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Review Article

Recent trends in the development of smart bacterial cellulose wound dressings

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Though several advancements occurred in the wound management and wound dressing sector, still there is scope for improvement in this area. Recently, several researchers focused on the use of bacterial cellulose in the wound dressing area. However, the use of bacterial cellulose is not yet commercialized widely. The three-dimensional fibre assembly, nano-sized fibre, and very high swelling and water holding capacity are the unique characteristics of bacterial cellulose. This review aims at analyzing the recent advancements in the use of bacterial cellulose in wound dressing application. The first part of the review evaluates the intrinsic properties of bacterial cellulose and its importance in wound healing. The latter part of the review consolidates the recent research works and advancements in bacterial cellulose wound dressing. Finally, the review details the potential merits and demerits of bacterial cellulose along with the scope for future research.

Keywords: Bacterial cellulose, Composite, Mechanical properties, Natural drugs, Synthetic drugs, Nanoparticles, Polysaccharides, Physical properties, Wound dressing

1 Introduction

Bio cellulose is one of the cellulose-based biopolymers that originate from microorganisms, like bacteria, seaweed, and fungi[1]. The first research on the cellulose production from the microorganism was performed by researcher Brown[2], who reported the cellulose producing capability of non-pathogenic species like *Komagateibacter,* such as *K. xylinus*, former *Acetobacter,* and *Gluconacetobacter.* Bacterial cellulose is biodegradable, and non-toxic, unlike other cellulose obtained from plant species; these are highly pure, free from lignin, hemicellulose, and other impurities[3, 4]. The cellulose produced from the bacterial species can be grouped under two categories, namely Cellulose I and cellulose II, in which a highly crystalline structure noted as Cellulose I, and the Cellulose II is reported as a more thermodynamically stable amorphous structure[5]. Though both plant and bacterial cellulose are made of the same molecular structure, bio-cellulose from bacteria is produced in the form of three-dimensional structures. In contrast to the plant cellulose, the diameter of the bacterial cellulose fibrils is in the nano size and provides higher elasticity, flexibility, surface area, and gas permeability[6,7]. The three-dimensional network structures with fibre diameters in nanosize are the main reason for the unique characteristics of bacterial cellulose[8]. When the mechanical properties are concerned, bacterial cellulose possesses higher crystallinity, tensile strength, elongation-at-break, and Young's modulus than the plant cellulose[9, 10]. The higher aspect ratio of the fibres provides a tremendous amount of water holding capacity and prolonged drying time at the wet stage[11]. The bacterial cellulose also possesses higher air permeability, and biocompatibility as it is free from toxic substance[12]. The structure of the bacterial cellulose is closely mimicking the structural properties of several biological tissues, and hence it has higher cell adhesion ability and antigen immobilization properties[13].

Wound healing is a complex process and wound dressing plays an important role in the healing process. The dressing material typically provides a suitable microenvironment to promote the wound healing process. The microclimate is responsible for cell proliferation and it motivates the migration of epithelial cells[14]. Further, the dressing materials also act as a barrier to the outer environment, bacterial infection and it also helps in absorbing excess wound fluid, creating opportune conditions for healing[14]. The specific functional requirements expected out of any wound dressing widely differ based on the type of wound addressed[15]. Though a significant amount of research work was performed in wound dressing development, still there are numerous requirements to be addressed. The fundamental requirements of wound dressing[16,17] are: (i) a wound dressing should remove excess exudates and toxic components from the wound surface, (ii) the dressing should be capable of

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maintaining a proper environmental condition at the wound and dressing interface, (iii) the dressing should possess enough pores to allow or transfer air to the wound surface, (iv) the dressing should protect the wound from microorganisms and toxic external particles, (v) it should also provide thermal insulation, and (vi) it should aid the removal process without disturbing the wound[17]. Out of several materials explored, natural polymers always provide several advantages, like biological activities, degradability, and potential biocompatibility[18]. As the bacterial cellulose structure and properties indicated its potential towards wound dressing application, many researchers evaluated its performance in wound healing. When specifically the wound dressing application is considered, bacterial cellulose can provide higher structural stability, retains wounds exudates or liquids, promotes cell proliferation, regulates proper air exchange between wound and skin due to its higher porosity and it does not induce any undesirable effect on the host tissue[19]. Often bacterial cellulose materials were identified as one of the best materials to maintain the moist wound environment due to their higher hydrophilic nature. The porosity of the structure also plays a vital role in the swelling ratio of the material. The fibril arrangement, pore size, and other related properties are highly influenced by the cultivation methods[20]. Detailed information on the cellulose formation mechanism and different cultivation methods used in bacterial cellulose production can be found elsewhere[21]. Figure 1 represents the intrinsic properties of bacterial cellulose concerning wound dressing application.

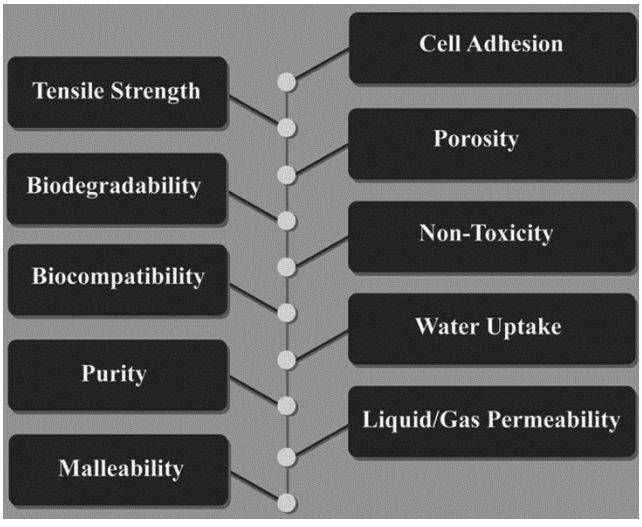

Fig. 1 — Intrinsic properties of bacterial cellulose for wound dressing application

In view of above, this review aims at analyzing the potential of bacterial cellulose in various wound dressing applications. The first part of the review analyses the structural aspect of the bacterial cellulose along with its production mechanism, and the latter part consolidates the various recent research works in the wound dressing application. The review also summarizes the existing gaps in the current research and future scope of the bacterial cellulose in the wound dressing domain.

2 Synthesis and Functional Properties

Several bacterial strains have been reported for their cellulose-producing capacity by past researchers. *Acetobacter, Azotobacter, Rhizobium, Pseudomonas, Salmonella, Agrobacterium, Aerobacter, Achromobacter, Alcaligenes, Sarcina ventriculi*, *Salmonella,* and *Escherichia* are some types to name[21]. Out of these, *Acetobactor xylinum* was noted as the most viable species that can also be adapted for the commercial production of bacterial cellulose due to their versatility in growth medium[22]. Cellulose production by the bacteria is the protective shield that species creates to safeguard it from UV-light exposure[23]. The studies reported that the amount of bacterial cellulose production is linearly correlated with the cell concentration[24]. *Acetobacter xylinum* strains are capable of converting 50% of the carbon components into cellulose[25]. The bacterial cellulose synthesis is a two-step process, in which, the first step aids in the formation of uridine diphosphoglucose UDPGIc. In the second step, glucose molecules are polymerized into β-1→4 glucan chains through cellulose synthase[26-28]. In this process, UDPGIc is the precursor for the formation of cellulose. The cellulose is formed through the surface of the cell wall and aligned in the direction of the cell movement[29]. In the latter stage, these individual fibrils are laid side by side and form microfibril bundles. The three-dimensional structure of the bacterial cellulose is formed due to the grouping of such microfibrils bundles through hydrogen bonds. Thus, it establishes inter and intra fibre linking and creates a three-dimensional network structure[30].

Apart from biochemistry, cellulose production is mainly influenced by several other factors, like media used, temperature, moisture, and other environmental condition. The production of cellulose through the fermentation process is largely dependent on the availability of carbon sources. Along with that, it is also important to maintain a small amount of nitrogen

source[31]. Hence, for the commercial production of bacterial cellulose, several carbon sources like glucose, sucrose, starch, fructose, etc. were used. Though these materials are used often, several recent research works reported the use of industrial and agricultural wastes in bacterial cellulose production[32]. Technically, the use of a higher amount of glucose forms an intermediate product gluconic acid in the fermentation bath, and it reduces the cellulose production capacity due to the rapid *p*H change in the fermentation[33]. Hence, the use of other resources for bacterial cellulose production is one of the major focuses of the current researchers. A detailed biochemical mechanism of bacterial cellulose can be found in the study of Han and Robyt[34] and the physical production from the cell structure can be found in the study of Saxena, and Brown[28].

When the functional properties of the bacterial cellulose are considered, physical properties like three-dimensional structure, porosity, water absorption, holding and release capacity, and swelling capacity are noted as some of the unique properties that add value to the wound dressing material.

2.1 Nanostructure and Porosity

The intrinsic properties of bacterial cellulose are highly influenced by the fibril structure and pore size of the bacterial cellulose sheet. A compact and denser structure results in a reduced porous structure, and less surface area that results in a lower holding capacity due to reduced interaction sites[35]. The pore size of the bacterial cellulose structure is widely influenced by the condition in which the fermentation/cultivation process was carried out. Cellulose produced from the static fermentation process has a lower porosity in the range of 11 – 164 µm, whereas the agitated culture shows a pore size range of 165 – 330 µm. Similarly, the effect of additional compounds, like drugs or polymers, on structural morphology and pore size is found significant[36]. Though the increased pore size may aid in loading of a larger amount of drugs as a wound dressing, the reduction or increment in the pore size also has a significant effect on the mechanical characteristics of bacterial cellulose. Fig. 2 shows the physical appearance and morphological structure of the pure bacterial cellulose

2.2 Water Absorption, Holding, and Retention/Swelling Behavior

Moisture properties of the bacterial cellulose material mainly depend upon structural and chemical properties. In the case of structural aspects, the fibril diameter, arrangement, and internal porosity are the main factors that influence the water absorption capacity. However, in the case of chemical structure, the amount of amorphous and crystalline region highly influences the moisture properties. The type of bacteria used, the production method adapted and the environmental condition of the fermentation process are the parameters that influence the fibril production, arrangement, surface area, and porosity[37]. Hence, the influence of these factors on moisture characteristics is unavoidable. In general, the water holding capacity of the bacterial cellulose will be in the range of 100 – 1000%. A two-stage interaction mechanism was reported in the case of water absorption and holding properties. In the first step, the cellulose chain reacts with water molecules through their binding sites and

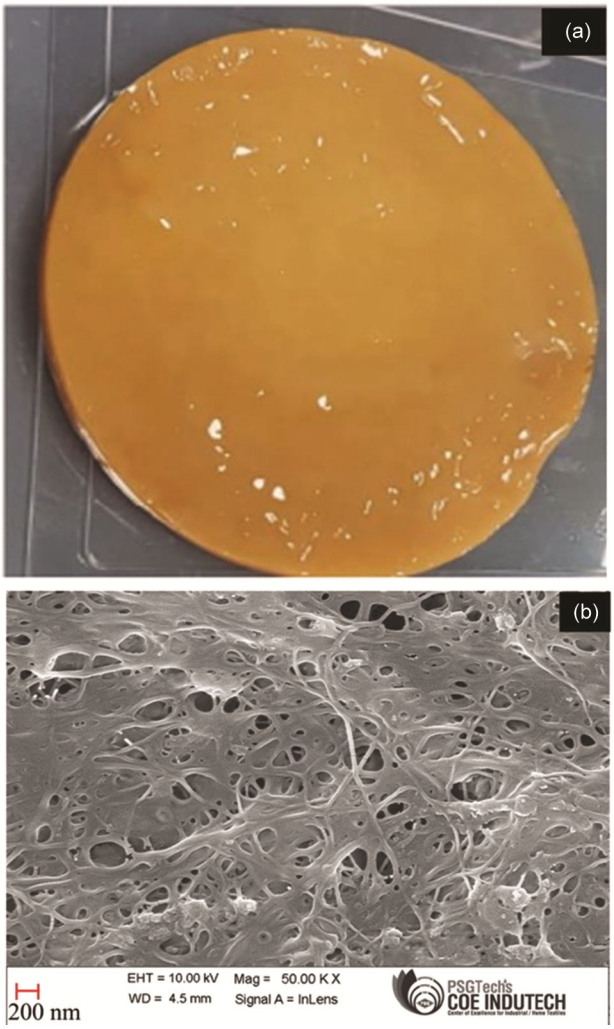

Fig. 2 — (a) Physical appearance of fermented bacterial cellulose after 20 days without purification, and (b) SEM image of three-dimensional fibre network structure

forms a monolayer. In the second stage, the partially interacted sites are completely exhibited to water molecules and form multiple layers in the structure[38]. A further increment in the water content allows the water molecules to get trapped inside the structure physically due to the three-dimensional fibril structure. The chemical interaction of the water and cellulose happens through hydrogen bonding between the adjacent glucan units of the cellulose and water molecule[39]. The water absorption mechanism of the bacterial cellulose structure is provided in Fig. 3[39].

2.3 Water Vapour Permeability

The water vapour permeability determines the water vapour or sweat transmission ability of the materials, particularly for fabrics in a given environment. In the case of bacterial cellulose, this property becomes essential as it is used in the wound healing process. In the case of wet bacterial cellulose, the moisture loss was higher at the initial stage. Previous research reports showed a transmission rate of 1503 g/m^2/day[40]. In the reported mechanism, it showed that the increased moisture content highly facilitates the moisture or water vapour transmission ability of the bacterial cellulose. The water molecules, that are absorbed initially, react with the amorphous region and swell the material. As these molecules bind the reactive sites, later absorbed molecules are effectively transmitted outside. Hence, the initially absorbed water molecules act as a plasticizer and aids in improved moisture transmission. After a certain amount of moisture content, further increment does not have any increment in the transmission ability and it remains constant[38].

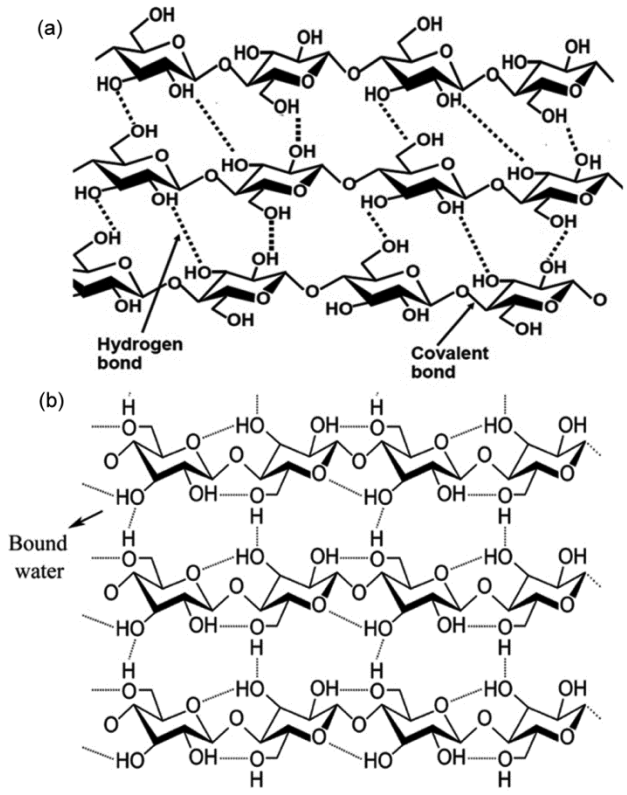

Fig. 3 — Interaction between bacterial cellulose structure and water molecule (a) structure of dry and (b) wet state bacterial cellulose

3 Composite Wound Dressing

One of the important properties of bacterial cellulose dressing is that it possesses high surface area [6, 41]. The larger surface area of bacterial cellulose probably contributes high absorption of wound exudates and aids sustained release of antibacterial agents for managing infected wounds. Though bacterial cellulose materials have more desirable properties for wound dressing applications, it lacks in functional properties. Hence, to achieve the medicinal properties to heal the wounds, often it is blended with drugs having antimicrobial properties. Combining two or more materials with a clear interface and obtaining superior or mixed properties of the components is generally known as composites [41]. The development of such composite material from bacterial cellulose is one of the common methods available in the literature. Though bacterial cellulose has unique physical, structural and mechanical properties, it does not have the healing properties for a wound dressing. Hence, to include properties, like antibacterial ability, and anti-inflammatory, four different methods are adapted, as shown below:[42]

(i) By genetically modifying the cellulose producing organism
(ii) By including a polymer or an active ingredient into the bacterial cellulose matrix *(in-situ),* during the cultivation of the cellulose
(iii) Incorporation at post-synthesis via saturation (*in-situ*)
(iv) Chemical modifications after the purification process (*ex-situ*)

However, a suitable method can be selected based on the various chemical and physical characteristics of the drugs that need to be loaded into the bacterial cellulose. A composite wound dressing was generally achieved either by including a polymer or an active

ingredient into the bacterial cellulose matrix *(in-situ),* during the production or at the post-treatment [41]. In *in-situ* method, the active component with functional properties will be added to the inoculation media during the growth of bacterial cellulose. After the fermentation process, a bacterial cellulose sheet or pellicle will be developed as a composite material along with the added component[43]. However, in the case of *ex-situ,* the fermented bacterial cellulose will be kept immersed in the drug or chemically modified to introduce the drug. Polysaccharides, natural and biodegradable polymers, synthetic nanoparticles, metal oxides, antimicrobial agents, herbal extracts, proteins, amino acids, and enzymes are the common materials used in the bacterial cellulose composite wound dressing. The general mechanism of bacterial cellulose composite wound dressing preparation is provided in Fig. 4.

3.1 Polysaccharide Based Composites

Chitosan and alginates are the most common polysaccharide materials that are frequently incorporated with bacterial cellulose matrix. Though the antibacterial properties are the main reason, the addition of polysaccharides also influences the water holding capacity and water releasing rate of the bacterial cellulose composite[44]. Pasaribu et al[45]. evaluated the antimicrobial ability and hemocompatibility of the bacterial cellulose, chitosan, and collagen composite. The results show an increase in the porosity of the composite material as compared to the native bacterial cellulose structure. When the antimicrobial properties were analysed, improved performance of bacterial cellulose/collagen/chitosan composite was reported over bacterial cellulose/chitosan/collagen composite. Though direct wound healing studies were not performed, a hemocompatibility study was performed, and found excellent with all the composites developed in this study[45]. Chitosan along with carboxymethyl cellulose (CMC) was added in the bacterial cellulose suspension solution to develop a composite dressing through the solvent casting method. The addition of chitosan and CMC created a higher dense structure in SEM analysis. When the functional properties of the materials were evaluated, a higher vapour transmission property was noted with the composite dressing than with the native bacterial cellulose. A reduction in mechanical properties was noted with native cellulose, as the bacterial cellulose was used in the form of suspension. However, a higher amount of antibacterial activity was noted with the developed composite film[46]. Other researchers compared the properties of bacterial cellulose composite with chitosan or Chito oligosaccharide. Apart from the regular, structural, thermal, and mechanical analyse, the study also reported the swelling kinetics of the developed composite film by focusing on the wound dressing application. The results showed a reduction in the actual swelling ratio of the bacterial cellulose with the addition of chitosan and Chito oligosaccharide. Out of these two composites, a

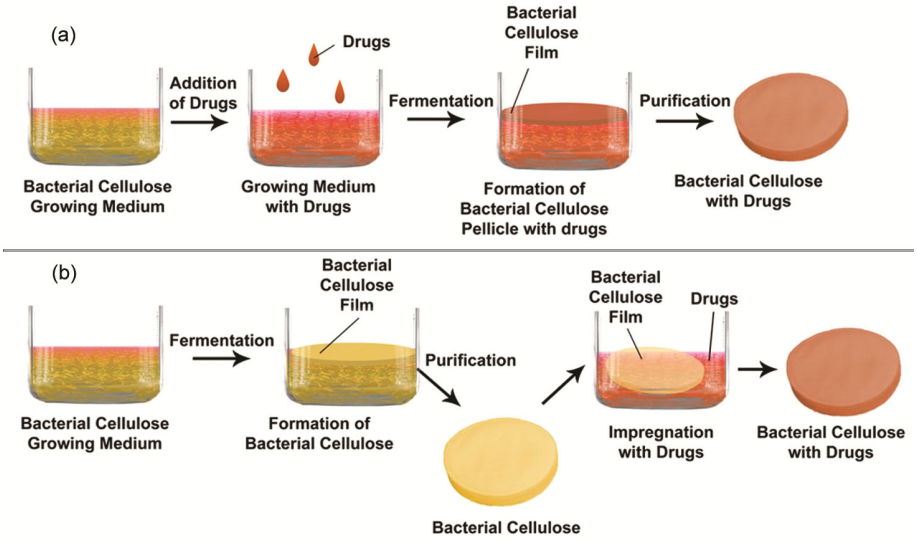

Fig. 4 — Schematic illustration of bacterial cellulose based composite wound dressing development by (a) *in-situ* method and by (b) *ex-situ* method

higher swelling ratio was noted with bacterial cellulose – Chito oligosaccharide. In the case of antibacterial activity, chitosan composite showed superior performance with both Gram-negative and Gram-positive strains. In the case of antioxidant activity, higher performance was noted with Chito oligosaccharide composite[47].

A similar study by Ju *et al*.[48] reported a comparison between the chitosan and chitosan nanoparticle composite with bacterial cellulose and polyvinyl alcohol (PVA). The structural analysis results showed no structural variation in the x-ray diffraction studies. Nanoparticles coated composite showed a lower tensile strength and elongation compared to chitosan composite. Higher moisture content was noted with chitosan-bacterial cellulose over nano chitosan composite. However, a lower solubility was noted with nano chitosan-bacterial cellulose composite than chitosan composite. Similarly, a higher performance of nano chitosan composite was reported against the antibacterial analysis over regular chitosan bacterial cellulose composite[48]. The cytotoxicity studies of chitosan – ciprofloxacin loaded composite wound dressing showed a slight reduction (85%) in the cell viability as compared to a control bacterial cellulose (90%). Based on the results, the study reported moderate cell cytotoxicity for the developed composite. On the other hand, higher antibacterial properties were reported with the ciprofloxacin-loaded bacterial cellulose chitosan composite against *P. aeruginosa* and *S. aureus*[49]. To increase the interface compatibility of the bacterial cellulose and drug, the researcher used oxidized bacterial cellulose with chitosan. The results against the L929 cell growth showed that either oxidized bacterial cellulose or chitosan and oxidized bacterial cellulose composite did not have any potential cytotoxicity. Further, at a higher concentration of chitosan, a higher antimicrobial property was also noted for the developed composite wound dressing[50].

3.2 Composite with Nanoparticles

Researchers have used various nanoparticles including metal oxides in the preparation of composite wound dressing to enhance the antibacterial ability of the wound dressing. The silver nanoparticle is one of the common materials, that is frequently used in the wound healing process due to its higher antibacterial ability. Zeolites, silver sulfadiazine, and silver nitrate are the common forms of silver nanoparticles used in wound dressings. In bacterial cellulose composites also, nanoparticles are widely used along with other polymeric materials. Recently, silver nanoparticles along with polydopamine were used to develop a bacterial cellulose-based composite. As the conventional impregnation of drugs results in a very short duration of antibacterial activity, researchers used dopamine as an adhesive polymer. In this research, polydopamine coated bacterial cellulose was immersed into a silver nanoparticle solution and the end product was developed (BC-PDAg). The developed composite dressing showed higher antibacterial properties against both Gram-positive (*Staphylococcus aureus*) and Gram-negative bacterial strains (*Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae*). When the cell compatibility is measured, higher growth is reported after 24, 48, and 72 h with the developed composite dressing than the control bacterial cellulose. The *in-vivo* analysis results on a rat wound model showed a significant wound closure with higher wound healing efficiency (94.35%) with the BC-PDAg as compared to that with BC-PD (74.58%) and BC dressing (65.35%). The higher healing ability is highly associated with the structure of bacterial cellulose, and their necrotic residue clearance effectiveness accelerated the re-epithelialization. The use of Ag nanoparticles restricted the infection and so complete healing was evident with BC-PDAg as compared to other selected dressings. The results were also confirmed by the histopathological examination of wound skin[51].

Melnikova *et al*.[52] reported the use of zinc oxide nanoparticles (ZnO NP) and betulin diphosphate (BDP) in the bacterial cellulose composite preparation. Along with complete physical and mechanical characterization, they measured the cell viability and *in-vivo* wound healing. The results of the study reported no restriction in cell viability during the use of developed bacterial cellulose composite dressings (with ZnO Np, BDP). On the *in-vivo* wound healing analysis, burn wounds were created on the wound models of the rats and the developed bacterial cellulose composites were used. The results showed an increased wound healing ability with bacterial cellulose ZnO NPs-BDP composite films in terms of wound area contraction, improved healing, biochemical parameters and microcirculation, and morphological picture[52]. Other researchers[53] measured the ability of silver nanoparticles (Ag NP) bacterial

cellulose composite through various methods. In cytocompatibility analysis against U251, MSTO, and Panc 1 cell lines, Ag NP loaded bacterial cellulose did not show any cytotoxic effect, whereas the free Ag NP showed cytotoxic effects. The study reported that the delayed release of Ag NP from bacterial cellulose matrix reduces the adverse effect of free Ag NP. The results of the study also reported that the developed Ag NP-loaded bacterial cellulose was a hemolytic material as per ASTM F756 standards. The authors also tested the antibacterial and antioxidant properties of the developed composite wound dressing and found it effective against a wide range of bacterial species and DPPH assay respectively[53]. Figure 5 represents the scanning electron microscopic image of bacterial cellulose and composite bacterial cellulose structure along with its photograph.

Graphene oxide (GO) was included in the growth phase of the bacterial cellulose and then the bacterial cellulose composite dressing was prepared with dopamine, silver nanoparticle [Ag-pDA/BC(GO)]. The developed dressing was evaluated for its electrical conductivity, antibacterial ability, and biocompatibility properties. The addition of GO in the bacterial cellulose composite film helps in electrically heating the wound dressing and speed up the healing process. In the case of antibacterial property analysis, control bacterial cellulose did not show any property, whereas Ag-pDA/BC(GO) dressing showed a higher antibacterial ability even after multiple washes. The performance was reported best among the recently reported results. In the cytotoxicity analysis, the developed bacterial cellulose composite film showed better performance against the NIH3T3 human fibroblasts. After 24 h evaluation, compared to the blank, Ag-pDA/BC(GO) composite film showed a 90% survival rate of NIH3T3 human fibroblasts[54]. Other researchers[55-57] also evaluated the use of gold nanoparticles (Au NPs), copper nanoparticles (Cu NPs) along the bacterial cellulose membrane to create a prolonged release of these nanoparticles due to their three-dimensional structure.

3.3 Biopolymers and Natural Material Composite

ε-Poly-L-lysine (ε-PL) is a water-soluble biopolymer that has very good compatibility with mammalian cells and so they are widely used in food and biomedical fields. The higher antibacterial activity of ε-PL is also one of the main reasons of their use in wound dressing materials. Hence, researchers used this polymer along with bacterial cellulose to increase wound healing and biocompatibility. In their research, the ε-PL- bacterial cellulose composite wound dressing was developed and measured for biocompatibility *in-vitro.* Standard CCK-8 assay with mouse embryonic fibroblast cells NIH3T3 is used to measure cytotoxicity. After an exposure of 12h, bacterial cellulose with higher ε-PL content showed 95% cell viability. It was also evaluated till 24 and 48h to measure the long-term effect on cell growth. Similarly, the composite wound dressing exhibited lower hemolysis and proved its compatibility with blood cells[58]. Natural antibacterial agent curcumin, a derivative of turmeric was also used as a drug in the bacterial cellulose wound dressing due to their potential wound-healing capabilities, antioxidant, and antineoplastic properties. Bacterial cellulose-curcumin composite wound dressing was developed and evaluated for its burn wound healing effectiveness and antibacterial

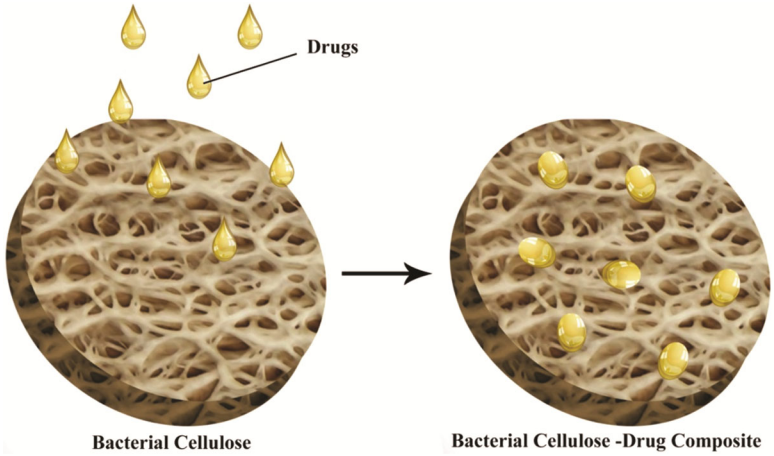

Fig. 5 — Structure of bacterial cellulose composite dressing

properties[59]. The study evaluated the wound healing ability in an animal model and compared the effectiveness of bacterial cellulose-curcumin composite and positive control (silver sulfadiazine treated) against an untreated wound. The study results reported that after 15 days of monitoring, the developed bacterial cellulose-curcumin composite showed a higher wound contraction (64.25%) as compared to other samples. Though several researchers mentioned silver sulfadiazine as a standard drug for burn wound treatment, the current research showed a higher potential of bacterial cellulose-curcumin composite dressing in wound healing. The researcher mentioned that continuous drug release behavior and the presence of nanostructured cellulose matrix enhanced wound healing by preventing infection[59].

To confirm the wound healing effectiveness, Sajjad *et al*.[59] measured the cell growth using histological analysis. The results showed a complete migration of epithelium and showed re-epithelialization on the wound area of the curcumin-loaded composite wound dressing. The absence of necrotic tissues and ulceration were also noted as positive signs, indicating an efficient wound healing under the developed composite dressing[59]. Extracts of ginger (*Zingiber officinale)* were well known for their anti-inflammatory effect, anti-cytokine activity[60], anti-nausea, anti-thrombotic, antimigraine[61,] and the wound-healing property[62]. Researchers performed a comparative analysis of honey, bacterial cellulose, *Zingiber officinale* extract, and *Zingiber officinale* extract loaded composite dressing. The findings showed a higher wound contraction after 14 days with bacterial cellulose wound dressing, followed by herbal extract and composite wound dressing. However, in the microscopic analysis, the developed bacterial cellulose- *Zingiber officinale* drug-loaded composite dressing showed a better wound healing in terms of collagen content, re-epithelialization, and other internal factors. Hence, the researchers concluded that, on macro analysis (wound contraction), the composite dressing did not perform well, but at the same time when the quality of the wound healing was considered, composite dressing showed a better performance[63]. Similar research reported the loading of human epidermal keratinocytes and human dermal fibroblasts into a bacterial cellulose/acrylic acid hydrogel wound dressing. In this study, burn wound sites were created on the athymic mice and evaluated for their healing efficacy. The results showed that bacterial cellulose composite dressing loaded with cells was very effective with a 77.34% reduction after 13 days. Whereas the control wounds contracted to a percentage of 64.79. The researchers also mentioned that the use of human epidermal keratinocytes and human dermal fibroblasts accelerated the wound healing as compared to the control sample, and this was proved further through histology and tunneling electron microscope (TEM) analysis[64].

Developed bacterial cellulose was immersed in the polyvinyl alcohol (PVA) solution for the development of composite wound dressing. The study measured the swelling ratio, dehydration percentage, antibacterial analysis, and drug release profile. Results reported that the addition of PVA in the bacterial cellulose reduced the swelling ratio of the material, but increased the rehydration ability. The researchers[65] also loaded ampicillin and their release characteristics were analysed. The results showed bacterial cellulose/PVA composite dressing adhered to the Higuchi and Korsmeyer-Peppas models for the drug release profile. Whereas the ampicillin considered the release behavior highly fitted with 'super case II' transport model that includes the details of polymeric material erosion. The antibacterial test was performed against *E.coli* and *S.aureus* for the ampicillin-loaded bacterial cellulose/PVA composite film and found very effective against the selected strains[65]. Other researchers measured the efficacy of the keratin/ bacterial cellulose composite scaffolds against the burn wound healing *in-vivo* with rabbits. After 21 days of incubation, a significant amount of healing was noted with keratin/bacterial cellulose composite scaffolds than the control wound. The researcher reported a higher epidermal regeneration for the keratin/bacterial cellulose composite scaffolds. While comparing with the control batch, the developed product showed the formation of pavements for epithelium on the animal models that represent healthy wound closure[66]. Cherng *et al*. [67] reported that the plain bacterial cellulose membrane itself is capable of curing skin wounds. They developed full-thickness skin wounds on rats and applied the bacterial cellulose membrane. After 14 days of observation, they reported positive effects on wound beds like increased skin extracellular matrix deposition and controlled excessive inflammation due to the reduction of scavenger receptor-A. They also

reported that the bacterial cellulose scaffold actively enhanced the epithelialization process[67]. The details of the literature in this field can also be accessed in the particular research reviews[68-71]. Table 1 consolidates the other recent research in the field of the bacterial cellulose wound dressing[72-91].

4 Commercialization and Future Scope

Few commercial dressings developed using bacterial cellulose are already there in the market. BioFill® is one of such dressings that was developed a couple of decades ago and their properties were evaluated for skin wound application. After more than 300 treatments, BioFill® dressing showed immediate pain relief, effective wound healing, improved wound exudates management, and expontaneous detachment following re-epithelization along with reduced cost and time[92]. Other researchers[93] evaluated the effectiveness of Dermafill® (bacterial cellulose wound dressing) against a commercial dressing for skin tear. Compared to the commercial dressing, bacterial cellulose dressing was rated as very effective in reducing the pain by the patients. Similarly, the nursing staff also rated these dressings higher than the commercial dressing, as it did not require a frequent dress change. In the skin tear healing process, Dermafill® showed a faster wound closure than the commercial dressing[93]. XCell® is another brand that produced wound dressing from bacterial cellulose. Researchers evaluated wound healing ability and biocompatibility using animal models and human studies. The results showed a higher potential of Xcell® dressing against hard to heal chronic wounds. The study also reported numerous advantages of the XCell® dressing compared to conventional dressing[94]. Other researchers[95] evaluated the effectiveness of Epiprotect®, bacterial cellulose dressing against silver –sulfadiazine for partial-thickness burn wounds. The research compared two groups of patients (20 participants/group) and evaluated the efficacy of wound healing. The results showed that Epiprotect® treated patients experienced a shorter wound healing period, patients reported lower pain during and after wound care and the dressing also needed fewer changes during healing time[95]. Application of Membracel®, a bacterial cellulose membrane dressing was evaluated for their performance against the wound on a sea bird, Chilean skua. The results were promising and the dressing completely cured the wound in 14 days[96].

Due to their established chemical and physical properties, bacterial cellulose is one of the top choices for wound dressing application. Their mechanical stability, biocompatibility, gas permeability due to porosity, exudates control characteristics, and ability to promote cell proliferation are the main reasons for their preferences[19]. The drug release behavior of the bacterial cellulose is one of the other important properties that attracted many researchers[97]. Additionally, the presence of an enormous amount of hydroxyl groups and hydrogen bonding sites enables their higher moisture-holding ability. This property is responsible for maintaining the moisture on the wound sites and aids in increasing re-epithelialization rapidly[95]. Through this review, we can also see some of the demerits associated with the bacterial cellulose dressing that required some more attention. First of all, other than their physical structure and improved moisture characteristics, bacterial cellulose does not have any healing abilities. Hence, it is very essential to include antibiotics into the structure and also the performance of the dressing depends on the efficacy of the antibodies that are used as a drug. This was evident from the results reported by researcher[63] who reported poor performance of the *Zingiber officinale* loaded bacterial cellulose composite but several others mentioned it as effective[59, 64, 67]. From the research review, it is also noted that most of the studies performed *in-vitro* cytotoxicity and antimicrobial activity rather than *in-vivo* analysis. The conducted *in-vivo* analysis also focused on the skin wounds model rather than other types of wounds. Hence, it is important to explore the potential of bacterial cellulose in multiple wound-related applications.

Similarly, the drug release behavior of the bacterial cellulose is another concern for medical practitioners. Bacterial cellulose had good drug release behavior, however, for prolonged-release conditions, they were found less suitable. Most of the drug-loaded bacterial cellulose composite showed rapid release of the drug in the initial stage[97]. This kind of rapid release also causes agglomeration of the drug, in the case of nanoparticles, and creates cytotoxicity at the wound bed[98]. Hence, greater attention needs to be given to this area to improve drug release behavior. The *in-vivo* drug release analysis was also found meager and hence it is necessary to analyze bacterial cellulose-based drug delivery systems in a real-time environment[99]. This issue can be effectively addressed

Table 1 — Summary of recent literature on bacterial cellulose applications as wound dressing materials

Wound dressing composition	Physical and mechanical properties	Moisture and thermal related properties	Biocompatibility study	Anti-microbial properties	Wound healing properties	Drug release behaviour	Reference
Polysaccharide composites							
Bacterial cellulose -graft-polyacrylic acid/chitosan composite	Increment in tensile strength and elongation in composite dressing	Higher swelling percentage in composite dressing cellulose	Cell viability of 75% drug loaded composite film showed a cell viability of 85%	• Composite dressing – antibacterial activity against both Gram (+) and (-). • Pure bacterial cellulose – no antibacterial activity	90% wound contraction in composite dressing noted over the control sample	Initial burst release of 35% at first 18 h. 57% release after 42 h. A maximum of 84 % of release after 120 h of incubation	72
Bacterial cellulose/ alginate/gelatin biocomposite film	Alginate and plasticizer increased the elongation & reduced tensile strength	• Higher water holding capacity than pure cellulose. • Reduction in water contact angle	More viable cells were found for both HaCat and L929	-	-	-	73
Nanoparticles (NP) based composites							
Selenium nanoparticles-bacterial cellulose/ gelatin hydrogel	Mechanical properties gradually increased with the addition of NP	Addition of NP reduced the swelling properties.	• NIH3T3 cells showed more than 80%. • Higher concentration (60%) a toxic effect reported	Higher antibacterial activity against MDR *E. coli,* MDR *S. aureus.*	A full-thickness wound healing on the rat model showed a higher healing	Slow and sustainable drug release profiles without any burst release	74
Bacterial cellulose/ silver nanocomposite	Deposition of NP confirmed through SEM	• Composite dressing showed lesser absorbency than raw bacterial cellulose. • Vertical wickability is poor	-	100% antibacterial activities against *S. aureus* and *E. coli* through AATCC 100 and AATCC 147 methods	-	-	75
Bacterial cellulose and Titanium dioxide nano composites	Physical characterization of NPs performed	-	-	Higher antibacterial activity of 81% and 84% was noted against *E. coli* and *S. aureus.*	• Composite dressing – 70.24% reduction in wound area in 15 days. • Pure bacterial cellulose – 49.03% reduction	-	76
Polyvinyl alcohol/ bacterial cellulose/ nano-silver hydrogels	• Tensile strength increased first and then reduced • Elongation-at-break increased		Cell viability against L929 cells was noted as 96- 134%.	• A higher antibacterial property of 65.63 ± 2.63% and 51.17 ± 1.49% was noted against *E. coli* and *S. aureus* respectively.	• A higher wound contraction and better healing than control on mice models.		77

(*contd.*)

Table 1 — Summary of recent literature on bacterial cellulose applications as wound dressing materials (*contd.*)

Wound dressing composition	Physical and mechanical properties	Moisture and thermal related properties	Biocompatibility study	Anti-microbial properties	Wound healing properties	Drug release behaviour	Reference
TEMPO-oxidized bacterial cellulose film with Ag NPs	-	• TEMPO oxidised cellulose showed 194% water retention. • Ag NP loaded bacterial ellulose had water retention of 173% • Thermal stability reduced after TEMPO – oxidation and increased with Ag NP composite	The composite dressing showed a cell viability of 95% after 48 h incubation against NIH3T3 cells	Reported to have 100% and 99.2% antibacterial activity against *E. coli* and *S. aureus* respectively	-	• The average release rates of day 0–3 and day 5–16 were approximately 12.2%/day and 4.2%/day, respectively. • A rapid and complete release of Ag NP was observed (97%)	78
Silver nanoparticle/bacterial cellulose nanocomposite	-	A reduced swelling ratio noted	Showed good biocompatibility with peripheral blood mononuclear cells	• An inhibition zone of 5 mm for *S. aureus* and about 2 mm for *E. coli* was noted • 100% and 99.99% reduction noted in viable *E. coli* and *S. aureus* respectively	-	-	79
Nano ZnO and bacterial cellulose membrane	-	-	• Lower concentration (5%) ZnO composite showed no cytotoxicity • At a higher concentration of ZnO, drastic cytotoxicity noted	• The study reported the antibacterial activity of 78.64% and 37.67% to *S.aureus* and *E. coli* respectively • Against Rabin skin, 5% ZnO Composite showed no irritation	At 14 days, only 7.5% of the wound appeared compared to control samples	-	80
Polymers, drugs, and other natural material based composites							
Bacterial cellulose/ methylglyoxal nanocomposite	Higher tensile strength and brittleness with an increase in methylglyoxal content	Thermal stability of composite was noted slightly lower than pure bacterial cellulose	-	Higher antibacterial properties against *M. luteus*, *P. aeruginosa*, *S. aureus*, & *E. coli*	-	-	81
Highly aligned bacterial cellulose/ gelatin membranes	Tensile strength and modulus of bacterial cellulose/gelatin membranes increased.	-	Excellent cytocompatibility, hemocompatibility, and adhesion, and migration of NIH3T3 cells.	-	Composite dressing exhibited a better effect than Tegaderm™ film in electrical stimulation and wound healing.	-	82

(*contd.*)

Table 1 — Summary of recent literature on bacterial cellulose applications as wound dressing materials (*contd.*)

Wound dressing composition	Physical and mechanical properties	Moisture and thermal related properties	Biocompatibility study	Anti-microbial properties	Wound healing properties	Drug release behaviour	Reference
Bacterial cellulose and fusidic acid composite	-	-	-	After 24 h exposure, higher concentration has the best antibacterial activities against *S. aureus*	-	-	84
Montmorillonite (MMT) clay mineral and bacterial cellulose composite	Physical-mechanical and thermal properties of the composites were significantly improved	• The addition of MMT increased the water absorption and reduced the water holding capacity • A higher uniformity in water release rate noted	-	-	-	Composite dressing showed an improved water release rate beahviour than pure bacterial cellulose.	85
Papin (papaya latex)-bacterial cellulose composite	The addition of drug reduced the tensile strength and Young's Modulus	The swelling ratio of the composite dressing was less than pure bacterial cellulose	-	Higher antibacterial activity against *E. coli, P. aeuroginosa, and S. aureus*	-	• Hydrolytic degradation method used • A steady-state release behavior noted	86
Bacterial cellulose and plant extract composite (*E. schimperi)*	-	-	-	Higher antibacterial activity was noted against *S.aureus* and no activity was reported against *E. coli.*	-	-	87
Bacterial cellulose with disodium phosphate, sodium bicarbonate, ammonium bicarbonate, and their mixtures	-	3 – 4 times higher swelling ratio, water holding, and retention capacity noted	Higher compatibility against L929 fibroblast	-	-	-	88
Vancomycin and cipro floxacin loaded bacterial cellulose	Stress-strain analysis on the composite dressing performed	-	-	Antimicrobial against *S.aureus* (*S. aureus*) and *K. pneumoniae* (*K. pneumonia*)	-	Around 80mg of drug released in 100 min	89
Dehydrogenative polymer of coniferyl alcohol and bacterial cellulose composite	-	• Increasing the dehydrogenative polymer of coniferyl alcohol-reduced swelling. • 0.5% concentration showed similar swelling like pure bacterial cellulose	-	Minimum inhibitory concentration and minimum bactericidal concentration studies showed the effectiveness against *P. aeruginosa, S. aureus*, and *Serratia sp.*	-	• After 72 h of in-vitro analysis, 46.2% of the drug was released from the composite. • The drug release profile fitted with the Korsmeyer-Peppas model.	90

(*contd.*)

Table 1 — Summary of recent literature on bacterial cellulose applications as wound dressing materials (*contd*.)

Wound dressing composition	Physical and mechanical properties	Moisture and thermal related properties	Biocompatibility study	Anti-microbial properties	Wound healing properties	Drug release behaviour	Reference
Dilinoleic acid (DLA) and tyrosine (Tyr), ethylenediamine (EDA) coupled bacterial cellulose	Mechanical properties of pure bacterial cellulose were evaluated	-	-	Reported the antibacterial activity against *S. aureus* and *S. epidermidis,* in composite dressing	-	The study did not show release profile but mentioned a long release behavior	91

by carefully controlling the drug loading methods. Out of several drug loading methods discussed in Section 3, the simple impregnation method was the most adopted one in the research. Hence, most of the research reported the rapid release of drugs[99]. In this aspect, future studies need to be done to standardize the drug loading and releasing behavior of bacterial cellulose dressings. The next major issue raised by researchers on the commercialization of bacterial cellulose is their bulk production, storage, and handling related properties. The production duration and the costs associated with the production medium are still one of the major constrain reported[12]. Though many researchers reported the secondary production of bacterial cellulose through different methods like electrospinning, bacterial cellulose showed a major obstacle for dissolving in solvents[69]. Though these aspects were not discussed in the review, providing an alternative method for secondary production will increase the commercial viability.

5 Conclusion

Bacterial cellulose is widely used in wound dressing applications due to its intrinsic properties. The review analysed different composite wound dressings developed using bacterial cellulose as a base material to load drugs. Out of several drug loading methods reviewed, *in-situ* drug loading in the cultivation process and modification after the cultivation (*ex-situ*/immersion) are the common method adapted due to their simplicity. In review, it is also noted that several drugs in different forms were used in the bacterial cellulose as a medicine. However, the majority of the researchers performed *in-vitro* analysis. The animal studies were majorly done only on the skin and burn wounds rather than other specific wounds. This area has a very bright scope for future research. Further, it is reported that very few manufacturers came up with commercial products with bacterial cellulose. The complication, time, and cost involved in the bacterial cellulose were noted as the main reason. Hence, a viable method for industrial-scale production is the current need of the industry. Other than these factors, bacterial cellulose is a perfect material for wound dressing and tissue engineering application due to its bio-mimicking nature as discussed earlier.

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