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Innovative Progress in Bacterial Cellulose for Biomedical Applications

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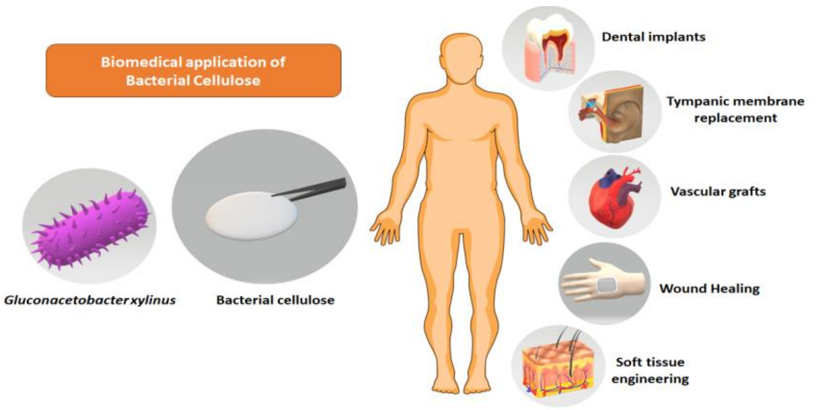
Advances in science materials and the development of biopolymers have gained attention mainly as a substitute for traditional plastic. Bacterial cellulose (BC) is a great candidate as it is a very important biopolymer with possible biocompatibility, non-toxic and sterilizable, and can be used in several biomedical applications. This article presents a bibliometric search of scientific documents showing the growth of research related to the use of this material in biomedicine emphasizing BC as a substitute for plastic. Original research articles and review articles published up to 2023 were considered, resulting in 330 documents. The work focused on titles and abstracts that contained the chosen keywords related to the topic in question. The results of the investigation emphasize the necessity of more research in the area and a greater need of collaboration. Studies have shown the potential for the use of bacterial cellulose in wound healing, tissue repair, and other healthcare applications. Therefore, the results of the investigation emphasize the need for more research in the area and also highlight the need for greater collaboration.

Graphical abstract



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1. Introduction

The development and improvement of plastic is of great importance to human beings because these materials are cheap, light, and resistant. They are used as packaging for food, as protection against mechanical shocks, in construction, and in medicine, making them ideal materials for a wide range of products and applications, obviously with broad social benefits [1, 2].

Despite their extraordinary use, tens of millions of tons of these materials are discarded into the environment annually,

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with an estimated 8 million tonnes of plastic waste entering the ocean each year [2].

Due to this, pollution caused by the widespread use of plastic can be considered one of the most alarming environmental problems of modern humanity, as it affects the water and land alike [3].

This plastic residue wrongfully discarded on the streets and beaches can become literal islands of trash. Being a non-biodegradable material, it cannot be decomposed by microorganisms, and once they have been discarded, they become a problem of monumental proportions [3].

These materials can also easily end up in marine environments where they decompose into small particles called microplastics (small solid particles of polymer-based materials) [4].

Due to this problem, several studies are currently looking for alternatives to the use of plastic materials, with the aim of building a sustainable future, with reduced impacts on nature. Therefore, replacing plastic, which comes from non-renewable raw materials, with paper (from renewable sources) is an extremely viable alternative.

Recent advances in the field of biomaterials and their applications in biomedical areas show the great potential of various polysaccharides in the development of new classes of medical materials. Bacterial cellulose belongs to one of the most promising classes of these biopolymers.

Cellulose is the most abundant natural polymer and an inexhaustible raw material on earth [5]. It is a first-rate biopolymer due to its extensive productive importance, being one of the main constituents of plants. Cellulose is synthesized in a sustainable way by several entities belonging to the kingdoms Plantae, Animalia, Fungi and Bacteria [6]. Chemically, it is a linear homopolysaccharide, composed of repeating β-D-glucopyranose units linked by β-1,4 glycosidic bonds [6].

Cellulose is a group of carbohydrates that contains considerable amounts of hydroxyl groups which remain in the form of a polymer chain and has wide applications in many industries, such as cellulose and paper, pharmaceutical and even as a source of renewable fuel [7,8]. However, obtaining pure cellulose as a substrate has been a hard task to achieve, mainly because in plants, cellulose is often associated with lignin, pectin, hemicellulose and other biogenic products [9]. In addition to cellulose nanoparticles obtained from plants, algae, fungi and bacteria can also produce cellulose, which are called microbial cellulose [10]. Among them, bacterial cellulose (BC) is a natural nanomaterial produced by some species of bacteria [11].

Therefore, the objective of this article is to explore growing research related to the topic of bacterial cellulose for specific use in medicine through a bibliometric review emphasizing BC as a substitute for plastic.

2. Historical Overview

2.1 Bacterial Cellulose Producing Bacteria

Bacterial cellulose (BC) was first mentioned in 1886 [12]. During acetate fermentation, Brown (1886) [13] observed a white, gelatinous, elastic film about 25 mm thick floating on the surface of a liquid medium. The bacteria responsible for the synthesis of this exopolysaccharide turned out to be *Bacterium xylinum*, which is now classified as *Komagataeibacter xylinus* [14].

Several types of bacteria are known to produce bacterial cellulose, which is considered an extracellular polysaccharide, generally formed by bacteria of the genera Acetobacter, Achromobacter, Acetobacter, Aerobacter, Agrobacterium, Alcaligenes, Azobacter, Gluconacetobacter, Pseudomonas, Rhizobium, Salmonella and others, through acetic fermentation [15, 16].

However, the Gram-negative bacterium, Gluconacetobacter xylinus (conventionally known as Acetobacter xylinum), proves to be the most efficient in the producing of BC [17]. This group of rod-shaped aerobic Gram-negative bacteria, due to their high yield of cellulose, is considered a reference organism in the production of BC for commercial fermentation [18]. This bacterium has a highly efficient metabolism, which allows the conversion of sugars present in the growth medium into cellulose effectively and generally with higher yield compared to other bacteria [19].

In comparison to vegetable cellulose, both are chemically equivalent, but bacterial cellulose has higher porosity, a higher degree of crystallinity and higher purity (free from lignin, hemicellulose, pectin and other biogenic components) [20]. It has a high degree of crystallinity, resulting in a more organized and stronger structure. Additionally, it is biocompatible, meaning the cellulose derived from microorganisms is non-toxic and biocompatible [21].

Furthermore, it also has high wet tensile strength, large surface area, high water retention capacity, excellent permeability, flexibility, elasticity and durability. Due to its distinct physico-chemical characteristics, it has widespread applications in various sectors, such as food industries, biomedical sectors and for the formation of bio-based polymers and nanocomposites [8].

2.2 Chemical structure and physical properties of BC

BC is formed by linear chains of 1,4-β-glucan, which are bound by internal and external hydrogen bonds, hydrophobic interactions, and van der Waals forces. These β-glucan chains build regular elementary fibrils that aggregate into microfibrils [22]. The width of microfibrils is 50–100 nm, the thickness is 3–8 nm (Lin et al., 2020). Packets of microfibrils form macrofibrils. These very tightly arranged, ultra-thin, 1–9 μm long macrofibrils form an organised three-dimensional structure, which helps to provide very high mechanical resistance to cellulose [23]. Its unique chemical structure and exceptional physical properties make it highly valuable for various industrial and biomedical applications.

The reticulated network originally provides a safe and nutrient- and oxygen-rich living environment for bacteria [24]. In the term of performances, the unique structure endows BC outstanding mechanical properties, high water holding capability, high suspension stability, and excellent gas permeability [25]. It is demonstrated that BC has a very high wet tensile strength, although it varies depending on the genera and strains of bacteria as well as the fermentation conditions [26].

2.3 Production of Bacterial Cellulose

The choice between the methods for BC production depends on the application scenarios as the morphologies and properties of BC yielded by the two methods are very different [27,28]

If BC microbial producers are cultivated in liquid media by a static method, cellulose is generated in an air/liquid interface as a gelatinous membrane [29, 30]. The membrane helps bacterial survival, acting as a protective barrier against adverse conditions (e.g., UV radiation, periods of dehydration, and redox processes) and other microorganisms, or by enhancing the availability of oxygen because of its proximity to the air phase [27]. However, the low production rate and its high cost are the main characteristics of the static culture method [28].

If BC production is carried out in agitated or stirred conditions, instead of the static method, the resulting BC small irregular pellets are fully suspended in the culture media [17]. Agitated cultures emerge as a necessity for improving the low rates in BC production associated with static cultures and to scale up the process, achieving a feasible industrial production [29,17]. In this case, more bacteria can attract oxygen from the air, leading to faster cellulose synthesis. The agitated fermentation is easily amplified to a large scale of industrial production [22], but it frequently induces an adverse conversion of bacteria into the non-cellulose producing mutants that reduce the yield [30]. There is extensive hydrogen bonding between the hydroxyl groups of the glucose units within and between the cellulose chains. This network of hydrogen bonds imparts high tensile strength and rigidity to the structure of BC [22].

BC demonstrates high thermal stability, retaining its properties at elevated temperatures besides the films of BC are transparent and flexible.

Applications of BC produced by the two different methods also differ, considering their own morphologies and properties [17]. One key example is the static fermentation being preferable to produce materials which require a fixed geometry, good wet tensile strength and high-water retention capability - such as face masks or wound dressings. In comparison, BC produced by agitated fermentation is fermentation represents the superiority in suspending stability, which is majorly used for particulate suspension in the beverages [17].

2.4 Biopolymer applications for use in biomedicine as a substitute for conventional plastic

The application of BC as a material in the biomedical field has attracted a lot of attention in recent years, due to its structure, mechanical properties and biocompatibility to its high purity, hydrophilicity, structure forming potential, chirality and biocompatibility, additionally, it is a promising alternative to conventional plastics [18].

Because it has a cross-linked network of fine fibers with coating, bonding, thickening and suspension characteristics, bacterial cellulose has a wide range of applications. These distinguishing features make BC a very special material to demonstrate its superiority in biomedical applications [31].

This biopolymer (derived from biological sources, such as plants, animals or microorganisms, or produced by biotechnological processes) can be used as a substitute for synthetic materials, such as synthetic Teflon, Vinyon fibers, which are commonly used in the production of synthetic blood vessels. BC presents a lower risk of clot formation, which makes it an innovative option to overcome problems arising from vascular diseases [27].

The native bacterial cellulose has mechanical properties, including shape retention and tear resistance, which are superior to many synthetic materials. Compared to organic sheets such as polypropylene, polyethylene terephthalate or cellophane, BC processed into a film or sheet exhibits remarkable mechanical strength [18].

In the early 1980's Johnson & Johnson pioneered in exploratory investigations on the use of microbial cellulose as a liquid loaded pad for wound care. Since that time, a company in Brazil, Biofilm Industries, has continued to investigate the properties of microbial cellulose and is beginning to market specific microbial cellulose products in the wound care market [32].

Currently, BC membranes are widely used as dressing devices, marketed under several brands, such as Bionext®, Membracell®, and Xcell®, as they mimic the extracellular matrix to increase epithelialization [18,33]. They show rapid epithelialization and tissue regeneration rates in wound-healing treatments, such as diabetic foot wounds, chronic wounds, and burns [33]. The treatments of wounds using BC membranes are more efficient compared with conventional gauze or synthetic materials such as Tegaderm®, Cuprophan®, or Xeroform™ [33].

In addition to commercialized dressings, BC also has great potential in other areas of biomedical application [33], including artificial skin, contact lenses, dental implants, controlled-release drug administration, hemostatic materials, vascular grafts, tympanic membrane replacement, scaffolds for tissue engineering, biosensors and diagnosis [34 – 36].

Biopolymers such as PLA and PHA are used to manufacture sutures and stents that naturally degrade in the body, eliminating the need for a second surgery for removal [37].

The implantation of BC into living organisms, using diverse in vivo models, demonstrated a low inflammatory response, the absence of a foreign body reaction, blood compatibility, and the absence of hemolysis [31]. Due to their mechanical stability and flexibility, they adapt to different parts of the body [31, 24].

3. Material and Methods

3.1 Bibliometric Review

In this paper was bibliometric review was conducted because it offers a global perspective and how they progressed over time it is a rigorous method for exploring large volumes of scientific data [38, 39]. Bibliometric Review uses quantitative methods to analyze academic production in each area of knowledge.

This research, a bibliographic review, was carried out using scientific databases such as PubMed, Scielo and Science Direct using the following keywords: ‘bacterial cellulose’ to analyze in general and ‘bacterial cellulose in biomedicine’ to analyze the title and abstract of each article read, and those that did not align with the theme were excluded.

The bibliographic review work is relevant from a scientific point of view, which allows for greater depth of the subject covered and developed based on materials already prepared.

The inclusion criteria of the papers were according to Bianchet et al., (2020) [40], that contained the keywords in the title, abstract, or article body. The exclusion of the papers was performed in repeated articles. And with the bibliometric review applied to this research, it was possible to select the articles that addressed to the theme of the use of cellulosic fiber synthesized by bacteria for medical use.

4. Results and Discussion

A total of 72,037 articles were initially found with use the keywords: 'bacterial cellulose' analyzing the last 10 years (2013 – 2023). Being a total separated by scientific databases PubMed 7871 articles, Scielo 54 articles and Science Direct 64,112 articles.

Fig. 1 shows the years of publication in parallel with the scientific database PubMed.

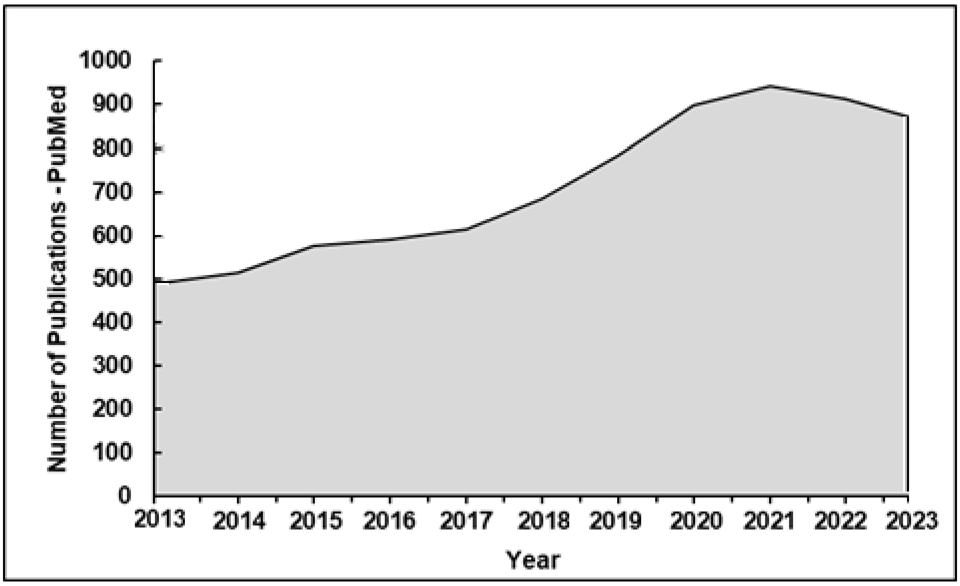

Fig. 1. Correlation of the number of publications using the keyword 'bacterial cellulose' over the 10 years in the scientific database PubMed.

It was possible to evaluate a growing number of publications over the ten years analyzed. Still according to the PubMed platform, it was in 1922 that the first paper containing the keyword in question was published.

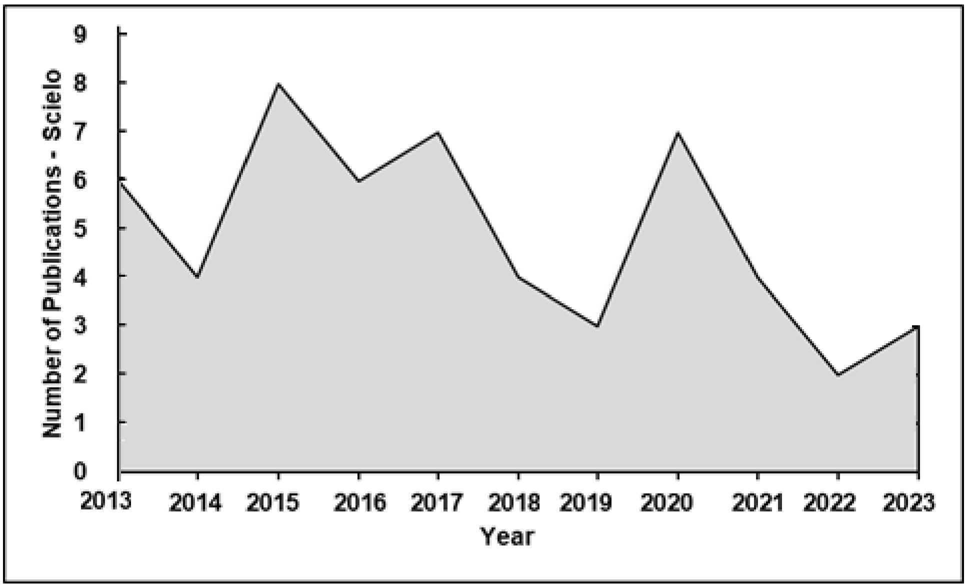

Fig. 2. Correlation of the number of publications using the keyword 'bacterial cellulose' over the 10 years in the scientific database Scielo.

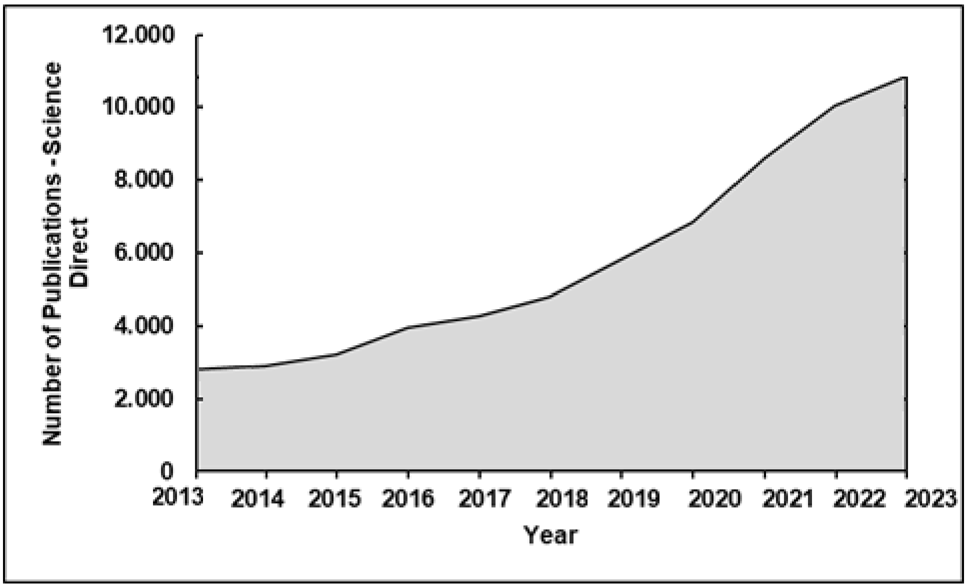

Fig. 3. Correlation of the number of publications using the keyword 'bacterial cellulose' over the 10 years in the scientific database Science Direct.

In figures 1 and 3, research related to the topic studied in this article is increasingly developing. Only for the Scielo database there was variation, but this data can be explained by the fact that few articles were found.

But according to figures 1 and 3 it is possible to clearly observe a growing interest in publications related to the topic. This growth over the years is expected because in addition to bacterial cellulose being able to replace conventional plastic in many applications, excellent results could be evaluated in several areas such as pharmaceutical and biomedical [22, 41].

A total of 3.139 articles were initially found using the keywords: 'bacterial cellulose in biomedicine' analyzing the last 10 years (2013 - 2023). Being a total separated by scientific databases PubMed 88 articles, Scielo 0 article and Science direct 3.051 articles but 330 were subsequently excluded following the criteria established in the methods. Only review articles and research articles that addressed the theme of biomaterials for use in biomedicine were included in the selection.

For final selection only review articles and research articles with the theme of bacterial cellulose for use in biomedicine were used totalizing 15 papers to the Science Direct platform (Table 1), 17 papers to the Pubmed (Table 2), 0 papers for the Scielo and 5 papers for both databases (Table 3) totalizing 37 papers.

Table 1. Analysis of the 15 Articles Relating to bacterial cellulose for use in biomedicine to the ScienceDirect.

Year	Authors	Title/*Journal*
2014	Almeida et al., [42]	Bacterial cellulose membranes as drug delivery systems: An in vivo skin compatibility study/*European Journal of Pharmaceutics and Biopharmaceutics*
2020	Oprea et al., [43]	Recent advances in composites based on cellulose derivatives for biomedical applications/ *Carbohydrate Polymers*
2021	Silva el al., [44]	Microbial production of medium-chain length polyhydroxyalkanoates/*Process Biochemistry*
2021	Gregory et al., [45]	Bacterial cellulose: A smart biomaterial with diverse applications/*Materials Science and Engineering: R: Reports*
2021	Salinas et al., [46]	Production of bacterial cellulose tubes for biomedical applications: Analysis of the effect of fermentation time on selected Properties/ *International Journal of Biological Macromolecules*
2021	Mbituyimana et al., [47]	Bacterial cellulose-based composites for biomedical and cosmetic applications: Research progress and existing products/*Carbohydrate Polymers*
2022	Navya et al., [48]	Bacterial cellulose: A promising biopolymer with interesting properties and applications/*International Journal of Biological Macromolecules*
2022	Jose et al., [49]	Bacterial biopolymers: From production to applications in biomedicine/*Sustainable Chemistry and Pharmacy*
2023	Mondal et al., [50]	Hydroxyapatite: A journey from biomaterials to advanced functional materials/ *Advances in Colloid and Interface Science*
2023	Janmohammadi et al., [51]	Cellulose-based composite scaffolds for bone tissue engineering and localized drug delivery/ *Bioactive Materials*
2023	Chandel et al., [52]	The versatile world of cellulose-based materials in healthcare: From production to applications /*Industrial Crops and Products*
2023	Emenike et al., [54]	Advances in the extraction, classification, modification, emerging and advanced applications of crystalline cellulose: A review /*Carbohydrate Polymer Technologies and Applications*
2023	Muiuri et al., [54]	Bacterial cellulose: Recent advances in biosynthesis, functionalization strategies and emerging applications/*European Polymer Journal*
2023	Mohammadi et al., [55]	Bacterial cellulose-based composites as vehicles for dermal and transdermal drug delivery: A review/ *International Journal of Biological Macromolecules*

Table 2. Analysis of the 15 Articles Relating to bacterial cellulose for use in biomedicine to the ScienceDirect.

Year	Authors	Title/*Journal*
2016	Hu et al., [56]	Bioabsorbable cellulose composites prepared by an improved mineral-binding process for bone defect repair/ *Journal of Materials Chemistry B*
2019	Revin et al., [57]	Production of Bacterial Exopolysaccharides: Xanthan and Bacterial Cellulose/*International Journal of Molecular Sciences*
2019	Carvalho et al., [36]	Latest Advances on Bacterial Cellulose-Based Materials for Wound Healing, Delivery Systems, and Tissue Engineering/*Biotechnology Journal*
2019	Nóbrega et al., [58]	From a Basic Microalga and an Acetic Acid Bacterium Cellulose Producer to a Living Symbiotic Biofilm/*Materials*
2021	Mensah et al., [59]	Membrane Technological Pathways and Inherent Structure of Bacterial Cellulose Composites for Drug Delivery/*Bioengineering*
2021	Blanco et al., [60]	From Residues to Added-Value Bacterial Biopolymers as Nanomaterials for Biomedical Applications/*Nanomaterials*
2021	Nunes et al., [61]	Development of Bacterial Cellulose Biocomposites Combined with Starch and Collagen and Evaluation of Their Properties/*Materials*
2021	Ciecholewaska-Jusko et al., [62]	Potato Juice, a Starch Industry Waste, as a Cost-Effective Medium for the Biosynthesis of Bacterial Cellulose/*Molecular Sciences*
2022	Zhu et al., [63]	Clinical application of a double-modified sulfated bacterial cellulose scaffold material loaded with FGFR2-modified adipose-derived stem cells in urethral reconstruction/*Stem Cell Research & Therapy*
2022	Fatema et al., [64]	Modifications of cellulose-based biomaterials for biomedical applications/*Frontiers in Bioengineering and Biotechnology*
2022	Arriaga et al., [65]	When microbial biotechnology meets material engineering/*Microbial Biotechnology*
2023	Bimmer et al., [66]	Analysis of cellulose synthesis in a high-producing acetic acid bacterium Komagataeibacter hansenii/*Applied Microbiology and Biotechnology*
2023	Netrusov et al., [67]	Exopolysaccharides Producing Bacteria: A Review/*Microorganisms*
2023	Liu et al., [68]	Optimization of Surface-Engineered Micropatterns on Bacterial Cellulose for Guided Scar-Free Skin Wound Healing/*Biomolecules*
2022	Fusco et al., [69]	Small-diameter bacterial cellulose-based vascular grafts for coronary artery bypass grafting in a pig model/*Frontiers in Cardiovascular Medicine*

Table 3. Analysis of the 5 Articles Relating to bacterial cellulose for use in biomedicine to both databases.

Year	Authors	Title/*Journal*
2016	Barud et al., [41]	A multipurpose natural and renewable polymer in medical applications: Bacterial celulose/ *Carbohydrate Polymers*
2017	Wilkens et al., [70]	GH62 arabinofuranosidases: Structure, function and applications/*Biotechnology Advances*
2019	Chen et al., [22]	In situ preparation of bacterial cellulose with antimicrobial properties from bioconversion of mulberry leaves/ *Carbohydrate Polymers*
2019	Hu et al., [71]	Surface engineering of spongy bacterial cellulose via constructing crossed groove/column micropattern by low-energy CO_2 laser photolithography toward scar-free wound healing/ *Materials Science and Engineering: C*
2020	Liu et al., [72]	A simultaneous grafting/vinyl polymerization process generates a polycationic surface for enhanced antibacterial activity of bacterial celulose/ *International Journal of Biological Macromolecules*

The summary of the 330 articles found with the keywords defined in the methodology was examined and after this examination 37 articles were chosen as being specific to the topic in question. Most of the articles found are not bibliometric reviews, which highlights the need for new theoretical studies on the topic.

According to Bimmer et al., (2023), [66] the microorganism *Komagataeibacter hansenii* ATCC 53.582 is a well-characterized high-yield producer of bacterial cellulose used in the industry. However, other microorganisms have also been evaluated for cellulose production how *Gluconacetobacter xylinus* (syn *Komagataeibacter xylinus*) is a Gram-negative bacterium belonging to the Acetobacteraceae family [46].

Jose et al., (2022), [49] discussed the use of this bacterial cellulose to obtain controlled/sustained drug release used in wound healing dressings, orthodontic applications, and hydrogel production for biomedical use. The biosynthesis of bacterial cellulose needs to be carefully thought out because of this, [46] developed a study resulting in biosynthesis in cylindrical oxygen permeable molds allowing the production of hollow tubular structures for applications how ureters, urethra, trachea, artificial blood vessels, etc (Figure 4).

Additionally, bacterial cellulose is hydrophilic, and this often becomes a problem depending on the application of biomedicine. However, studies indicate that the application of micropatterning technology can increase surface hydrophobicity with the aim of alleviating the problem [71].

Furthermore, to be applied in biomedicine it is important that the material has inherent antibacterial activity and for this, [25] studied a strategy to chemically anchor a quaternary ammonium salt (RN $(CH_3)^+$) with a special vinyl group (2-methacryloyloxyethyl trimethylammonium chloride, METAC). With this study, it was possible to observe antibacterial activity on the surface of the material, against *Escherichia coli* and *Staphylococcus aureus*, important microorganisms that cause several hospital infections.

Besides most cases, bacterial cellulose is not used alone, and a composite is produced, which are materials formed by the union of other materials with the aim of obtaining a higher quality product [73].

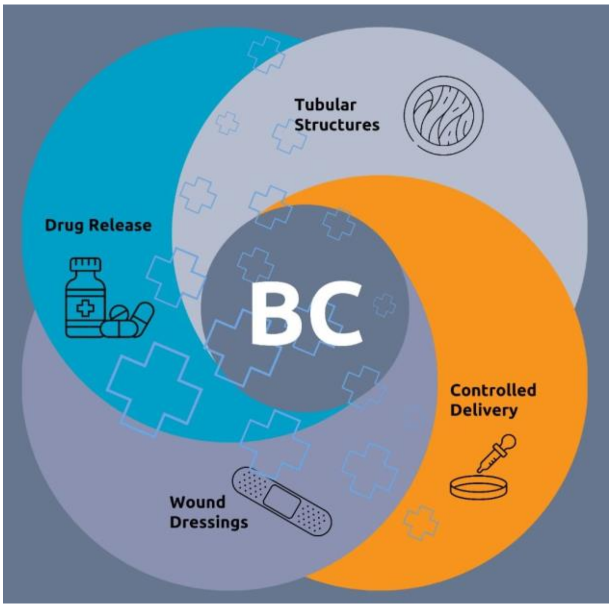

Fig. 4. Diagram illustrating the various applications of bacterial cellulose in biomedicine.

Therefore, Nunes et al., (2021), [61] produced a bio composite based on bacterial cellulose with different concentrations of collagen and starch, thus offering a great solution to the ineffectiveness of current dressings, that is, current dressings are used without considering the type of injury and may harm the healing process of different types of wounds, especially in cases where traditional adhesive dressings can damage the skin when removed, causing small injuries, and these injuries can be sources of contamination [20, 74].

Almeida et al., (2014), [42] the skin irritation potential of bacterial cellulose was evaluated in human subjects only with the addition of glycerol which acts as a plasticizer and also as a moisturizer. In only five volunteers, clinical scores showed weak reactions after 24 hours of testing, but in all others the scores were zero, demonstrating efficacy and low irritation to human skin. As glycerol also acts as a moisturizer, the authors recommend its use in the treatment of patients with skin diseases characterized by dryness such as psoriasis and atopy.

Another study carried out by Nunes et al., (2021), [61] developed nine different formulations based on bacterial cellulose together with collagen, starch and glycerolde. Bio composites to improve injury treatment.

Zhu et al., (2022), [63] via physical drilling and sulfonation the bacterial cellulose composite became more conducive to cell fixation and degradation to be used in urethral reconstruction for the treatment of patients with urethral strictures.

5. Conclusions

In this review article, the main biomedical applications of bacterial cellulose in the world were presented. Based on the search indexes, relevant articles were found, which provided an overview of the main characteristics of bacterial cellulose, and the increasing production of BC-based materials in recent years can be observed. As it is a biodegradable and non-toxic polymer, it offers good biocompatibility and has high mechanical and tensile strength, high chemical stability, high water absorption capacity and the possibility of inserting materials to obtain composites.

Furthermore, bacterial cellulose has been shown to have superior properties to plant-derived cellulose and has been used in several studies. For these reasons, BC meets the essential criteria to be used as a material for biomedical applications, including its various physical-chemical aspects and functionalities. Since wound healing, tissue repair and other applications in healthcare are of great social importance, bacterial cellulose can significantly reduce patients' pain. The more studies we have in this area, the more we will expand its use as a vital biomaterial that, due to its unique properties and effectiveness, can be used safely.

Author Contributions

Sharise Beatriz Roberto Berton: Methodology; Resources; Writing – Original Draft; Validation; Writing – Review & Editing. Lívia Mainardes Rafael: Investigation; Writing – Original Draft; Resource; Writing – Review & Editing. Vinícius Campos Ferreira: Writing – Original Draft; Supervision; Writing – Review & Editing. Jomar Berton Junior: Writing – Original Draft; Resources; Project Administration; Supervision; Writing – Review & Editing.

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