

# Bacterial Cellulose and Extracellular Matrixes Hydrogels

Subjects: **Veterinary Sciences**

Contributor: Izabela Rodrigues da Silva , Bruna Tássia Pantoja , , Ana Claudia Carreira , Maria Angelica Miglino

Application of biomaterials is one of the most innovative treatments for heart regeneration, involving the use of hydrogels from decellularized extracellular matrix, and their association with nanomaterials, such as alginate, chitosan, hyaluronic acid and gelatin. A promising material is bacterial cellulose hydrogel, due to its nanostructure and morphology being similar to collagen. Cellulose provides support and immobilization of cells, which can result in better cell adhesion, growth and proliferation, making it a safe and innovative material for cardiovascular repair.

extracellular matrix

biomaterials

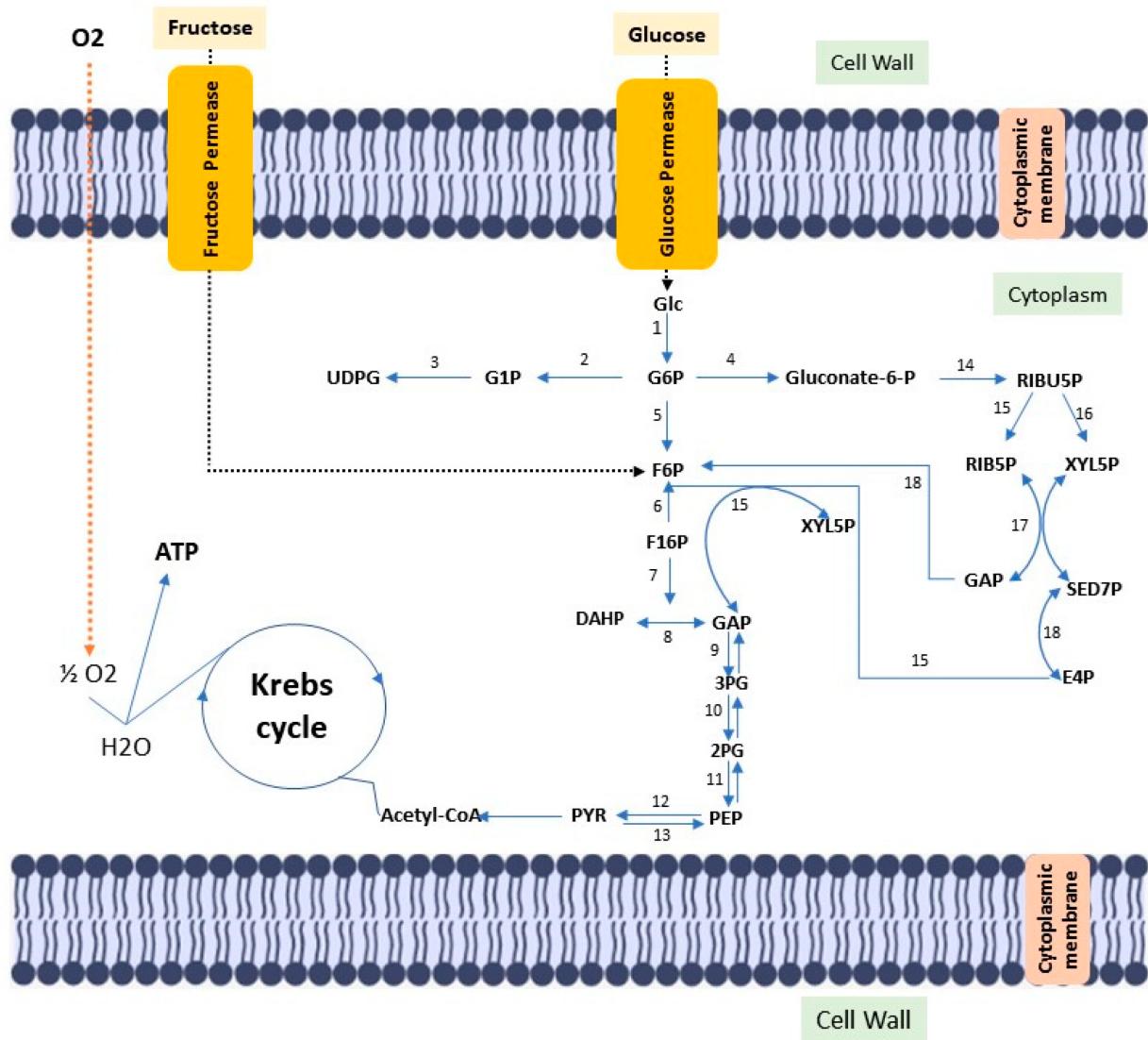
hydrogels

bacterial cellulose

## 1. Bacteria Cellulose: An Innovative Biomaterial

Bacterial cellulose was discovered two centuries ago, however, only in the last few decades, with the development of green chemistry and nanotechnologies, is it gaining space in the research community both in the academic and industrial fields. It is a versatile nanomaterial of commercial interest due to its natural purity, biodegradability, biocompatibility and non-cytotoxicity [\[1\]](#). Since its discovery, significant research has focused on its production, manufacturing and new applications. Currently, bacterial cellulose has been widely used in drug delivery, tissue engineering, wound dressing, food and cosmetics [\[2\]](#)[\[3\]](#).

Cellulose is the most abundant biopolymer on the planet, despite the vast biochemical and phylogenetic diversity of living beings. It is a fibrous, resistant substance insoluble in water, found in the protective cell walls of plants, mainly in stems, trunks and woody portions, being the main structural component of plants giving them mechanical and structural integrity. However, some animals (such as urochordates), fungi and some bacteria also produce it [\[4\]](#) [\[5\]](#)[\[6\]](#)[\[7\]](#)[\[8\]](#). There are other routes of cellulose synthesis, such as chemosynthesis and enzymatic synthesis from glucose derivatives. Cellulose can be classified into two types according to the production origin. There is cellulose from plant biomass, which stands out as a source of raw material for the production of bio-based fuels, paper, packaging and biomedical applications [\[9\]](#)[\[10\]](#). Cellulose is derived from a variety of microorganisms such as fungi, algae (*Valonia ventricosae*, *Glaucoma*), and bacterial strains belonging to the genera *Agrobacterium*, *Aerobacter*, *Achromobacter*, *Sarcina*, *Acetobacter*, *Rhizobium*, *Salmonella* and *Azotobacter* that produce acetic acid [\[11\]](#)[\[12\]](#)[\[13\]](#). *Gluconacetobacter xylinus* (formerly known as *Acetobacter xylinus* and later *Komagataibacter xylinus*) can produce bacterial cellulose in greater amounts when compared to other species [\[14\]](#). Such bacteria produce bacterial cellulose in a biosynthetic pathway, involving the secretion of polysaccharides formed while using carbon sources in the medium. Carbon sources such as glucose, sucrose, fructose and glycerin are often used in culture media to produce bacterial cellulose [\[15\]](#). (Figure 1).



**Figure 1.** Diagram of the metabolic pathway, stimulated by fructose and glucose, for bacterial cellulose biosynthesis. Glc: Glucose; ATP: ATP glucokinase (1); GP6: Glucose 6-phosphate; Phosphoglucomutase (2); G1P: Glucose 1-phosphate; UTP-glucose-1-phosphate uridylyltransferase (3); UDPG: UDP-glucose; Glucose 6-phosphate dehydrogenase (4); Gluconate-6-p: Gluconate-6-phosphate; Phosphoglycoisomerase (5); F6P: fructose 6-phosphate; Fructokinase ATP (6); F16P: Fructose 1,6-bisphosphate; Aldolase (7); Triose phosphate isomerase (8); DHAP: Dihydroxyacetone phosphate; GAP: glyceraldehyde 3-phosphate; Glyceraldehyde 3-phosphate dehydrogenase (9); 3PG: 3-Phosphoglyceric acid; Phosphoglyceromutase (10); 2PG: 2-Phosphoglyceric acid; Enolase (11); PEP: 2-phosphoenolpyruvate; Pyruvate kinase (12); Pyruvate diphosphatase (13); PYR: Pyruvate; 6-phosphogluconate dehydrogenase (14); RIBU5P: Ribulose 5-phosphate; Phosphoribulose epimerase (15); Phosphoribulose isomerase (16); RIB5P: Ribose 5-phosphate; XYL5P: Xylulose 5-phosphate; Transacetolase (17); SED7P: sedoheptulose 7-phosphate; E4P: Erythrose 4-phosphate; GAP: glyceraldehyde 3-phosphate; Transaldolase (18).

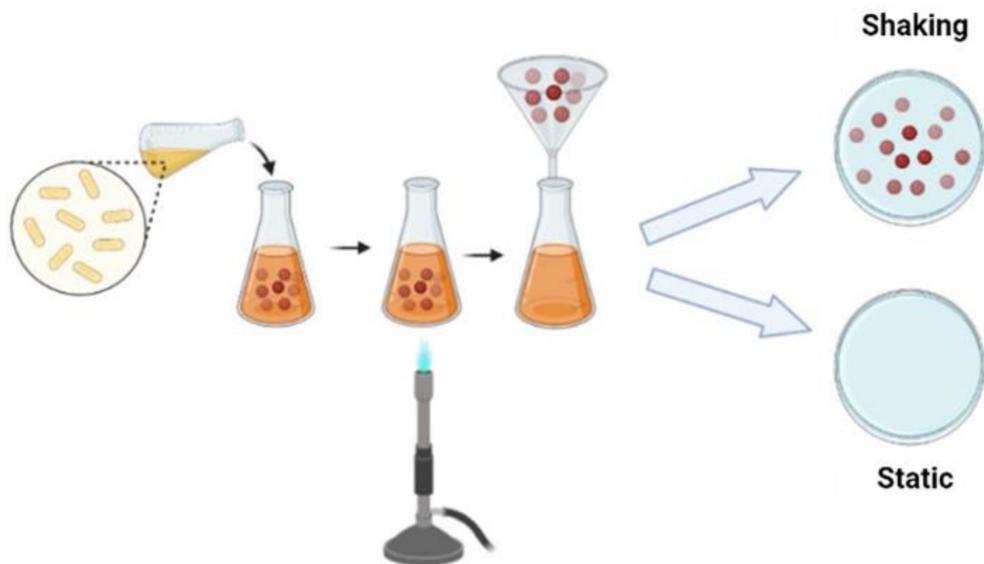
The chemical structure of vegetable cellulose and bacterial cellulose are the same. However, bacterial cellulose has advantages such as high purity (as it is free of lignin and hemicellulose), high crystallinity (84–89%), high water

retention (100 times its dry weight), good mechanical properties and 3D nanofibrous structure [16][17][18][19][20]. These characteristics make BC a potential material for different applications [21].

Louis Pasteur initially defined bacterial cellulose as a moist, gelatinous skin-like substance produced by the fermentation of coconut water. Later, in 1886, Adrian Brown systematically reported bacterial cellulose as a gelatinous membrane formed on the surface of *Bacterium aceti* culture medium during acetic acid fermentation [22]. Soon after its discovery, such a membrane was called the “vinegar plant”; the producing microorganism was initially called *A. xylinum* [23], according to the International Code of Nomenclature of Bacteria, after *G. xylinus* [24] [25]. This genus, *Komogataeibacter*, is currently the most studied species. It is a strictly aerobic gram-negative bacterium, present in fruits and vegetables in the process of decomposition. It is physiologically characterized by the production of acetic acid from ethanol, by the oxidation of acetate and lactate in carbon dioxide and water, being able to convert common carbon sources (glucose, glycerol, sucrose, fructose mannitol) at temperatures between 25 °C and 30 °C at a pH of 3–7.

There are different fermentation methods and such methods produce bacterial cellulose with different characteristics and applications; there are several methods to control fermentation and increase yield or obtain bacterial cellulose with different characteristics. Commonly, cellulose can be produced by static and agitated cultivation methods. To produce bacterial cellulose, bacteria use several carbon sources, such as glucose, fructose, mannose, glycerin, ethanol and pyruvate [26].

Under static conditions, bacteria need to float on the surface of the medium to obtain oxygen at the surface. Such bacteria produce cellulose at the interface of air and culture medium, similar to a film for a flotation mechanism, which allows the bacteria to stay in the air/liquid near the interface to get the oxygen needed for their metabolism. The film obtained forms a physical barrier protection against UV radiation, increases the ability to colonize other substrates and maintains its hygroscopic nature, enables moisture retention and prevents dehydration [15][21]. Bacterial cellulose produced under static conditions normally has high crystallinity and tensile strength [21]. Under agitation conditions, the bacteria form a fluffy, spherical or irregular cellulose in the medium; Unlike the static method, cultivation under agitation fills the culture medium with oxygen and enables faster cell growth. Cellulose obtained by stirring has a higher water retention capacity, lower Young's modulus and crystallinity [27]. (**Figure 2**).



**Figure 2.** Schematic representation of the BC production strategy.

## 2. Cellulose Structure

Vegetable cellulose is formed as a lignocellulosic polymer, that is, its cellulose molecules are strongly linked to others, such as lignin and hemicellulose and several others. Any accessory molecules that follow cellulose have specific functionalities in plant physiology. Furthermore, the cellulose content in plants depends on natural sources. Cellulose has a high content of impurities, which requires several molecular adjustments for later application, such as in biomedicine. Furthermore, the purification and isolation of plant cellulose is an arduous process, which involves complex mechanical treatments followed by chemical or enzymatic pre-treatments [28]. The pulp purification processes on an industrial scale generate high costs and great environmental risks due to the degree of toxicity. On the other hand, bacterial cellulose is obtained in a highly pure form, and its purification process is simple, ecologically correct and low cost [29].

Bacterial cellulose is a biomaterial, which can be obtained in a pure form, consisting of glucose and water units. It has a 6-membered cyclic structure with reactive primary and secondary hydroxyl groups; wherein the  $\beta$ -D-glucopyranose ring, all -OH groups are free, playing an essential role for the intermolecular H bond between two adjacent chains. Unlike plant cellulose, bacterial cellulose has a completely crystalline core surrounded by a less crystalline zone interpolated by the amorphous form of cellulose, as well as an arrangement of fibers in a 3D lattice structure. Its fibers tend to self-assemble because of strong interactions and hydroxyl groups, such fibers constitute a network structure interconnected by intramolecular hydrogen bonds, forming sheets with high surface area and high porosity [22]. It contains no hemicellulose or lignin and only a small amount of carboline and carboxyl moieties [30]. The tensile strength of cellulose is between 200–300 MPa, and its Young's modulus is up to 15–35 GPa [31]. Such mechanical properties are a direct consequence of the crystalline structures of nano and microfibrils. Furthermore, the association of high crystallinity, high content and water are responsible for the thermal stability of the biomaterial [32].

## 3. Bacteria Cellulose Properties

Bacterial cellulose has several properties, including porosity, mechanical properties, biocompatibility and biodegradability. Some studies in tissue engineering demonstrate that microporous and nanoporous scaffolds are suitable for cell growth [33]. In this way, the 3D porous structure, which allows better cell mobility, is a property of great importance in a biomaterial within tissue engineering, as this characteristic allows better mobility of cells or active agents in the transplant. Bacterial cellulose has membrane pores ranging from 100 to 300 nm, and the lack of macropores restricts the use of cellulose in some biomedical applications. Therefore, the association with gelatin, salt, sugar [34], polyethylene glycol [35], hydroxyapatite [36], sodium with calcium ions [37] is common to increase the porosity of the biomaterial.

The mechanical properties superior to those of vegetable cellulose are attributed to the cross-linked ultrafine fiber structure of bacterial cellulose [38]. Studies have shown that the force-deflection curves in single filaments present a value of  $78 \pm 17$  GPa, as well as fibers aligned with macrofibers based on bacterial cellulose, presented a Young's modulus of 16.4 GPa and the tensile strength of 248.6 MPa [39][40]. Wang et al. [41] prepared macrofibers based on bacterial cellulose through the drawing and wet twisting process. Such macrofibers showed deformation-dependent mechanical properties, that is, increasing the wet stretching stress, the tensile strength was increased to 826 MPa and the Young's modulus was 65.7 GPa. Such mechanical properties can be improved with the association of nanomaterials, such as graphene [42][43], graphene oxide [44], silver nanowires [45]; for example. The incorporation of 8% graphene increased tensile strength by 68.8%, while incorporation with 5% graphene oxide improved the Young's modulus of bacterial cellulose films by 10%, and the 30% graphene increased the tensile strength from  $\sim 15$  MPa to  $\sim 185$  MPa.

Biocompatibility can be defined as an adequate host response to the new material in each specific application and the absence of any toxic or allergic effects. Tissue compatibility is a basic and essential prerequisite for a new biomaterial. Such a property is possible due to the 3D nanofibrous network structure that allows cell penetration and proliferation [46]. Bacterial cellulose enables the growth of connective tissue cells, and it is a suitable material for the proliferation of different types of cells [47].

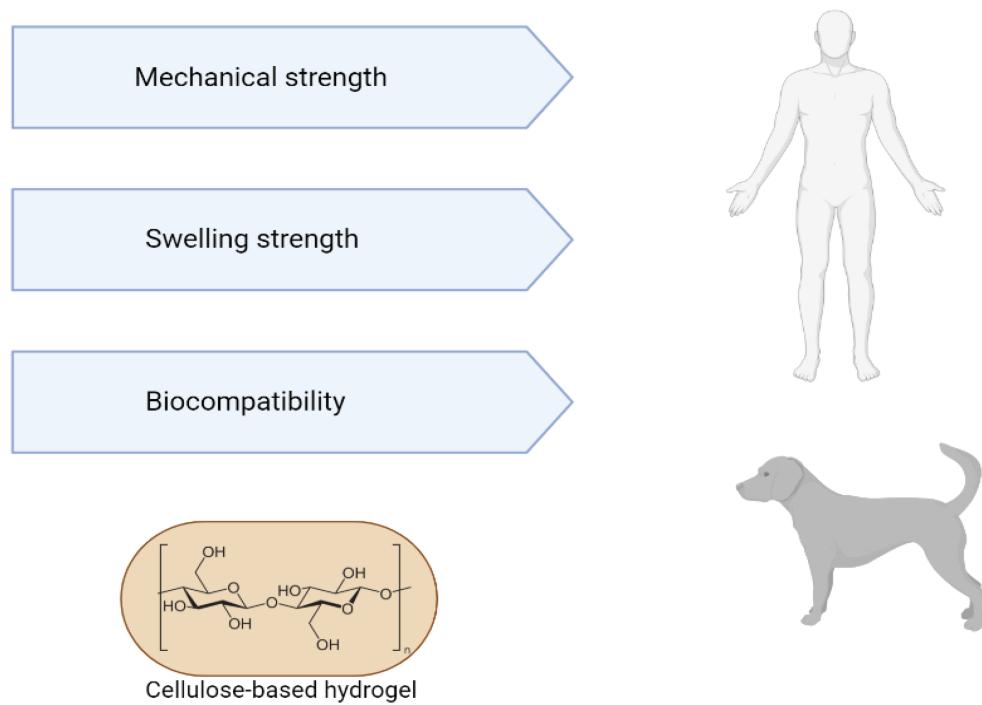
A material must be degraded in a timeframe that responds to the regeneration or healing process. There needs to be an adequate shelf life, no toxicity, and its mechanical properties must be biocompatible with the healing or regeneration process during degradation [34]. It is known that the cellulase enzyme degrades cellulose, and the absence of this enzyme in the human body makes the biomaterial non-biodegradable [48]. In this way, several works seek to increase its degradability, such as associating  $\gamma$ -radiations, which degrade rapidly "in vivo" within 2 to 4 weeks [49].

## 4. Hydrogel: Decellularized Extracellular Matrix and Cellulose

The characteristics of a suitable bioactive hydrogel scaffold need to be similar to the structure and biological properties of the extracellular matrix of natural tissue. Current bioactive polymer hydrogels are limited in simulating

various biological functions and mechanical properties of the matrix. A decellularized matrix consists of a natural scaffold prepared from tissues by removing cellular components and retaining the 3D structure of tissues or organs and some components of natural fibers, such as collagen. The scaffold is biocompatible, non-immunogenic and biologically active. A hydrogel-based on the use of decellularized extracellular matrix retains several transforming growth factors, which can enhance cell growth, migration, proliferation, differentiation and angiogenesis; such interaction with cells enables the remodeling of tissue and organ structure and is crucial for the regeneration and functional repair of tissues and organs [50].

Hydrogels from decellularized extracellular matrix have several advantages, such as injectability, since the viscous fluid pre-gel can be injected and polymerized at physiological temperature to form a hydrogel that adapts to the shape of the defect site; having biological activity inherent to the natural matrix; not containing immunogenic cellular material; demonstrate adjustability of their mechanical properties, which can be controlled by concentration or crosslinking. The gelled decellularized matrix has a three-dimensional structure suitable for cell growth. In turn, hydrogels are modifiable and can support cells, therapeutics, drugs and other bioactive molecules. The machinability of hydrogels represented by 3D geometric molecular shapes can be characterized by 3D printing. Thus, the applicability of hydrogels encompasses both “in vivo” tests (in organs such as the heart, liver, lung, brain, colon, spinal cord) and “in vitro” tests (as a substrate for cell culture, biliary tree reconstruction, organoid culture, bioinks derived from the decellularized extracellular matrix) [50][51][52][53] (Figure 3).



**Figure 3.** Advantages of using cellulose-based hydrogels for tissue engineering.

The characteristics of scaffolds derived from decellularized extracellular matrix have gained attention in tissue engineering. In the table below, researchers list some studies that produced extracellular matrix hydrogels for cardiac tissue regeneration.

Cellulose-based hydrogels are used in various fields related to tissue engineering, such as bioactive cartilage implants; prototypes of blood vessels [54]; dressings [55]; surgical implants [56]; drug delivery [57]; artificial corneal grafts [58]; and dental implants [59]. Some BC-based products have already been commercialized, such as BioFill®, Bioprocess®, XCell® and Dermafill™, which are examples of bio-based membranes that have the main characteristics necessary for an ideal dressing [57]. BASYC® is used for artificial blood vessels and Gegiflex® is available for tissue engineering [59]. Bacterial nanocellulose (NCB) has enormous potential for use as a scaffold in tissue engineering, as bacterial cellulose is more effective than plant cellulose, which justifies the fact that bacterial cellulose is the first choice in medical and health applications for tissue engineering [58]. This biomaterial has promising characteristics due to the similarity of its nanostructure and morphology to collagen, which makes cellulose an option for use in supporting and immobilizing cells. The architecture of bacterial cellulose-based materials can be designed at different scales, from the nano to the macroscale, controlling the biomanufacturing process. BC fibers are solid and, when used in combination with other biocompatible materials, produce nanocomposites particularly suitable for use in human and veterinary medicine [60].

Although bacterial cellulose has several properties that are of great value for tissue engineering and for several biomedical applications, numerous approaches are applied to change its physical-chemical and functional properties, such as porosity, crystallinity, chemical structures and functions, to fully explore the potential of bacterial cellulose. Bacterial cellulose can undergo both in situ and ex situ modifications (Figure 3). The in situ modification describes the exogenous molecules addition to the culture medium during cellulose biosynthesis, while the ex-situ modification describes the materials inclusion after bacterial cellulose biosynthesis and purification [15]. Such approaches seek to modify bacterial cellulose in order to expand its advantageous characteristics and solve its disadvantages (Figure 4).

Advantages	Disadvantages	Solutions
<ul style="list-style-type: none"> <li>• High porosity;</li> <li>• High crystallinity;</li> <li>• Mechanical properties;</li> <li>• 3D nanostructure;</li> <li>• Biocompatibility;</li> <li>• High elasticity;</li> </ul>	<ul style="list-style-type: none"> <li>• Absence of antimicrobial factor;</li> <li>• Non-degradability;</li> <li>• Limited Mechanical Property;</li> </ul>	<ul style="list-style-type: none"> <li>• Modifications <i>in situ</i></li> <li>• Modifications <i>ex situ</i></li> </ul>

**Figure 4.** Advantages and disadvantages of bacterial cellulose and solutions to improve its properties.

The new in situ properties interfere with the nanofibers crosslinking. The main objective of such modification are new characteristics in the matrix, changing its biophysical properties. The additives become part of the nanofibers, interacting with the –OH portions present in the bacterial cellulose chains and forming new hydrogen bonds. Chitosan, a polysaccharide derived from chitin, has biocompatibility, antibacterial and antifungal properties. The combination of bacterial cellulose, in a dressing, exhibited favorable antibacterial activities and no cytotoxicity [61].

Zhou et al. [62] demonstrated that their bacterial cellulose bandage associated with collagen I and hydroxypropyltrimethyl ammonium chloride chitosan exhibited excellent antibacterial activity, cytocompatibility and promoted the growth and proliferation of NIH3T3 cells and HUVECs cells. Silver nanoparticles and polydopamine incorporated into bacterial cellulose demonstrated antibacterial activity, increased cell viability, showed no cytotoxicity to fibroblast cells, granulation tissue formation, angiogenesis and re-epithelialization upon histopathological examination [63]. Several nanotubes, nanosheets were also incorporated into cellulose culture media. Park et al. [64] produced hybrid compounds of bacterial cellulose and carbon nanotubes that showed osteoconductivity and osteoinductivity. Likewise, Khalid et al. [65] demonstrated that the bandage, composed of bacterial cellulose and carbon nanotubes, acted as a mechanical and antibacterial barrier to fragile healing tissue, aided in moisture retention, reduced inflammation, and resulted in efficient wound healing. Graphene nanosheets were incorporated into the bacterial cellulose matrix, resulting in decreased crystallinity, improved mechanical and electrical properties. Luo et al. [66] produced a compound that exhibited high tensile strength with 93% improvement compared to pure bacterial cellulose film. In addition, the film also showed excellent flexibility with good conductivity. The association between nano zinc oxide and bacterial cellulose increased porosity and pore sizes, which increased water vapor permeability (an important factor for a bandage), it also showed antibacterial activity, good physical properties, non-cytotoxicity and good biocompatibility [67]. Although in situ modifications allow a uniform material distribution, the fermentation conditions of the biosynthesis process limit the incorporation of other materials.

Ex-situ modifications seek to alter the physicochemical and functional properties of the matrix after biosynthesis and purification of bacterial cellulose. The nanometric materials can be aggregated through diffusion to pass through the network pores. This type of modification can be divided into the chemical modification and composites development [68].

In the chemical modification process, bacterial cellulose is treated with several chemical reagents to modify its chemical structure and incorporate additional functionalities. The most common chemical modification is oxidation but there are also modifications by acetylation [69], benzoylation [70], succinylation [71] and phosphorylation [72].

Oxidation seeks to add new functional groups to cellulose. Oxidized cellulose is the most precious by-product of cellulose, and several chemical and physical properties of oxidized cellulose can be obtained under various oxidizing conditions (nature, temperature, pH and reaction duration) [73]. Many agents can be used, such as hydrogen peroxide, persulfates, permanganates, nitrogen dioxide, chlorine dioxide and phosphoric acids [74]. However, water-soluble 2, 2, 6, 6-tetramethylpiperidine-1-oxyl (TEMPO) is widely used to oxidize cellulose. Oxidized BC has been investigated for different applications such as adsorption of heavy metals, oil removal and various biomedical applications [75][76]. In etherification, the reaction is carried out in two steps; in the first step, cellulose is activated by treatment with an alkaline solution, followed by an etherification reaction with monochloroacetic acid or its sodium salt. Carboxymethylcellulose is one of the most important cellulose derivatives and can be used in pharmaceutical, cosmetic, food and biomedical areas [77]. Sulfation synthesizes cellulose in sulfuric acid in isopropyl alcohol or with SO<sub>3</sub>-pyridine complex in ionic liquids [78][79]. Cellulose sulfate has as its main characteristic, anticoagulating, antivirus and antibacterial properties [80]. Benzoylation treats bacterial

cellulose with benzoyl citrate, adding to the material the potential for sensors, piezoelectric materials and optical properties [81]. Phosphorylation is developed for textiles and flame retardant materials, as it can induce the formation of calcium phosphate making the material suitable for biomedical applications [16].

Despite its advantages, cellulose has no antibacterial capacity and moderate mechanical properties. The development of composites aims to improve some properties that limit the application of bacterial cellulose in biomedical and tissue engineering. To improve mechanical and biological properties, researchers have incorporated different types of materials into bacterial cellulose, including polymers, carbon-based nanoparticles, metal/metal oxide nanoparticles, and other inorganic nanoparticles [82].

Bacterial cellulose fragments were immersed in the chitosan solution followed by lyophilization to produce a scaffold to aid in ovarian cancer diagnosis. The scaffold obtained showed better interaction with the cells compared to pure BC [83]. JU et al. [84] produced a bacterial cellulose film, in which the cellulose suspension and the polyvinyl alcohol solution were mixed, followed by the incorporation of chitosan in bulk form or nanoparticle form. The bulk form of chitosan increased the mechanical and elastic properties of the film, while the nanoparticle form showed higher antibacterial properties. The gelatin and hydroxyapatite incorporation in bacterial cellulose showed a composite with high mechanical properties, positive cell adhesion, proliferation and differentiation [85]. Yan et al. [86] achieved a scaffold with reduced porosity, high mechanical properties and great in vitro biocompatibility, by incorporating bacterial nano-cellulose into alginate and collagen. The incorporation of graphene, a carbon nanomaterial with a 2D structure, and carbon nanotubes add to bacterial cellulose better mechanical, electrical and thermal properties [16][87].

In summary, several biopolymers and biomaterials can be incorporated into bacterial cellulose to improve its properties, reducing its applicability limitations. The in situ and ex-situ modifications are methods that work on the incorporation of these materials homogeneously. Although the in situ modifications present several advantages of materials aggregation, the method is limited because some materials do not support the biosynthetic process. On the other hand, ex-situ modification expands the range of materials that can be incorporated; however, scientists still seek completely homogeneous incorporation in this process.

## 5. Bacterial Cellulose for Cardiac Tissue Regeneration

Understanding the environment nanoscale is essential to produce biomaterials that mimic the cellular microenvironment. The environment properties employ a total influence on cell adhesion, proliferation, maturation and differentiation, and consequently generate impacts on the function of a tissue. Cellulose is a very versatile material with its adaptable properties that allow its application in systems with different chemical and biophysical environments. Cellulose-based biomaterials provide important advantages over conventional synthetic materials, which demonstrates their promise of advancing scientific knowledge. The role of the extracellular matrix is established, and researchers know that it not only allows cellular attachment but also sends biochemical and biophysical clues to the nascent cells and tissues. Such data support studies on the application of scaffolds of decellularized tissues and organs in tissue engineering and regenerative medicine. The mimicry of natural

conditions both in the tissue and in the ECM requires adequate adhesion and growth properties that maintain the tissue's normal structure, and the results of biopolymers' application involving celluloses mentioned above reveal successful results.

The bacterial cellulose use in cardiac tissue regeneration still needs more studies. In the literature, only one study was found that tested the cellulose membrane viability, acting as an adhesive, loaded with co-cultured cells. Simeoni et al. [88] produced a patch loaded with skeletal myoblasts and mesenchymal stem cells that was surgically inserted into the epicardial region of the left ventricle, where they found that the cellulose patch can protect the myocardium against the deleterious effects and pathological remodeling of the ischemic heart; this beneficial result was not obtained only with cell therapy. Other studies demonstrated the applicability of cellulose, modified cellulose and its composites. Only Simoeni et al. [88] describe the bacterial cellulose use itself. Chen et al. [89] developed a polyurethane/cellulose scaffold that presented greater mechanical strength and essential characteristics for the survival and function of cardiac cells with native anisotropy. As such, Entcheva et al. [90] tested the potential of cellulose acetate and reduced cellulose scaffolds for the growth of cardiomyocytes in vitro. They attested that the surface of these materials promoted cell growth, while increasing gap junctions, and electrical functionality. Such studies open doors to new possibilities for applications of bacterial cellulose, at the same time highlighting the potential of this biomaterial in cardiac tissue regeneration.

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