide and 3–4 nm thick. These ribbons then haphazardly entwine with one another to create a dense matrix of cellulose fibers, which are created by strong intra- and inter-chemical bonds, mainly hydrogen bonds, which take place between successive cellulose sheets. The cellulose's high degree of hydrogen bonding also makes it possible for cavities to form within it. Because cellulose has an ionic charge, things like silver ions can be implanted in it [6-13]. This characteristic of cellulose will make it possible to manipulate it by loading it with particular antimicrobial drugs that have an ionic charge and can target the organisms that cause infections. Bacterial cellulose is naturally suited for biomedical applications since it is hydrophilic, non-pyrogenic, and permeable to liquids and gases. Bacterial cellulose's hydrophilicity and comparatively high swelling ratio enable it to keep the wound site wet while maintaining the optimal temperature range of 25.3–37.3 °C. The dressing's reversible swelling and de-swelling is made possible by the hydrophilicity of bacterial cellulose, which can be used to regulate wound exudate from severely emitting wounds. One of the primary benefits of bacterial cellulose over vegetal cellulose is its high degree of inherent purity, which

allows for direct use with little processing, in addition to being biodegradable and non-toxic. Although bacterial cellulose and vegetal cellulose are chemically identical, bacterial cellulose lacks hemicellulose, pectin, lignin, and other lignocellulosic substances [14-22].

The use of bacterial cellulose in biotechnology. As is typically the case, the most popular technique for loading medications into BC membranes is immersion in the drug solution, usually after lyophilization to maximize drug absorption. Antimicrobial medications and anti-inflammatory medications like diclofenac and ibuprofen are most frequently added to bacterial cellulose. By utilizing tensile strength and water uptake to load the cellulose with antimicrobial agents like antibiotics, the effectiveness of bacterial cellulose as a drug delivery material can be enhanced to give new features and functionalities. Immersion approaches have also shown interest in the incorporation of antimicrobials, including antibiotics, into bacterial cellulose. Bacterial cellulose was immersed in the antibiotic solution for 24 hours while being constantly stirred to achieve tetracycline loading. For the first three hours, the data displayed an exponential release, but for the next ninety-three hours, they plateaued to a continuous release. Another study demonstrated antibacterial efficacy against Staphylococcus aureus by immersing bacterial cellulose coated with fusidic acid for 24 hours [3-9]. According to reports, this combination exhibited high levels of action against both Gram-positive and Gram-negative bacteria and elevated bioactivity. The actual concertation of amoxicillin itself was found to be the overall regulating factor of drug release in an amoxicillin release investigation from bacterial cellulose matrices. Additionally, tetracycline release profiles were examined; these revealed an initial burst of activity followed by a steady release with adequate antimicrobial effects against Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Candida albicans. Additional testing revealed low cytotoxicity against HEK293 cells. Antiseptic substances, like octenidine, were also submerged into BC and exhibited minimal levels of cytotoxicity against keratinocytes. Their release profile was biphasic, with an initial release surge occurring within 8 hours and a continuous release lasting up to 96 hours. Additionally, this study demonstrated that the BC-Octenidine composite remained fully alive six months later with no loss of antimicrobial activity as long as it was maintained moist and in the dark. The ultimate result of emulsifying cellulose with different poloxamers was to adjust the release profile based on the kind and concentration of poloxamer. Coniferyl alcohol and other lignin-derived compounds have been used as antibacterial agents and, consequently, as a secondary component in bacterial cellulose. This produced a highly effective antibacterial wound dressing that showed a higher rate of revascularization of the wound site and a decrease in pain and erythema [12-21].

Prospects and Difficulties for the Future. Foods, cosmetics, personal care items, the biomedical industry, the textile industry, and other biotechnological sectors are just a few of the many uses for BC, a biomaterial with great adaptability. Because of its special qualities, ease of manufacture, and straightforward functionalization procedures, BC has a wide range of applications. However, there are still a number of restrictions that prevent BC from being used in a wider range of contexts. Finding an affordable, sufficient carbon source that doesn't interfere with food production is a significant obstacle to using this material. Early on in its manufacture, more work is required. Additionally, the productivity and unique traits of BC's many microorganism species and strains, along with the numerous carbon sources employed, highlight the need for creative study in this area [6,7,12,14]. Another drawback is that BC manufacturing is more expensive than VCs, but this can be mitigated by using inexpensive waste products and byproducts as substrates, such as sugarcane molasses, distillery effluents, crude glycerol made from biofuel, lignocellulosic wastes, etc. Because of their synergistic effects, using mixed raw materials instead of strictly synthetic reagents might increase BC production and reduce the possibility of substrate unavailability. Dextrose, monosaccharides, and polyol compounds are examples of

conventional carbon sources utilized during bacterial fermentation. These sources significantly raise the cost, making up around 30% of the entire cost, and have the potential to produce even better outcomes. The functionalization of BC should receive more attention in order to increase its uses across a variety of sectors [17,18,22]. The material's biosafety should also be taken into account, particularly when using it as a wound dressing because it comes into direct touch with wounds and even deeper layers of the dermis. As a result, BC membrane sterilization and purification are crucial. For BC to be widely used in the health sector, further challenges must be addressed. Nonetheless, the current wealth of research and patents, along with the application of safe sterilizing methods like radiation for membrane sterilization, suggests that this intriguing material may soon be used in a variety of cutting-edge biotechnological applications across the globe [1-5].

Discussion. Because of their high risk of infection and sepsis, chronic ulcers are among the leading causes of morbidity and mortality. As a result, they have a substantial impact on public health resources. Skin ulcers can be treated with a variety of dressings, each having unique benefits and drawbacks. Because of its biological, physical, and mechanical properties that make it possible to create polymer composites and blends with a wide range of uses, bacterial cellulose (BC) has attracted a lot of interest in the cosmetic, pharmaceutical, and medical industries. BC was initially utilized in the medical profession for artificial blood vessels, tissue regeneration, and wound dressings. This material's significant fluid retention and pharmaceutical loading qualities make it appropriate for treating a variety of skin conditions. Because BC membranes fit the body perfectly, reduce pain, and speed up epithelial regeneration, they are utilized as a temporary covering for skin treatments. To generate the perfect milieu for wound healing, BC-based composites and blends have been assessed and manufactured both in vitro and in vivo. This review emphasizes the characteristics of BC in depth, with a focus on biomedical findings that show its usefulness, and discusses several approaches to manufacturing and processing BC for use in the medical profession [2-10]. Additionally, it provides an overview of the biological uses that have been documented to date, particularly for tissue engineering and wound dressing materials. BC patents used as a material for wound dressings are also included in this review. Some patients may experience negative gastrointestinal side effects from anti-inflammatory drugs like diclofenac and ibuprofen, which would be a sign that a transdermal delivery route should be used. Bacterial cellulose and polymethanocryolyl-glycine have been combined to create a pH-sensitive scaffold that releases diclofenac. The medication is retained inside the membrane at pH 2. However, diclofenac is delivered gradually over a 96-hour period when exposed to the skin's normal pH of 7.4. Drug delivery methods typically take the shape of a patch and use the entire bacterial cellulose pellicle; however, a hollow spherical ball was created to release fluorescein gradually. *K. xylinus* and growth media suspension were added dropwise to a combination of silicone oils to create the hollow spheres, which were subsequently cultured for 14 days at 30 °C. Cellulose fibrils produced spherical structures surrounding the droplet of growth media and cells as the bacteria expanded. After purification, these structures left a hollow gap in the center that can be used to deliver tiny doses of medication straight to the intended site [13-19]. The primary justification for BC's application as a material in medicine is its structural morphology, which makes wound dressings stable. Additionally, BC provides biocompatibility, non-toxicity, wound protection against bacterial invasion, heat and gas exchange assurance, an optimal environment for the skin's accelerated healing process, and the absorption of excess exudate from the wound. Additionally, BC is a more cost-effective choice than traditional dressings. BC's potential for a wide range of applications, including as drug delivery, tissue engineering, and other uses in the pharmaceutical and medical areas, is demonstrated by the numerous studies and patents [20-24].

Conclusions. To sum up, bacterial cellulose has been found to be a highly versatile material that may be used to create medically relevant materials including gels, composites, dental grafts, and wound dressings. Each of these materials has unique properties that are appropriate for its intended use. These materials offer a practical and affordable substitute for petroleum-based analogs. Because of the nanofibrillar matrix, bacterial cellulose has exceptional physicochemical qualities and is extremely biodegradable. Because of its high level of native purity, this substance also shows no toxicity in almost all applications, making it possible to use this dressing directly.

Numerous applications centered on biomedical goals and the creation of wound dressings for moderate to severe wounds have been studied using bacterial cellulose biomaterials. Despite the paucity of in vivo research, these investigations have clarified the huge potential of these composites to be beneficial in treating wounds. The attempts and developments to maximize the use of bacterial cellulose in the manufacturing of bioactivated wound dressings are discussed in this review. However, none of these approaches currently address all of the problems that must be resolved to make this material a truly feasible choice for a wound dressing, chief among them being the high expense of increasing manufacturing.

Worldwide, a significant amount of waste, including pollution of the air and land, is caused by disposable synthetic medical items. As a result, studies have concentrated on sustainable options as a substitute for materials that are typically used. Due to their adaptability, many materials—mostly natural polymers like chitin, cellulose, starch, and others—have gained attention. To ensure their safe application in medicine, such materials underwent a regulated alteration. BC is a naturally occurring polymer that is very controllable. The manufacturing of BC and its intriguing uses in the biomedical industry were the main topics of this review paper. Because of its unique and adaptable qualities, such as its high mechanical strength, high WHC, high WRR, high crystallinity, gas permeation, high purity, and others, the microbial polymer seems to be a big advantage over VC and synthetic polymers.

References.

1. Swingler S, Gupta A, Gibson H, Kowalczuk M, Heaselgrave W, Radecka I. Recent Advances and Applications of Bacterial Cellulose in Biomedicine. Polymers (Basel). 2021 Jan 28;13(3):412. doi: 10.3390/polym13030412.
2. Pandit, A., Kumar, R. (2025). Bacterial Cellulose-Based Materials for Biomedical Applications. In: Baskar, C., Ramakrishna, S., Rosa, A.D.L. (eds) Encyclopedia of Green Materials. Springer, Singapore. https://doi.org/10.1007/978-981-97-4618-7_66
3. Gutierrez E, Burdiles PA, Quero F, Palma P, Olate-Moya F, Palza H (2019) 3D printing of antimicrobial alginate/bacterial-cellulose composite hydrogels by incorporating copper nanostructures. ACS Biomater Sci Eng 5:6290–6299.
4. Halib N, Ahmad I, Grassi M, Grassi G (2019) The remarkable three-dimensional network structure of bacterial cellulose for tissue engineering applications. Int J Pharm 566:631–640.
5. He W, Zhang Z, Zheng Y, Qiao S, Xie Y, Sun Y, Qiao K, Feng Z, Wang X, Wang J (2020) Preparation of aminoalkyl-grafted bacterial cellulose membranes with improved antimicrobial properties for biomedical applications. J Biomed Mater Res A 108:1086–1098.
6. Jalili Tabaii M, Emtiazi G (2018) Transparent nontoxic antibacterial wound dressing based on silver nano particle/bacterial cellulose nano composite synthesized in the presence of tripolyphosphate. J Drug Deliv Sci Technol 44:244–253.

7. Pandit A, Kumar R (2021) A review on production, characterization and application of bacterial cellulose and its biocomposites. J Polym Environ 29:2738–2755.
8. Poddar MK, Dikshit PK (2021) Recent development in bacterial cellulose production and synthesis of cellulose based conductive polymer nanocomposites. Nano Sel 2:1605–1628.
9. Swingler S, Gupta A, Gibson H, Kowalczuk M, Heaselgrave W, Radecka I (2021) Recent advances and applications of bacterial cellulose in biomedicine. Polymers 13:412.
10. Vega-Vásquez P, Mosier NS, Irudayaraj J (2020) Nanoscale drug delivery systems: from medicine to agriculture. Front Bioeng Biotechnol 8:79.
11. Vinogradov MI, Makarov IS, Golova LK, Gromovykh PS, Kulichikhin VG (2020) Rheological properties of aqueous dispersions of bacterial cellulose. PRO 8:423.
12. Wang J, Tavakoli J, Tang Y (2019) Bacterial cellulose production, properties and applications with different culture methods – a review. Carbohydr Polym 219:63–76.
13. Zheng L, Li S, Luo J, Wang X (2020) Latest advances on bacterial cellulose-based antibacterial materials as wound dressings. Front Bioeng Biotechnol 8:593768.
14. de Amorim JDP, da Silva Junior CJG, de Medeiros ADM, do Nascimento HA, Sarubbo M, de Medeiros TPM, Costa AFdS, Sarubbo LA. Bacterial Cellulose as a Versatile Biomaterial for Wound Dressing Application. Molecules. 2022; 27(17):5580. https://doi.org/10.3390/molecules27175580
15. Andriani, D.; Apriyana, A.Y.; Karina, M. The optimization of bacterial cellulose production and its applications: A review. Cellulose 2020, 27, 6747–6766.
16. Amorim, J.D.P.; Nascimento, H.A.; Silva Junior, C.J.G.; Medeiros, A.D.M.; Silva, I.D.L.; Costa, A.F.S.; Vinhas, G.M.; Sarubbo, L.A. Obtainment of bacterial cellulose with added propolis extract for cosmetic applications. Polym. Eng. Sci. 2022, 62, 565–575.
17. Medeiros, A.D.M.; Silva Junior, C.J.G.; Amorim, J.D.P.; Nascimento, H.A.; Converti, A.; Costa, A.F.S.; Sarubbo, L.A. Biocellulose for Treatment of Wastewaters Generated by Energy Consuming Industries: A review. Energies 2021, 14, 5066.
18. Costa, A.F.S.; Rocha, M.A.V.; Fernandes, L.M.A.; Queiroz, J.A.; Agra, A.C.M.G.; Amorim, J.D.P.; Sarubbo, L.A. Bacterial cellulose: Characterization of a biomaterial for apparel products application. Res. J. Text. Appar. 2021.
19. Park M.-A., Lee S.-G., Choi K.-H., Cho B.-U. Effects of Surface Coating of Cellulose II-based MFC on Paper Properties. J. Korea Tech. Assoc. Pulp Pap. Ind. 2019;51:28–36. doi: 10.7584/JKTAPPI.2019.02.51.1.28.
20. Shpichka A.I., Butnaru D., Bezrukov E.A., Sukhanov R.B., Atalaa A., Burdukovskii V.F., Zhang Y., Timashev P. Skin tissue regeneration for burn injury. Stem Cell Res. 2019;10:1–16. doi: 10.1186/s13287-019-1203-3.
21. Gorgieva S. Bacterial Cellulose as a Versatile Platform for Research and Development of Biomedical Materi-als. Processes. 2020;8:624. doi: 10.3390/pr8050624.
22. Du R., Wang Y., Zhao F., Qiao X., Song Q., Li S., Kim R.-C., Pan L., Han Y., Xiao H., et al. Production, Optimization and Partial Characterization of Bacterial Cellulose from Gluconacetobacter xylinus TJU-D2. Waste Biomass Valorization. 2020;11:1681–1690. doi: 10.1007/s12649-018-0440-5.
23. Chopra, H.; Gandhi, S.; Gautam, R.K.; Kamal, M.A. Bacterial Nanocellulose Based Wound Dressings: Current and Future Prospects. Curr. Pharm. Des. 2022, 28, 570–580.
24. Huang, J.; Heng, S.; Zhang, W.; Liu, Y.; Xia, T.; Ji, C.; Zhang, L.J. Dermal extracellular matrix molecules in skin development, homeostasis, wound regeneration and diseases. Semin. Cell Dev. Biol. 2022, 128, 137–144.