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Antimicrobial Synthetic and Natural Polymeric Nanofibers as Wound Dressing: A Review

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Since ancient times, wound dressings have experienced many significant improvements. Evolution began using natural materials to merely cover wounds and advanced to used innovative techniques that can be customized to perform different impressive functions. Recent wound dressings, which are made of electrospun polymers, contain different active compounds, such as antimicrobial agents, that aid in wound healing and prevent dehydration and infection. The mentioned issues may influence the healing process, leading even to serious health risks for the patients. As a result, scientists are now working on novel wound bandages with improved antimicrobial properties. Electrospun polymeric nanofibers, because of their structural similarities to normal skin's extracellular matrix (ECM), bactericidal activity, and appropriateness to distribute bioactive molecules to the wound location, are regarded as good resources for enhancing skin regeneration and controlling wound infection. Herein, the latest findings on approaches for producing antimicrobial polymeric nanofibers using electrospinning and related processes are discussed. Recent advances in antibacterial biopolymeric nanofibers incorporating antimicrobial nanoparticles (silver, zinc oxide, copper oxide, etc.) are discussed. This review paper may raise significant issues, encourage additional research, and offer important insight into the potential area of antibacterial polymeric fibers.

1. Introduction

In recent years, polymer NFs, an important class of nanomaterials, have received much attention. NFs are fibers with a diameter in nanoscale, but fibers manufactured through certain ultrafine fiber fabrication methods like electrospinning having a diameter in the nanometer range are also considered nanofibers (NFs).[1–6] The techniques of NF fabrication have been extensively studied. Several methods have been applied to manufacture suitable polymer NFs for various applications, including melt blowing, force spinning, template synthesis, and electrospinning, while electrospinning is the most common.[7–13] The usage of electrospinning to manufacture nanofiber materials loaded with antibacterial or anticancer medicines for pharmaceutical applications such as wound dressings and local cancer treatment has ignited significant concern over the past decade.[13,14] Different medications can be readily integrated into electrospun

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adem.202101460.

DOI: 10.1002/adem.202101460

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products, and their release profiles could be regulated by altering the fibers' morphology, porosity, and composition.[15,16] The electrospun materials have low cytotoxicity and high drug therapeutic influence because of their high specific surface area, the potential of incremental release, and site-specific local distribution of the active compounds.[17,18] **Figure 1**A displays the major biomedical applications of electrospun fibers.[4] Skin wounds are correlated with high morbidity and mortality rates. This is because of the insufficient efficacy of currently available therapies, which in certain instances do not enable the restoration of the structure and functions of injured tissue, resulting in wound infection and dehydration.[1–3] Bioactive dressings that replicate the structure of native skin and are compliant with cell loading have been designed or are being developed to address these disadvantages (keratinocytes, fibroblasts, and stem cells).[4–7] Dermal wound healing is a very dynamic process comprising four subordinate phases, as shown in Figure 1B.[2,3] Hemostasis, the process by which blood loss is contained to the wound site, is the first instant reaction to injury.[5] The second stage starts immediately after the injury and is characterized by inflammation lasting between 24 h and 6 days. Proliferation is the third stage, during which new granulation tissue is produced and begins to develop on the wound site, forming new ECM. Finally, remodeling is the last step of healing. The matrix composition changes throughout this period, and type III collagen changes to type I collagen, resulting in an improvement in the resultant tissue's tensile strength.[5]

They are classified as epidermal, dermal, or epidermal–dermal replacements based on their capacity to replace the skin's epidermis, dermis, or both layers.[1,2] Despite this, the related manufacturing costs are substantial, and bioactive dressings cannot completely restore all native skin characteristics.[4] The process of phase separation self-assembly and electrospinning has been used to fabricate micro-to-nanosized meshes intended to be utilized as wound dressings.[19] NFs produced by the electrospinning process are commonly nonwoven, making them ideal for applications such as wound dressings. Electrospun mats' unique characteristics, including a large specific surface area and small pores, make them ideal for adsorption of body

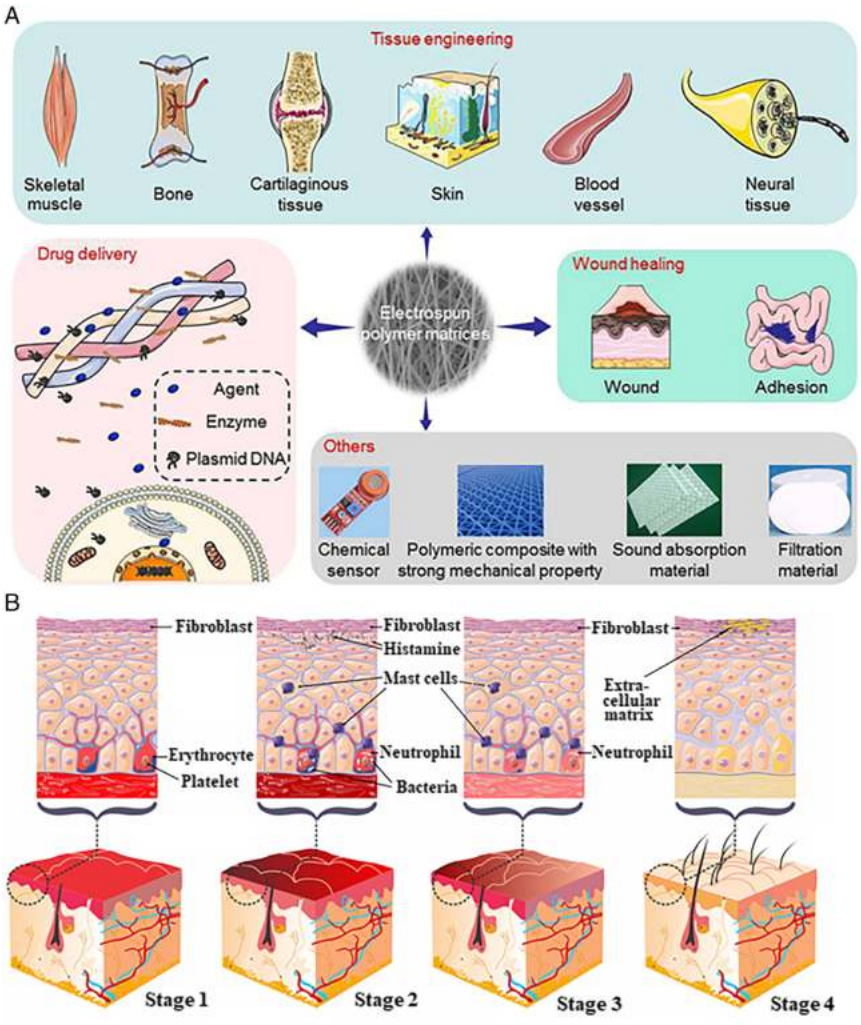

Figure 1. A) Possible biomedical applications of electrospun fibers. Reproduced with permission[4] Copyright 2019, Elsevier. B) Wound healing process. Reproduced with permission.[2] Copyright 2020, The Authors, published by Materials MDPI, and Reproduced with permission[3] Copyright 2018, Elsevier.

fluids and avoiding bacterial invasion, making them ideal for wound healing.[20] Furthermore, efforts have been made to load bioactive molecules into the electrospun nanofibers to enhance the membranes' biological efficiency.[21] Various nanomaterials make excellent platforms for the local distribution of therapeutic agents because of their intrinsic nanoscale morphological properties and functionality.[22] The nanofibers made by electrospinning have a large specific surface area, that can increase the drug's solubility and, as a result, its therapeutic efficacy.[23] Using mix, coaxial, and emulsion electrospinning, multiple agents (antimicrobials, growth factors, and so on) have been integrated into nanofiber meshes.[19] With the introduction of modern biopolymers and fabrication methods, wound dressing materials should have exceptional properties that can help heal wounds.[20] Properties of the wound type, wound healing period mechanical, physical, and chemical characteristics of the dressing must all be considered when designing a functional wound bandage. The primary goal is to attain the fastest possible rates of wound healing and the finest cosmetic wound recovery.[20]

NFs made of synthetic polymers like polycaprolactone (PCL),[24] poly(lactic acid) (PLA),[25] poly(L-lactic acid) (PLLA),[26] and cellulose acetate (CA),[27] as well as biopolymers such as collagen,[28] hyaluronic acid (HA),[29] chitosan (CS),[30] alginate,[31] and elastin,[32] have been tried to fabricate wound dressing.[23,33] Collagen, HA, CS, alginate, and elastin, among other biopolymers, are used to produce bioactive wound dressing products. Biopolymers with active additives, including antimicrobials and antibiotics, have recently been used in wound dressing products to prevent contamination and infections.[20] To control the infection, antimicrobial agents, also known as antimicrobial medicine, have been used. An antimicrobial agent is a substance that may destroy or slow the development of microorganisms. Antimicrobial agents are classified according to the main microorganisms they attack, like viruses and bacteria. They are classified into two categories depending on the chemical compounds they contain.[31–33] The first category is synthetic or chemical antibacterial agents, like antibiotic drugs as well as metal and metal oxide nanoparticles (NPs) such as silver and silver oxide. Herbal antimicrobial agents make up the second category.[33,34] A summary of new investigations on the synthesis, surface functionalization, and assessment of antimicrobial polymeric nanofibers membranes' efficiency as a wound dressing is given in the following parts of this study.[31–33] In addition, in the present review, the most relevant research regarding antibacterial polymeric nanofibers and the primary mechanism of microbial attachment to the biopolymeric and composite fibers are evaluated in detail.

2. Antimicrobial Polymeric Nanofiber

Wound infections are a significant problem in wound care treatment because they slow down the healing process, resulting in disfigurement or even death of the patient.[35,36] Researchers are actively developing nanofibers made by electrospinning functionalized with antimicrobial agents like NPs, antibiotics, and extract of plants to reduce the likelihood of a wound being contaminated.[33] Recently, polymer NFs have been a significant research topic in nanotechnology. They are commonly used in tissue engineering and wound healing. In wound healing, drug-loaded biopolymer-based NFs are used. They are also utilized to produce tissue engineering scaffolds. NFs exhibit remarkably improved mechanical, chemical, electrical, and biological properties compared with microfibers because of their large ratio of surface to volume.[37] PCL, PLA, polyvinyl alcohol (PVA), poly (lactic-*co*-glycolic acid) (PLGA), and CS are some of the polymers utilized to make antibacterial NFs because of their intrinsic properties, including nontoxicity and great mechanical properties such as biocompatibility and biodegradability.[38] Polymer products are classified into two classes depending on their chemical composition. The first category includes synthetic polymers like PCL, PLA, and PLLA. Collagen, HA, CS, alginate, elastin, and other biopolymers make up the second category. Bioactive groups exist in natural polymeric chains, providing a stable and safe environment for cells, particularly stem cells, to grow, proliferate, migrate, and differentiate. Repeatable inert units cover synthetic polymeric networks. In terms of mechanical properties and immunogenic responses, they are typically superior than natural polymers.[39] Depending on the sources of the used raw material and the production method, biopolymers may be classified into different groups, including 1) natural biopolymers like CS, agar, starch, cellulose, as well as animal or plant-derived proteins such as soy protein, whey protein, gelatin, casein, collagen; 2) synthetic biodegradable polymers like PLA, poly(glycolic acid) (PGA), PVA, PCL, and poly (butylene succinate) (PBS); and 3) biopolymers fabricated using microbial fermentation such as microbial polyesters, like poly(hydroxyalkanoates) (PHAs) including poly(β-hydroxybutyrate) (PHB), poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV).[40] The typical polymer structure is shown in **Figure 2**A. As a result, several studies have focused on using antimicrobial NFs made of synthetic and natural polymers as wound dressings.[33] In this respect, numerous methods have been developed for the incorporation of antibiotics into NFs, including electrospinning of polymers and antibiotics in the same solvent, emulsion electrospinning, which is based on the emulsion of an antibiotic solution with an immiscible polymer solution, coaxial electrospinning, which utilizes two concentric nozzles for electrospinning antibiotic and polymer solutions separately, and surface coating of antibiotic molecules on the NFs' surface chemically or physically, as shown in Figure 2B.[1,6] **Table 1** shows diverse antimicrobial polymeric nanofibers as a wound dressing.

2.1. Polycaprolactone (PCL)

PCL has been used for tissue regeneration and has many advantages, like biocompatibility, cost-effectiveness, and ease of the manufacturing process. On the other hand, PCL is a synthetic biomaterial with a hydrophobic surface and no functional groups, making it an ineffective cell adhesion substrate. Various methods have been used to improve PCL nanofibers scaffolds' hydrophilicity and biological characteristics, such as antimicrobial properties.[41]

The fabrication of electrospun mats with excellent characteristics that condone the usability in biomedical applications such as tissue regeneration because of the refined porosity with similar average sizes available in human tissues has been thoroughly

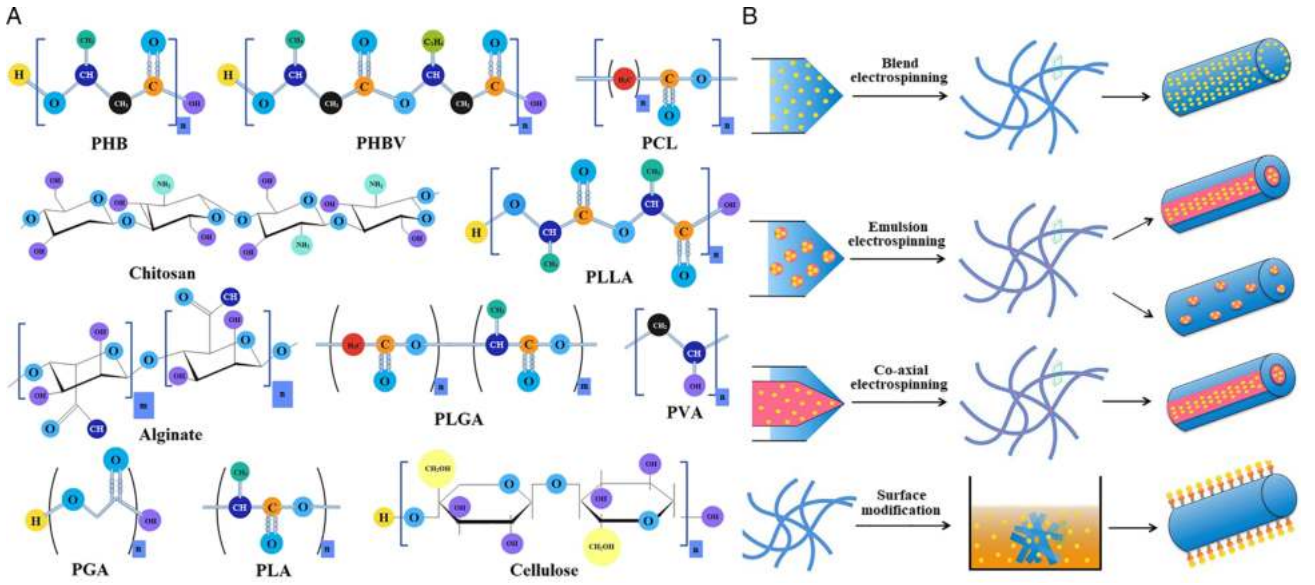

Figure 2. A) Representative chemical structure of the most investigated synthetic and natural polymers for electrospinning and B) different adopted routes to add antibiotics into nanofibers. Reproduced with permission[1] Copyright 2017, Elsevier, and Reproduced with permission[6] Copyright 2020, Elsevier.

explored through the manufacture of bioactive particles through electrospinning processes and the subsequent use of these treated NPs in combination with a biocompatible polymer matrix such as PCL. Due to its low stiffness, hydrophobicity, and bioactivity, PCL as a matrix has limited biomedical applications. However, using bioactive materials in combination with PCL in the fabrication of mats made by electrospinning has received much interest as a route to creating new membranes that have excellent cell proliferation and wound healing properties.[42,43] Miguel et al.[44] explored the usage of extracted aloe Vera CS nanofiber materials and their eventual manufacture utilizing the electrospinning process for skin regeneration and wound healing. Electrospun membranes have been discovered to facilitate cell proliferation and migration rapidly. Furthermore, the antimicrobial function of these electrospun mats is critical for wound dressing and healing.[44] PCL fiber needs to be free of beads in medical applications. This is significant in medical applications because fiber diameters must mimic natural extracellular morphology to facilitate ideal cell growth. In the process of PCL electrospinning, various solvents, including chloroform, methanol, dimethylformamide, dichloromethane, or a combination of them, have been utilized.[45–47] Functional groups could be applied to the polymer to make it more adhesive, hydrophilic, or biocompatible, allowing for better cell responses. Sutures, wound dressings, and dental work are only a few medical devices that use PCL.[40,47,48]

2.2. Poly (Lactic Acid-*co*-Glycolic Acid) (PLGA)

PLGA is a biodegradable synthetic polymer with excellent biocompatibility. It has significant advantages over natural polymers, including a lower price, a well-defined structure and degradation kinetics, reliability, better mechanical properties that make it easier to electrospin, and the existence of lactate as a degradation agent, which has been shown to promote wound healing.[49,50] Fusidic acid, a protein synthesis inhibitor extracted from fungi, was blended into PLGA fibers to prevent bacteria growth. The severity of the wound determined the amount of medicine released by these fibers. The bioburden-triggered drug release of fusidic acid from PLGA mats was used to treat both slightly and highly infected wounds.[51] According to the findings, overnight cultures of wound bacteria (107 CFU mL^{-1}) incubated with antibacterial fusidic acid-laden PLGA ultrafine fiber mats resulted in substantial bacterial colonization and the formation of a dense biofilm over the mat.[52] This was attributed to a significant increase in the initial drug release. Because of this increasingly faster release of bioactive fatty acid, planktonic bacteria were eliminated, and biofilm was significantly reduced. This dressing material–wound milieu interaction may have significant therapeutic ramifications as pristine fibrous mats may inhibit infection spreading by sequestering bacteria, albeit reinfection of the wound becomes more likely. Biodegradable drug-loaded wound biomaterials can be negatively affected by the enzymes and toxins produced by colonization bacteria, which can impair the structural integrity and drug release capabilities of the wound biomaterials.[52] A wound dressing based on PLGA and Aloe vera containing nanostructured lipid carriers (NLCs) has been developed in one study. In this research, NLCs were added to give the dressing a lipid component that would prevent it from adhering to the wound and increase its handling.[50] A study tested and determined the antimicrobial effect of PLGA/CuO hybrid NF scaffolds on different bacterial strains. Another study investigated how fibroblasts (skin cells) interacted with PLGA/CuO hybrid NF scaffolds as an internal and external wound dressing.[53] Another study aimed to use the electrospinning technique to fabricate and characterize biodegradable

Table 1. Diverse antimicrobial polymeric nanofibers as a wound dressing.

Polymer	Materials including antimicrobial agents	Condition	Result	Ref.
PU/CA	Zein + Antibiotic drug	In vitro	Inhibition zones: *E. coli*:12 mm; *B. subtilis*:15 mm; *S. aureus*: 8 mm	[112]
PVA	Octyl methoxycinnamate (OMC), peppermint oil, amphiphilic octenidine	In vitro	99% resistance against *E. coli* K-12 and *B. Subtilis*	[113]
PVA	Ag NPs	In vitro	Higher inhibition zone against *E. coli*	[114]
PVA	Gum tragacanth	In vitro	Capability to resist *P. aeruginosa* and *S. aureus* bacteria	[115]
PVA/CS	Graphene	In vitro	Resistance against *E. coli*	[116]
PCL/gelatin	APA (6-Aminopenicillanic acid)-coated Au NPs	In vitro	High bacterial resistance against *E. coli* and MDR *E. coli*	[117]
PCL	Silver NPs	In vitro	Adequate resistance to bacteria like *S. aureus, E. coli, P. aeruginosa, S. pyogenes*, and *K. pneumonia*	[118]
CS/ethylenediaminetetraacetic acid (EDTA)/PVA	Garcinia mangostana extracts with α-mangostin	In vitro	Bacterial inhibition against *E. coli* and *S. aureus*	[119]
CS/PEO	Cefazolin	In vitro and in vivo	Antibacterial activity against *S. aureus* (inhibition zone: 12 mm) and *E. coli* (inhibition zone: 10 mm) bacteria.	[120]
CS/PEO	Silver NPs	In vitro	Higher inhibition zone than pristine CS/PEO NF (0.01 mm)	[121]
CS/PVA	ZnO	In vitro and in vivo	Higher inhibition zone against *E. coli, P. aeroginosa, B. subtilis*, and *S. aureus* compared with pristine CS/PVA NFs	[122]
Sodium alginate/PVA	Nano-ZnO	In vitro	Improved inhibition zone diameter of *S. aureus* (15–16 mm) and *E. coli* bacteria (14–15 mm).	[123]
PCL	Curcumin and gum tragacanth	In vitro and in vivo	Antibacterial activity of 99.99% and 85.14% against GNB (*MRSA*) and GPB (*extended spectrum b lactamase*–ESBL)	[124]
Poly (3-hydroxybutyric acid)-gelatin (PG) and collagen	Coccinia grandisplant extracts (CPE)	In vitro	Antimicrobial activity against *S. aureus* and *E. coli*	[125]
Sodium alginate/PVA	Essential oils (cinnamon, clove, and lavender)	In vitro	Good antibacterial properties against *S. aureus*	[126]
CA/ PCL/PVP	Nisin	In vitro	High antimicrobial activity	[127]
SF-PVA	Elaeagnus Angustifolia (EA)	In vitro	Antibacterial activity against both GPB (*S. aureus*) and GNB (*E. coli*)	[128]

scaffolds composed of polymeric PLGA NF matrix and Ag NP reinforcement appropriate for soft tissue replacement without using any foreign-reducing agent. In addition, the morphological and thermal properties of the obtained NF matrices were studied. The obtained findings clearly suggested that NF mats could be used as antimicrobial agents in biomaterials or water purification systems.[54] Another research found that PLGA–HACC fibrous membranes had good cytocompatibility and greatly increased human dermal fibroblast (HDF) and HaCaT adhesion, spreading, and proliferation. The wound healing efficacy of PLGA–HACC was verified in *S. aureus*-infected mice, utilizing a complete thickness excision wound model. The outcomes of this research show that PLGA–HACC may be a promising therapeutic biomaterial to treat infected wounds.[55] Except for *P. aeruginosa*, electrospun PLGA NFs containing the antibiotic chloramphenicol were reported to control the growth of bacteria on the solid agar plate in one research. Chloramphenicol-loaded NFs inhibited *E. coli, B. cereus*, and *S. typhimurium* growth by 93% or more in liquid culture, while *P. aeruginosa* and *S. aureus* growth were inhibited by 42% and 56%, respectively.[56]

On the PLGA–HACC membranes, considerably fewer living bacteria (visible as green fluorescence) were detected than on the PLGA and PLGA–CS membranes, indicating much fewer adhering surviving bacteria on the PLGA–HACC membranes than on the PLGA membranes. A high density of dead bacteria (visible as red fluorescence) suggested the presence of dead colonies on the PLGA–HACC membranes (**Figure 3**A).[8] Scanning electron microscopy (SEM) micrographs of bacterial morphology on PLGA, PLGA–CS, and PLGA–HACC membranes are shown in Figure 3B.[8] *S. aureus* and *P. aeruginosa* adhered to PLGA

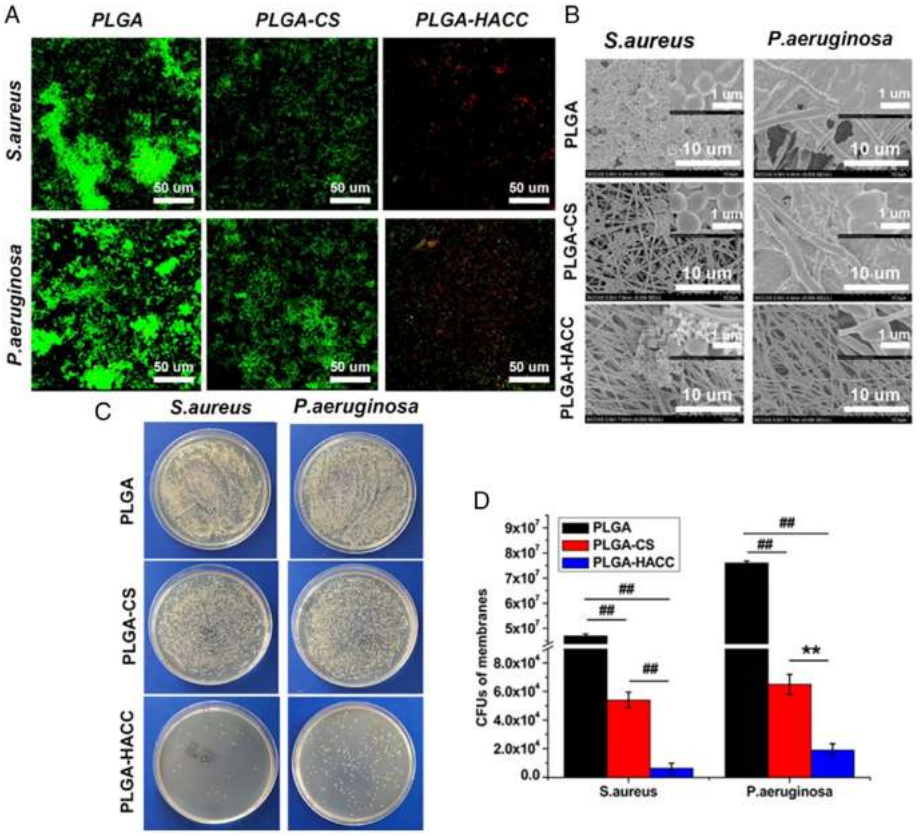

Figure 3. A) Confocal laser scanning microscopy (CLSM) images of *S. aureus* and *P. aeruginosa* activity on PLGA, PLGA–CS, and PLGA–HACC fibrous membrane surfaces after 24 h. B) SEM micrographs of *S. aureus* and *P. aeruginosa* incubated with PLGA, PLGA–CS, and PLGA–HACC fibrous membranes after 24 h; the inserted image depicts the SEM micrographs at a higher magnification. C) Photos of *S. aureus* and *P. aeruginosa* colonies formed after 24 h of incubation on PLGA, PLGA–CS, and PLGA–HACC fibrous membranes. D) Quantity of adhering bacteria on the three membranes after 24 h of incubation; ## denotes $p < 0.01$, and ** denotes $p < 0.05$. Reproduced with permission.[8] Copyright 2017, The Authors, published by Polymers MDPI.

membranes more than they did to PLGA–CS and PLGA–HACC membranes. Bacterial adhesion was similarly reduced in PLGA–CS membranes as compared with PLGA membranes. *S. aureus* and *P. aeruginosa* were found sparsely dispersed over the whole surface of the PLGA–HACC fibrous membranes. *S. aureus* and *P. aeruginosa* were shown to be considerably less abundant on PLGA–HACC membrane surfaces than on PLGA and PLGA–CS membrane surfaces (Figure 3C,D).[8]

2.3. Poly(Vinyl Alcohol) (PVA)

PVA is a biocompatible, biodegradable, water-soluble, and non-toxic synthetic polymer that is commonly used in biomedical applications. PVA in fiber form has been marketed since 1950s and has good fiber shaping and extremely hydrophilic properties. Attempts have been made in recent years to fabricate and synthesize PVA composite or blended NF materials.[57] Coating is the process of immersing a manufactured electrospun mat in a solution to impart desired properties to the mats. PVA electrospun fibers were coated with CS by immersing them in a solution containing 1.0 wt% of CS for 1 h at 30 °C.[58] Apart from the ease of use, another benefit of coating was that the CS coating chemically resembled glycosaminoglycans in the ECM more strongly than the control sample (CS–PVA blend fibers).[58] Nguyen et al.[59] used PVA as a reducing agent of Ag NPs/PVA blended fibers. After electrospinning, a heat treatment method was used to attract Ag NPs to the fibers' surface, where they can be more useful. The research outcomes showed that the utilized process was quicker, easier, and less expensive than traditional processes.[59] To eliminate bacteria at the wound site, it is preferred that a high dose of the drug be released in the early stage, while a slow release of the medicine helps in infection prevention. Jannesari and her co-workers[60] developed PVA/poly(vinyl acetate) (PVAc) composite NF mats containing ciprofloxacin HCl, fabricated by electrospinning, which had a doubled initial burst release rate by increasing the drug loading from 5 to 10 wt%. The results showed that the hydrophilic drug probably migrates to the surface of the fibers during evaporation of the solvent if the hydrophobic polymer, PVAc, is incorporated into the fibers.[60] Furthermore, as the PVAc mats have a lower rate of sustained release and are more flexible, they are ideally engineered for wound healing. Taepaiboon et al.[61] discovered that the model drugs' molecular weight affected both the rate and overall amount of drug released from drug-loaded electrospun PVA mats.[61] He et al.[62] investigated the drug loading ability by electrospinning polyvinylidene fluoride fibrous

membranes integrating enrofloxacin drugs for wound dressing. Electrospun natural NFs were fabricated for drug delivery systems using a new method for encapsulating therapeutic agents in core–shell NFs or core–multi sheets. Their findings revealed that not only the natural mats containing the essential oils exhibit excellent cell compatibility and minimal cytotoxicity, but also that even minimal amounts of essential oils completely inhibited the development of *E. coli*. In addition, antimicrobial mats made of natural electrospun NFs have been used to promote skin wound healing (**Figure 4**A).[10] Lan et al.[7] used electrospinning coaxially for the fabrication of a series of PVA/PCL NFs with the dual release of tea polyphenols and ε-poly (L-lysine), as presented in Figure 4B.[7] Antibacterial tests against *E. coli* and *S. aureus* revealed that incorporating ε-PL into coaxial NFs resulted in significant antibacterial activity through cell wall/membrane lysis (Figure 4C).[7] In addition, bacteria exhibit variable sensitivity to ε-PL, due to variations in membrane composition. Figure 4D illustrates the antibacterial activity of PVA–berberine (Ber) NFs and PVA–berberine–hydroxypropyl–cyclodextrin inclusion complex (Ber–IC)–NF against *E. coli* and *S. aureus*.[9] With the exception of PVA–NF, PVA–Ber–NF, and PVA–Ber–IC–NF showed significant antibacterial activity against both bacteria, as can be observed in the figure. These findings suggest that Ber has a superior antimicrobial effect when it is released and diffused from the PVA–NF. PVA–Ber–IC–NF exhibited more antifungal effects than PVA–Ber–NF using the same dosage. This is because of the

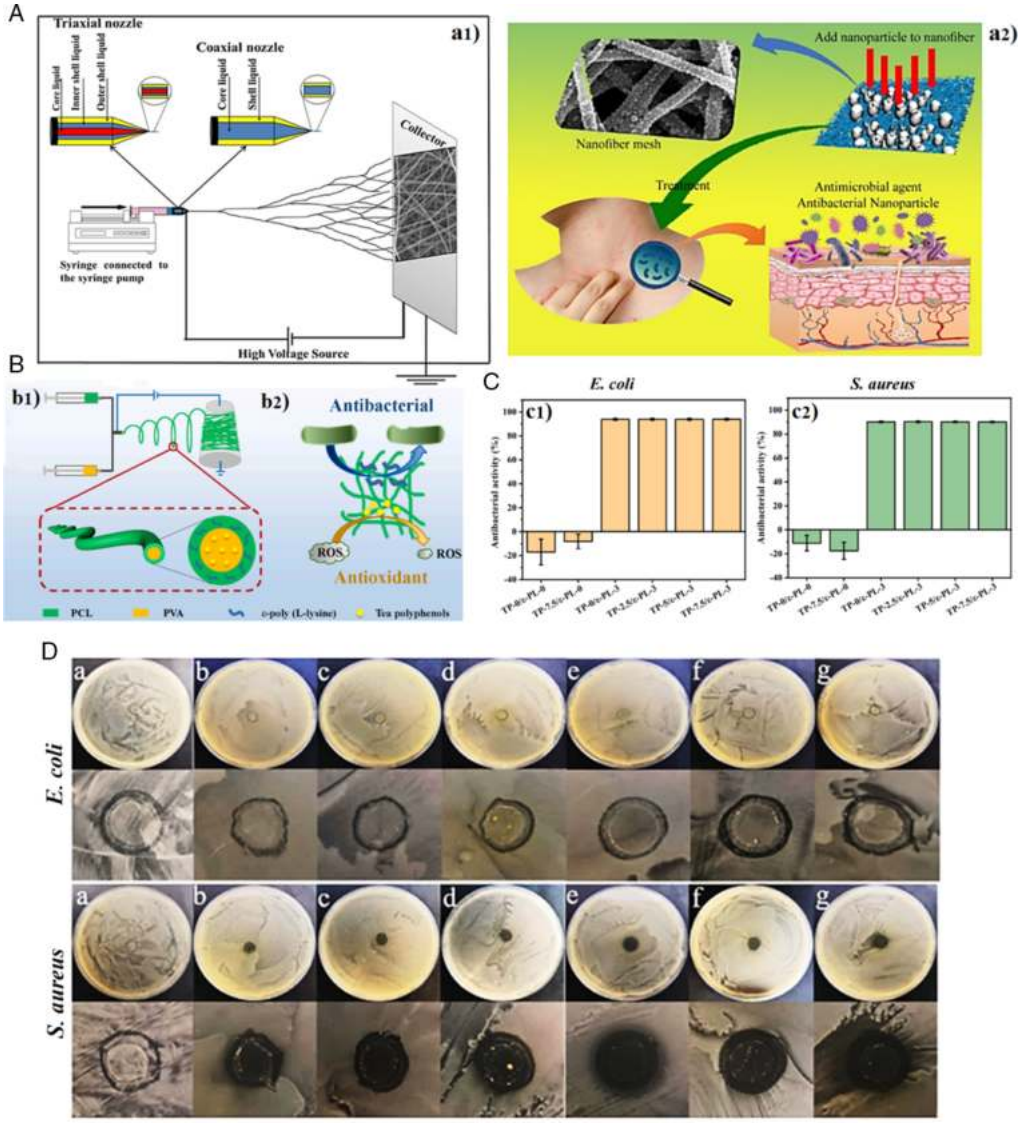

Figure 4. A) a1) Multiaxial electrospinning setup for DDSs and a2) illustration of antibacterial mechanism for skin wound healing. Reproduced with permission.[10] Copyright 2018, Elsevier. B) Schematic representation of the fabrication and use of coaxial NFs. b1) Coaxial electrospinning is used to produce PVA/PCL coaxial NFs containing tea polyphenols and -ε-PL. b2) Antioxidant and antibacterial activity of coaxial NFs. C) Antibacterial activity of coaxial NFs against c1) *E. coli* and c2) *S. aureus*. Reproduced with permission.[7] Copyright 2021, Elsevier. D) Antibacterial activity of a) PVA, b) PVA–Ber–NF 0.5%, c) PVA–Ber–NF 1%, d) PVA–Ber–NF 1.5%, e) PVA–Ber–IC–NF 0.5%, f) PVA–Ber–IC–NF 1%, and g) PVA–Ber–IC–NF 1.5%. Reproduced with permission.[9] Copyright 2021, Elsevier.

existence of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), which has a higher affinity for cells and facilitates access to and release of Ber from them.

2.4. Cellulose Acetate (CA)

Among the numerous biocompatible polymers that could be utilized to manufacture electrospun NFs, CA has many advantages, including its recycling capacity, cost-effectiveness, and simple mass production process. It is also very soluble in organic solvents, making it an outstanding option for use in the electrospinning process. CA is a biodegradable, nonirritating, and nontoxic material. It has been thoroughly investigated and utilized for wound dressings, dermal substitutes, and engineered skin tissues for effective wound healing because of its outstanding mechanical properties, high chemical affinity with other chemicals, and regenerative characteristics.[63] Antimicrobial agents have been applied to CA to control wound infection. Based on Son et al.'s[64] research, when CA NFs electrospun from CA solutions containing 0.5 wt% $AgNO_3$ were irradiated with UV light at 245 nm, Ag NPs were formed mostly on the CA NFs surface. The volume and size of Ag NPs were steadily increased for up to 240 min. Ag^+ ions and Ag clusters diffused and aggregated on the surface of the CA NFs after UV irradiation. The antibacterial activity of Ag NPs with an average size of 21 nm was outstanding.[64] In a previous research, CA NFs containing Ag NPs were produced by slow photoreduction of Ag^+ ions inside CA NFs over a 20 day period in a typical laboratory environment, using antibacterial separation filters for submicrometer particles.[65] Coelectrospinning or blend electrospinning is used to make a range of nanofiber membranes from CA and polyester urethane (PEU) in one research. The NF membranes' drug release, in vitro antibacterial behavior, and in vivo wound healing efficiency were assessed for wound dressing applications. Polyhexamethylene biguanide (PHMB), an antibacterial agent, was loaded into the electrospun fibers to avoid common clinical infections. The addition of CA to the NF membrane increased its hydrophilicity and air and moisture permeability. As CA fibers were exposed to the liquid phase, they swelled slightly. CA improved moisture absorption and provided a humid atmosphere for the wound, allowing it to heal faster.[66] CA–Manuka honey composite nanofibers mats were used to manufacture a biocompatible and antibacterial wound dressing.[67] Propolis-impregnated CA/PCL nanofiber mats for antimicrobial and antioxidant applications were reported by Khoshnevisan et al.[68] The propolis CA/PCL NFs were found to have strong antioxidant activity and were effective against both Gram-negative bacteria (GNB) and Gram-positive bacteria (GPB). CA may therefore be utilized as antibacterial membranes, tissue scaffolds, bionanocomposites, and biomedical separators and are especially useful as tissue scaffolds, antimicrobial membranes, biomedical separators, and bionanocomposites.[67,68]

2.5. Poly (Lactic Acid) (PLA)

PLA is a biocompatible synthetic polymer composed of lactic acid. It has tremendous potential because of its biodegradability, which makes it absorbable in the body, and its high bioresorbability that provide space for tissue expansion.[69] At the same time, many positive reports of PLA being used to assist antimicrobial activity and other biomedical applications have been reported. PLA was chosen as the coaxial electrospinning core material due to its outstanding properties like nontoxicity, superior mechanical properties, and great fiber-forming capability.[70] Spasova et al.[71] selected CS to coat their electrospun PLA and PLA/polyethylene glycol (PEG) wound healing mats to have immediate hemostatic activity. Nguyen et al.[72] used coaxial electrospinning to strengthen the CS shell with PLA as the core. The fabricated electrospun material demonstrated good antimicrobial activity against *E. coli* bacteria, indicating that they could be used as antimicrobial materials in biomedical and filtration applications.[72] As biocompatible PLA NFs have a large porosity and specific surface area, they may improve the functional properties of curcumin (antioxidation, anticancer, anti-inflammatory, and wound healing properties), and they were used as a carrier for curcumin in one sample. The findings showed that curcumin-loaded NFs with a sufficient loading of curcumin are nontoxic and could be used in wound healing patches.[72] In another research, coaxial electrospinning was used to construct NFs with a core of poly(γ-glutamic acid) (γ-PGA) and a shell of PLA. It was proposed as a substance that could be utilized for tissue engineering and wound healing applications.[73] In a research, to reach the aim of releasing encapsulated substances, polyvinylpyrrolidone (PVP)/PLA–PEO composite NFs encapsulating collagen and cefazolin dressing scaffold were manufactured using a coaxial electrospinning process. The scaffolds' antibacterial behavior was assessed using the disk diffusion method against *E. coli*, *S. aureus*, and *P. aeruginosa* bacteria. The findings showed that the samples positively impacted the antimicrobial function.[74] Karami et al.[75] fabricated thymol-loaded hybrid PLA/PCL (50/50) NFs and evaluated their antibacterial properties against *S. aureus* and *E. coli* bacteria and in vivo, finding that they can improve wound healing and histological efficiency and were more successful in closing wounds than traditional wound care products. In another research, herbal extracts were collected from different plants in Turkey utilizing water vapor distillation and soxhlet extraction methods. Following antibacterial testing against *S. aureus* and *P. aeruginosa*, it was agreed to load hortensis (SH), agrimonia eupatoria (AE), and hypericum perforatum (HP) into electrospun polymeric NFs commonly used in medical applications. The findings showed that composite NFs made from thermoplastic polyurethane (TPU), PLA, and PCL polymers combined with herbal extracts of HP, AE, and SH had strong structural integrity and morphology. TPU/SH composite NFs had the greatest polymer extract compatibility due to their antibacterial behavior and NF morphology. The study aimed to develop a compatibility strategy between plant extract and polymeric NFs to offer rapid prototyping of different wound dressings with antimicrobial and morphological properties that can be regulated by choosing the right polymer and extract forms.[76] Hydrotalcite ((Mg–Al)LDH) was utilized as a host matrix to attain an antibacterial structure effective in delivering silver sulfadiazine (SSD) from electrospun PLA scaffolds intended for wound skin healing, to combine the properties of PLA and SSD. SSD-(Mg–Al)LDH had strong inhibitory activity against *E. coli* and *S. aureus* in vitro antimicrobial experiments. The antibacterial efficacy of the 2.5 wt%

SSD-(Mg–Al)LDH-loaded PLA NFs was maintained, and they also had outstanding biocompatibility with human cells. The PLA/SSD(Mg–Al)LDH scaffold's multifunctionality is extremely important for various transdermal applications.[77] As a result, PLA is a flexible, bioabsorbable, and biodegradable polymer with outstanding biocompatibility and the potential to integrate a wide range of active agents, such as antimicrobial agents for bacterial infection prevention in external wounds.

2.6. Poly(L-Lactic Acid) (PLLA)

PLLA is an important polymer material because of its biodegradability and biocompatibility. Under normal physiological conditions, PLLA is assumed to be hydrolyzed in the body to convert to its initial monomers, lactic, and glycolic acids, which are also byproducts of different metabolic pathways. PLLA-based materials have been widely used in the biomedical and biological fields. In a research, Leo's group prepared ibuprofen-loaded PLLA microspheres and investigated their drug release characteristics, resulting in a controlled therapeutic system. As a result, PLLA was used as the wound dressing substrate material.[78] According to another study, biodegradable PLLA scaffolds have a well-connected macroporous and nanofiber architecture that can prevent bacterial development.[79] Paclitaxel (lipophilic) and doxorubicin HCl (hydrophilic) with different solubilities were encapsulated in electrospun PLLA fiber mats in a research by Zeng et al.[80]. The compatibility of the drug polymer and the rate of polymer degradation was found to be the most important factors in determining the release fashion. Paclitaxel was encapsulated in the PLLA NF mats, and doxorubicin HCL was found on or near the surface. As predicted, a burst release of doxorubicin HCl was seen, while a zero-order profile for paclitaxel dominated the release pattern.[80] Electrospinning was used to make nitrofurazone (NFZ)-loaded PLLA/sericin/PLLA dual-layer fiber mats in one study. Due to the inclusion of sericin, the dual-layer fiber mats had a strong hydrophilic property. The antibiotic drug NFZ was added to the blend NFs, which increased their antibacterial activity against GNB *E. coli* and GPB *B. subtilis* as compared with the fibers without the compound.[78,80] In another study, PLLA–PEG–NH_2 and PLLA emulsion electrospun into core–sheath NFs were used. After two functionalization reactions, the sample was shown to retain its antimicrobial ability, representing that multifunctional NFs might be developed into functional wound dressings or periodontal membranes or used in more complex tissue systems that need several growth factors and anti-infection precautions for optimal tissue implantation and regeneration.[81] According to another investigation, a biocompatible zinc prolinate catalyst was developed for the production of PLLA (>100 000) and PLLA–ciprofloxacin. Ciprofloxacin was covalently bound to the chain end of two-, three-, and four-arm PLA through the piperazine ring as an ester linkage. In both a static (agar) and dynamic (liquid) setting, the delivered ciprofloxacin from PLLA nonwoven NF was found to be structurally intact as well as successful in inhibiting the growth of *S. aureus* and *E. coli* bacteria.[82] As a result, the PLLA NF can be used as a wound covering with an antimicrobial effect.

Ahmadian et al.[11] showed the inhibitory activity of electrospun EC/PLA/ collagen loaded with AgSD against *Bacillus* and *E. coli* bacteria using the disc diffusion technique, as shown in **Figure 5**A.[11] The figure shows that the NFs had no inhibitory effect against bacteria prior to loading AgSD (control group) after

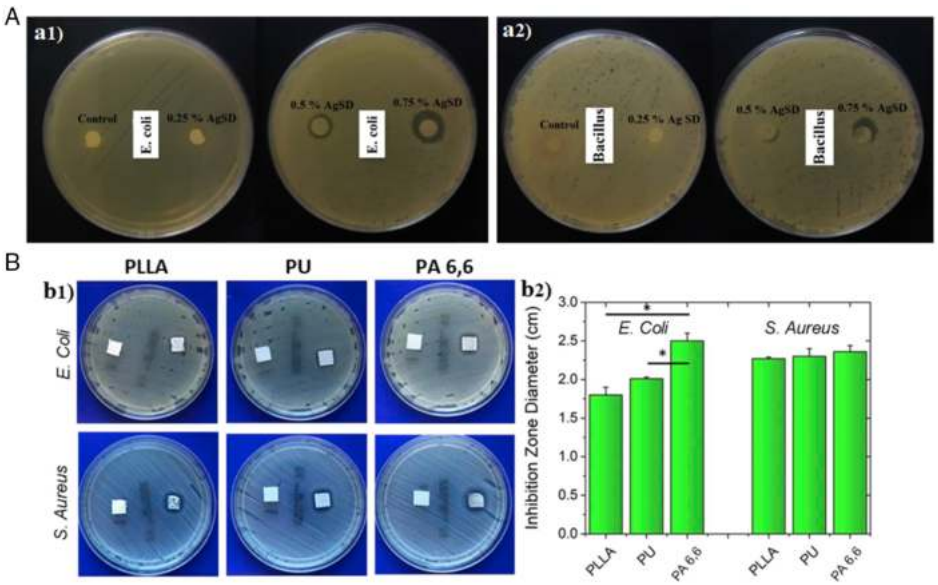

Figure 5. A) The antibacterial activity of optimal mat with different contents of AgSD (0.25%, 0.5%, and 0.75%) against a1) *E. coli* and a2) *Bacillus* bacteria. Optimal mat: EC/PLA (70:30) –collagen (10 wt%), AgSD: silver sulfadiazine. Reproduced with permission.[11] Copyright 2020, Elsevier. B) b1) Representative optical images of agar diffusion experiments with *E. coli* and *S. aureus* strains were conducted on uncoated reference (the left patch in each image) and coated electrospun mats (right patch). b2) Diameter of the inhibitory zone after 24 h of incubation with *E. coli* and *S. aureus* ($^*p < 0.05$). It should be noted that although the deposition period for Ag–PU and Ag–PA is 40 min., the deposition time for Ag–PLLA is 20 min, as a shorter deposition duration was chosen to prevent causing harm to the patch. Reproduced with permission.[12] Copyright 2020, Elsevier.

24 h of incubation. After putting AgSD into optimum mats, mats containing 0.75% of AgSD showed significantly larger inhibitory zones than mats carrying less AgSD for both bacteria. As previously stated, the release of Ag^{2+} ions from AgSD increases the penetrability of mats and allows them to pass through the bacteria cell wall. Bacteria may be killed by the interaction of Ag^{2+} ions with the cytoplasm. All coated electrospun NFs had significant antibacterial activity against *E. coli* and *S. aureus*, as evidenced by the presence of an inhibitory zone surrounding the Ag-coated patches, as shown in Figure 5B.[12] On the other hand, as expected, uncoated mats showed no antibacterial effect. More precisely, effectiveness against *S. aureus* was found to be greater than that against *E. coli*; the antibacterial activity of Ag-aliphatic polyamide (PA 6,6) was shown to be superior than Ag–PEU (abbreviated as PU) and Ag–PLLA against *E. coli*, whereas all coated mats displayed equal antibacterial activity against *S. aureus*.

Furthermore, the existence of the halo revealed that Ag coatings were antibacterial not just via direct contact with the bacterial membrane, but also through a diffusion-driven process of silver ions in the patch's proximity.

2.7. Collagen (Col)

Collagen is the protein found in the greatest abundance in animals, present in the dermis, tendons, and bones, and it is the primary structural portion of extracellular matrices found in connective tissues. Hepatocytes, spinal ganglion cells, fibroblasts, nerve cells, Schwann cells, epithelial cells, embryonic lung cells, and a variety of other cell lines survive on collagen type I. It has also been used to research tissue morphogenesis and cell lines' growth, differentiation, and migration during development. Collagen is a central component of the ECM, which gives tissues their structural stability and tensile strength. Collagen is needed to restore and repair structure and function after tissue damage.[83] In a research, a novel scaffold for successful wound healing care was produced using natural products containing collagen-based biocompatible electrospun NFs. The scaffolds were effective against *P. aeruginosa* and *S. aureus*, two important wound pathogens. PHB–Gel–OSA–Col provides a good case of therapeutic biomaterial suitable for wound healing and reconstruction with high infection tolerance in both in vitro and in vivo evaluations.[84] In the biomedical area, electrospun fibers have proven to be effective as wound dressings. Young's modulus increased under aqueous conditions as collagen electrospun fibrous membranes were crosslinked. Furthermore, these membranes have been seen to be able to replicate the native ECM, resulting in better wound healing and in vitro tissue regeneration as opposed to conventional gauze and industrial collagen dressings (e.g., bone, cartilage). Compared with topical agents, hybrid CS fiber dressings are required to speed up the healing process and recovery period by preventing bacterial growth and infection spread. When these fibers are mixed with agents or enzymes that facilitate wound healing and pain relief, their bioactivity is enhanced even further.[85] The aim of one research was to see if collagen NF mats with silver NPs could help with wound healing. Silver NPs produced by the chemical reduction process were incorporated in collagen NFs during the process of electrospinning. Minimum inhibitory concentration (MIC) of Ag NPs against *S. aureus* and *P. aeruginosa* were assessed using microdilution assay, and further antibacterial behavior of produced NFs was performed.[83] In this respect, Ahmadian et al.[11] manufactured and tested SSD-incorporated ethyl cellulose (EC)/PLA/collagen as a new antimicrobial NF mat. Antibacterial properties revealed that *Bacillus* and *E. coli* bacteria were inhibited. One research looked into the electrospinning of two proteins (collagen and zein) in an aqueous acetic acid solution to create biocompatible nanofiber membranes for wound healing. This nanofiber membrane was electrospun and showed controlled release and antibacterial action.[86,87] Another research used electrospinning to create zein/PCL/Collagen NFs incorporating ZnO NPs and aloe vera. Inhibition activity against *S. aureus* and *E. coli* bacteria was discovered in this study. The findings suggested that the fabricated sample could be used as an active scaffold for wound dressing application.[88] As a result, collagen-based NFs could be used as a wound dressing with an antimicrobial effect. Yuan et al.[13] used the layer-by-layer (LBL) self-assembly deposition method to effectively install lysozyme (LY) and collagen onto SF/nylon 6 (SF/N6) nanofibers mats in alternating layers. The LBL-structured mats displayed superior antibacterial and biocompatibility properties in comparison with the SF/N6 nanofibers mats, which were primarily due to the successful assembly of lysozyme; however, the SF/N6 mats promoted the proliferation of *E. coli* (11.4%) and *S. aureus* (69.6%), as illustrated in **Figure 6**.[13]

2.8. Elastin

Elastin is a polymeric ECM protein found in abundance in the skin, lungs, and arteries used to treat wounds. Because of their exceptional elasticity, biological activity, and long-term flexibility, elastin-based materials are gaining popularity in tissue engineering applications. Hydrolyzed elastin, elastin fibers, and recombinant tropoelastin are all examples of structural proteins that may be used in biomaterials. As elastin's insolubility restricted its use in biomaterials, certain hydrolyzed soluble elastins are created to create a variety of physical types. For example, soluble elastin was used to make hydrogels that were electrospun into fine fibers. Elasticity, biological function, and mechanical flexibility are both properties of elastin.[89] In a research, a triple-collagen–elastin–PCL (CEP) polymer scaffold composite was fabricated to improve the scaffold's mechanical properties while preserving its biological properties for cell adhesion, proliferation, and tissue regeneration. Elastin was shown to minimize stiffness while also lowering hysteresis and increasing elasticity when added to the scaffold. According to the research, electrospun collagen–elastin–PCL scaffolds may be used to enhance skin cell proliferation and tissue regeneration after significant burn damage.[90] Electrospun collagen and elastin mixtures have been used to manufacture a variety of scaffolds. The inclusion of elastin in nonelectrospun collagen scaffolds has been shown to reduce scaffold rigidity, modulate collagen contraction and degradation, and increase angiogenesis and elastic fiber development. The combination of collagen and elastin can enhance a dermal substitute's physical and biological properties.[91] Electrospinning collagen and/or elastin meshes

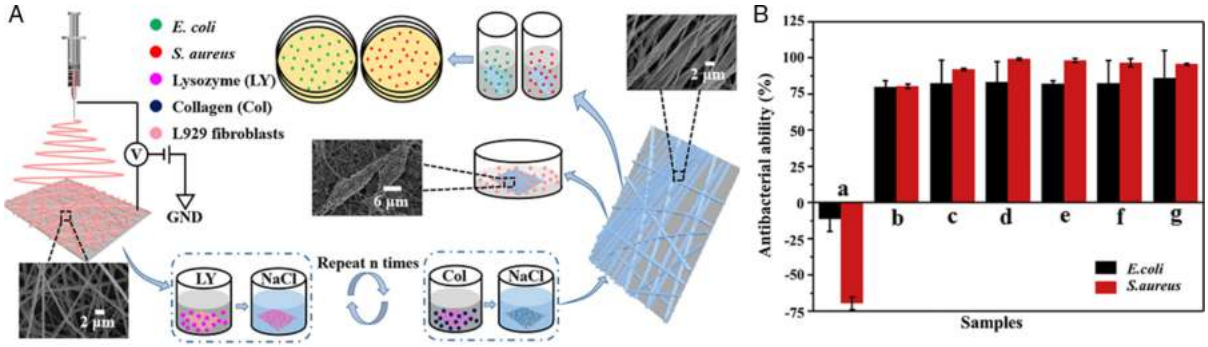

Figure 6. A) Illustration of manufacturing process of SF/N6- and LBL-structured nanofibrous mats and B) antibacterial ability of SF/N6 and LBL-structured mats against *E. coli* and *S. aureus*: a) SF/N6, b) (lysozyme/collagen)$_5$, c) (lysozyme/collagen)$_{5.5}$, d) (lysozyme/collagen)$_{10}$, e) (lysozyme /collagen)$_{10.5}$, f) (lysozyme/collagen)$_{15}$, and g) (lysozyme/collagen)$_{15.5}$. Reproduced with permission[13] Copyright 2020, Elsevier.

from aqueous solutions was successfully accomplished. This NF has been used to help in tissue engineering.[92] An electrospun synthetic human elastin–collagen composite scaffold for dermal tissue synthesis was reported in a research. The blends of electrospun human tropoelastin and ovine type I collagen examined included 80/20, 60/40, and 50/50 compositions in wt%, respectively.[93] Cao et al.[14] fabricated composites of CS/elastin and small intestinal submucosa (CS/ES-SIS) using the combination of SIS with electrospun CS/ES NFs (**Figure 7**A). According to Figure 7B, SIS exhibited an uneven texture, while CS/ES-SIS composites were pristine white and smooth.[14] As shown in Figure 7C,[14] the top surface of CS/ES-SIS composites was composed of CS/ES electrospun NFs with a high degree of porosity, interconnectivity, and microscale interstitial space. As shown in Figure 7D, SIS lacked apparent antibacterial activity, while the CS-SIS and CS/ES-SIS composites displayed distinct inhibitory zones against *E. coli* and *S. aureus*.[14] It was observed that CS-SIS composites had a somewhat greater antibacterial capability than CS/ES-SIS composites, which may be attributed to the increased CS concentration. In addition, the composites showed superior antibacterial activity against *E. coil* compared with *S. aureus*.

2.9. Silk Fibroin (SF)

Because of its excellent luster, softness, hygroscopicity, and mechanical ability, Mori Bombyx silk is used as a satisfactory textile fiber. Sericin glue proteins shape an adhesive around the main portion of SF, giving it a special hierarchical structure. The fibrous portion of SF was isolated after degumming with alkali, soap, or proteolytic enzymes. Due to the material's strong

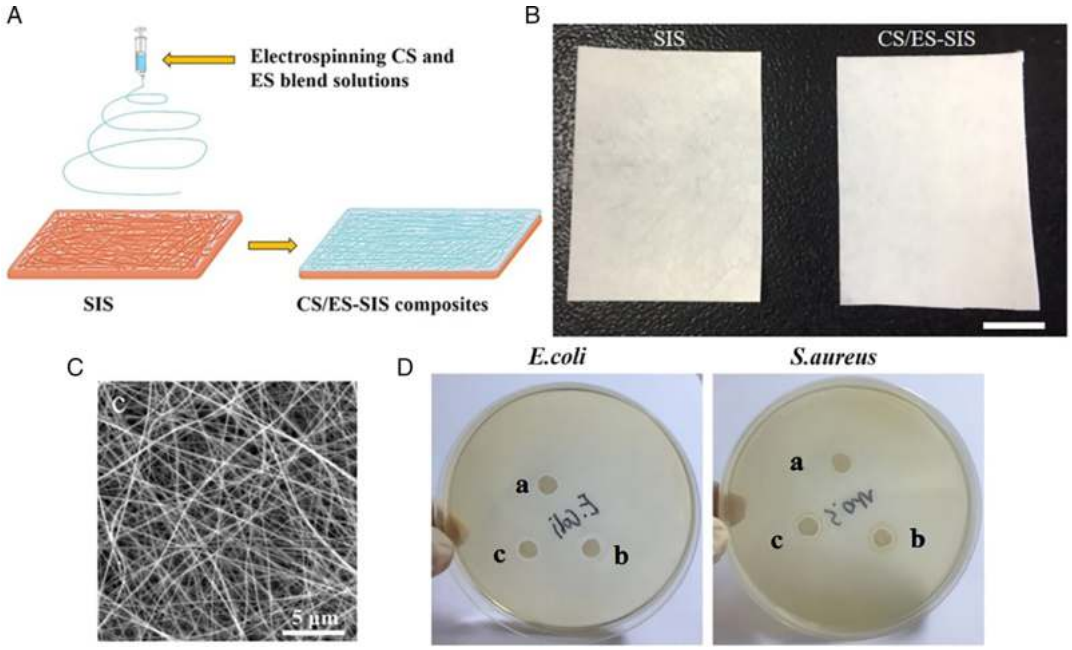

Figure 7. A) Illustration of the fabrication of CS/ES–SIS composites. B) Macroimages of SIS and CS/ES–SIS composites, scale bar: 1 cm. C) SEM images of upper and D) antibacterial activities of a) SIS, b) CS–SIS, and c) CS/ES–SIS composites against *E. coli* and *S. aureus*. Reproduced with permission.[14] Copyright 2020, Elsevier.

biocompatibility, acceptable mechanical properties, and promising physiological properties, recent studies have shown that SF could be used in the textile industry and medical and clinical fields.[85–88] SFs, including hydrogels, films, sponges, and electrospun fibers, are currently used for surgical sutures in the care of skin wounds and for tissue engineering without causing significant side effects. The structural and morphological characteristics of fibroin-based materials determine their performance. Secondary structures were given preference over random coils in regenerated SFs obtained through freeze drying or electrospinning, resulting in certain undesirable mechanical properties such as hardness, brittleness, low durability, and strong water solubility. Many chemical methods have been attempted to alter fibroin materials to extend their functionalities.[89,94] A silk NF electrospun scaffold with the epidermal growth factor improved wound closing by 90% in an in vivo experiment on mice, according to Schneider et al.[94]. The influence of fibroin morphology on Ag-ion release and concomitant antibacterial activity against *S. aureus*, *S. epidermidis*, and *P. aeruginosa* was investigated in a study that used glutaraldehyde vapor and methanol post-treatments to produce Ag/fibroin composite NFs in both random coil (Silk I) and sheet (Silk II).[95] Another study used electrospinning to produce SF/graphene oxide blended NFs with a single bioinspired nanostructure. The morphology, chemical structure, antibacterial activity, and biocompatibility of blended NFs were investigated. Based on the outcomes, the blended NFs have a lot of potential for wound dressing applications.[96]Another research used EDC/N-hydroxysuccinimide (NHS) and thiol-maleimide click chemistry to immobilize an antimicrobial peptide motif (Cys-KR12) derived from human cathelicidin peptide (LL37) onto electrospun SF nanofiber membranes to impart the various bioactivities of LL37 onto the membrane for wound treatment. Antimicrobial activity was found in this NF membrane against four pathogenic bacterial strains (*S. aureus*, *S. epidermidis*, *E. coli*, and *P. aeruginosa*).[97] One study's aim was to make cold plasma-treated thyme essential oil (TO)/SF nanofibers that can inhibit *S. Typhimurium* bacteria.[98] Another study found that SF nanofibers incorporated with SSD have cytotoxic results, which should be included in the production of silver-release dressings for wound healing because of their antibacterial activity. Wound dressings that optimize antimicrobial activity while minimizing cellular toxicity are difficult to develop.[99]

Hadisi et al.[15] synthesized an electrospun nanobiocomposite scaffold using SF, hardystonite (HT), and gentamicin (GEN), as shown in **Figure 8**. The antibacterial inhibition zone measurement findings showed that adding 3 to 6 wt% GEN might substantially enhance the scaffolds' antibacterial effect against *E. coli* and *S. aureus* bacteria.[15] The increased antibacterial effect of the

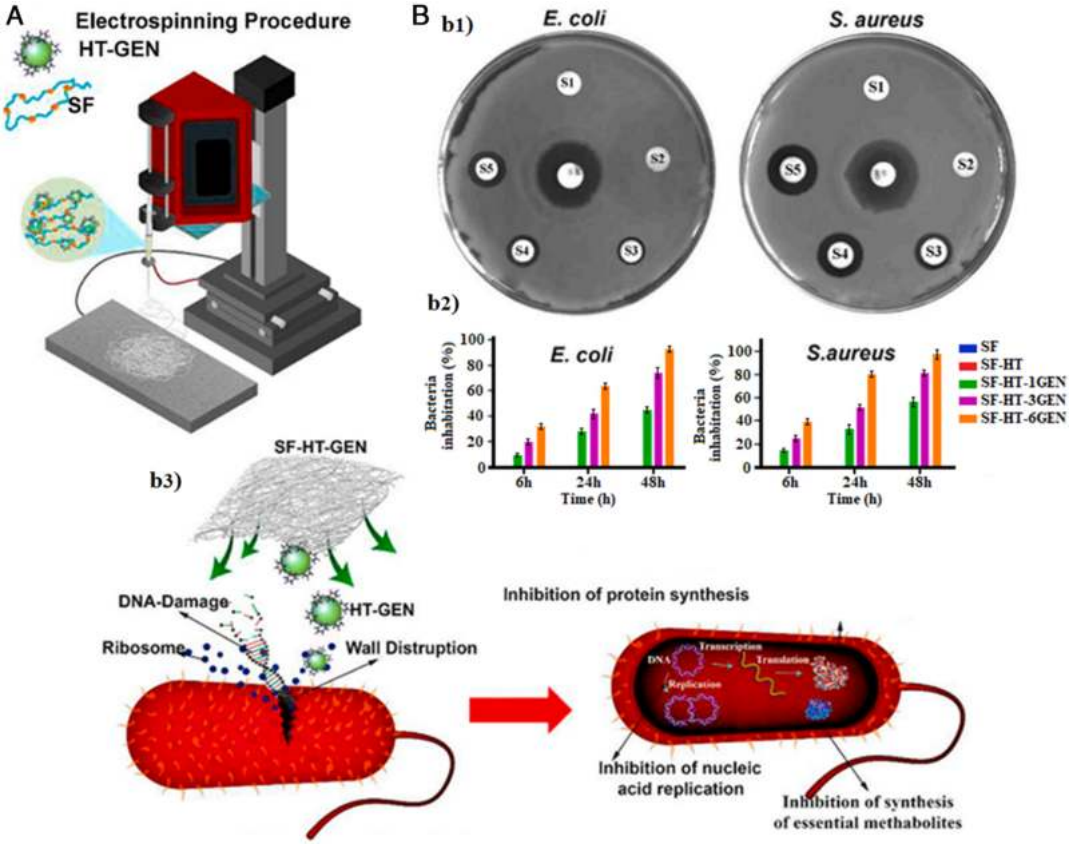

Figure 8. A) Schematic depiction of the fabrication of antimicrobial SF–HT–*x*GEN scaffolds and subcutaneous implantation in a rat model and B) antibacterial investigation. b1) The scaffolds' inhibition zone against *E. coli* and *S. aureus* after 24 h (S1 = SF, S2 = SF-HT, S3 = SF-HT-1GEN, S4 = SF-HT-3GEN, and S5 = SF-HT-6GEN). b2) Percentage of bacteria inhibited against *E. coli* and *S. aureus* after 6, 24, and 48 h and b3) representation of the SF–HT–*x*GEN scaffolds' antibacterial mechanism. Reproduced with permission.[15] Copyright 2020, Elsevier.

SF–HT–*x*GEN scaffolds was attributed to the diffusion of the gentamicin from the scaffolds into the agar plate, thus limiting the growth of bacteria. According to the researchers, GEN kills bacteria by damaging DNA and limiting protein synthesis, nucleic acid replication, and synthesis of essential metabolites.

2.10. Chitosan (CS)

CS is commonly used not only as a wound dressing material but also for its own effectiveness. Because of its beneficial features, such as biocompatibility, nontoxicity, biodegradability, hemostatic, bacteriostatic, and fungistatic properties, CS has also been used for wound healing. CS has been used in the shape of membranes, NFs, and sponges in wound dressings.[100] Due to its unique biocompatibility, strong biodegradability, and outstanding antimicrobial abilities, CS, a naturally occurring polysaccharide with plentiful supplies, has been widely used for numerous medicinal applications, most notably as wound dressings. Electrospinning was used to fabricate composite nanofiber membranes of CS and SF effectively. The antibacterial activities of composite NFs against GNB *E. coli* and GPB *S. aureus* were evaluated using the turbidity measurement process, with the findings indicating that the antimicrobial influence of composite NFs differed depending on the bacteria form.[101] Huang et al.[102] developed the biomimetic nanofibrous matrices that were coated with CS (positively charged) and type I collagen using the LBL assembly method (negatively charged). The LBL architectured nanofibrous membranes improved cell migration in vitro and facilitated skin re-epithelialization and vascularization in vivo. These findings show that LBL-structured nanofiber matrices have the ability to recover skin's structural and functional properties.[102] Two natural extracts (cleome droserifolia [CE] and allium sativum aqueous extract [AE]) were loaded onto fabricated honey, PVA, and hydroxypropyl chitosan (HPCS) to create biocompatible antimicrobial nanofiber wound dressings, according to one report. In vitro antibacterial evaluation was performed against *S. aureus, E. coli*, Methicillin-resistant *S. aureus* (MRSA), and multidrug-resistant *P. aeruginosa* in comparison with the commercial dressing Aquacel Ag and revealed that the HPCS–AE and HPCS–AE/CE NF mats enabled complete inhibition of *S. aureus,* and HPCS–AE/CE showed mild antibacterial activity.[103] Polysaccharides such as pectin, alginate, and CS are manufactured into the micrometer-scaled architecture (microfiber or particle) wound dressings that are commonly used in clinical wound care. Electrospun nanofiber dressings of these polysaccharides were described and contrasted in one study. Further tests revealed that the pectinate NF mat has superior antibacterial efficacy. As a result, it's possible that the pectinate NF mat is equivalent to the alginate and CS NF mats as a wound dressing.[104] Another research described a green method for making antibacterial NF mats encased in CS and filled with silver NPs (Ag-NPs, 25 nm diameter) after reduction with glucose.[105] In one research, a 30/70 blend of CS–ethylenediaminetetraacetic acid (CS 2 wt%–EDTA) and PVA solution (10 wt%) was electrospun to create fibrous mats with lysozyme (10, 20, and 30 wt%) utilized for wound healing.[106] Finally, this biomaterial NF has the ability to repair wounds.

2.11. Alginate (Alg)

Due to alginate's favorable properties, like biocompatibility and nontoxicity, it is a biopolymer used in a range of biomedical applications. To date, it has proven to be especially desirable in wound dressing applications. It may be applied to products that have wound healing properties. Alginate has been used to make a variety of wound dressing products, including hydrogels, films, wafers, foams, nanofibers, and topical formulations. Alginate wound dressings absorb excess wound fluid, preserve a physiologically moist atmosphere, and reduce the risk of bacterial infections at the wound location. The ratio of different polymers used in combination with alginate, the types of crosslinkers used, the time of crosslinking, the presence of excipients, the inclusion of NPs, and antibacterial agents may all affect the therapeutic efficacy of these wound dressings.[107] Electrospinning was used to construct sodium alginate (SA)/PVA fibrous mats in one research. NF was loaded with ZnO NPs with a size of 160 nm. The antimicrobial behavior of SA/PVA/ZnO mats was tested using *S. aureus* and *E. coli* bacteria, and it was revealed these mats exhibit antimicrobial effect because of the existence of ZnO in the composition.[108] In another study, honey was inserted into an alginate/PVA-based electrospun nanofiber membrane to create an effective wound dressing material. The honey-loaded NFs' antimicrobial activity against GPB *S. aureus* and GNB *E. coli* bacteria was demonstrated using a disc diffusion assay and a dynamic contact assay.[109] In another research, electrospinning was used to manufacture a nanocomposite web of calcium alginate and PVA in various proportions, and its use for wound healing was investigated.[110] The synthesis of CS–alginate (CS–Alg) NF dressings with different amounts of gentamicin (Gn; 0–10 wt%) as a drug delivery system was reported in one study. Antimicrobial tests revealed that the Gn-loaded NFs had high antimicrobial activity, as evidenced by bacterial growth inhibition. Higher Gn concentrations in CS–alginate NFs resulted in better antibacterial activity than lower Gn concentrations.[111] Antimicrobial agent-loaded alginate wound dressings are successful candidates for drug delivery systems and skin regeneration applications when used together. The antimicrobial polymeric electrospun fibers seen in Table 1 are used as wound dressings.[112–128] The physical and mechanical properties of diverse electrospun fiber are seen in **Table 2**.[129–140]

Figure 9A illustrates a depiction of a polymeric antibacterial dressing intended to serve as a physical shield of the wound from microbial invasion while promoting fibroblast migration and differentiation.[16] This image shows that an open wound is susceptible to bacterial infection, resulting in a prolonged inflammatory phase and enhanced metalloproteinase expression. These metalloproteinases participate in the breakdown of ECM components and also act as inhibitors of granulation tissue development. By covering the wound bed with the antibacterial dressing, it serves as a physical barrier, preventing infections from entering the wound, as well as a way of killing the invading microorganisms. In addition, the antimicrobial dressing stimulates the immune system and fibroblast/keratinocyte migration, which aids in the healing process.[16] Chen et al.[17] characterized and compared the dressing-related properties of pectinate, alginate, and CS electrospun NF mats. The SEM images shown in

Table 2. Physical and mechanical properties of diverse electrospun nanofibers.

Polymer	Fiber diameter	Result	Ref.
PCL/gelatin	1.13 μm	Tensile strength inner dope feed rate of 2 mL h^{-1}–1.16 MPa and inner dope feed rate of 5 mL h^{-1}–1.56 MPa	[129]
PCL	–	The tensile test shows that 15 wt% PCL (3.84 ± 0.25 MPa) has a higher modulus than 5 wt% PCL (2.46 ± 0.26 MPa). Wettability study shows that PCL has 122 ± 5°, whereas 30 days-immersed membrane in simulated body fluid has 72 ± 5° water contact angle.	[130]
PLA	<350 nm	Elastic modulus: 1.0 GPa	[131]
CS/PEO	250 nm	Porosity:84%; Tensile strength: 4.0 ± 0.3 MPa	[132]
PCL	1.35 μm	Tensile strength = 40 MPa, elastic modulus = 0.12 GPa, and elongation at break = 200%	[133]
PLA	800 nm	Tensile strength = 195 MPa, elastic modulus = 5.04 GPa	[134]
Bombyx mori SF	180–260 nm	Yield strength: 96.1 MPa. Young's modulus: 3.2 GPa	[135]
PLA	<250 nm	Elastic modulus: 0.7 GPa	[136]
PCL/Collagen	A-583.3 ± 55 nm, R- 556.3 ± 36 nm, C-573.3 ± 91 nm	Tensile strength: A) 6.8 ± 0.2 MPa, R) 14.6 ± 1.2 MPa, C) 24.0 ± 0.9 MPa	[137]
CS/SF	249.7 ± 157.1 nm	Tensile strength-4 MPa	[138]
PLA	610 nm	Tensile strength:183 MPa, elastic modulus:2.9 GPa, and elongation at break = 0.45%	[139]
PLA/CS	303 ± 165 and 396 ± 336 nm	Tensile strength of PLA NFs (3.3 MPa) was greater than CS NFs (0.5 MPa)	[70]
SF	Around 463 nm	The highest strengths were achieved at a hydroxyapatite concentration of 20 wt%. Increasing hydroxyapatite concentration up to 20 wt% improved the mechanical properties of the composite scaffolds, whereas increases beyond 20 wt% disrupted the polymer chain networks inside the SF NFs and decreased the mechanical properties.	[140]

Figure 9B demonstrate that all three types of polysaccharides could be converted into extremely porous mats comprising bead-free NFs.[17] Pectinate and alginate NFs had comparable average diameters (196.4 and 178.0 nm, respectively), while CS NFs had a lower average diameter (135.9 nm). SEM and fluorescence images revealed that *E. coli* reacted similarly with NF mats on plates as it did in solution (Figure 9C).[17] Numerous *E. coli* bacteria penetrated the pectinate NF mat's interfiber pores and attached to the NFs.[141–146] Only a few *E. coli* bacteria were trapped or adhered to the plate's alginate NF mat, while numerous *E. coli* were attached to the CS NF mat's surface. **Table 3** shows the advantages and limitations of synthesis and natural polymers, including PCL, PLGA, PGA, PVA, PLA, PLLA, CA, collagen (Col), elastin, gelatin (Gel), silk fibroin (SF), CS, alginate (Alg), and hyaluronic acid (HA).[1,147–164] Because of their inherent biocompatibility, comparable steric structure, and preceding biological simulations, including molecular signal transportation and ECM–cell interaction, natural polymers have received a lot of interest as wound dressing materials.[1,62,147–155] Furthermore, technological advancements have resulted in achieving large-scale isolation of high-purity natural compounds from plants and animal organs. The risk of immunological reactions, on the other hand, still limits their use. Furthermore, natural products frequently have low mechanical properties and an unstable structure when exposed to aqueous solutions when it comes to wound dressings. This advances the development of synthetic polymers that can be mass produced in large-scale factories with great reproducibility. Synthetic polymers are commonly used as control release carrier materials because of their mechanical characteristics such as elasticity and stiffness and their programmable degradation characteristics. However, when compared with natural products, their biocompatibility is worse, especially when residual solvents are considered. These advantages show a high ability to blend synthetic and natural polymers to prepare multifunctional antimicrobial electrospun nanofibers for wound dressing applications.[1,147–155]

3. Clinical Trials

One of the most critical therapeutic needs now is the clinical translation of NFs, particularly in tissue engineering. Tissue-engineered scaffold in vivo testing is the gold standard in preclinical studies before human clinical trials may begin. Cellular response, cellular rejection, and new tissue formation may all be evaluated in the context of in vivo conditions.[154] Finally, the matrices should be adapted to the therapeutic aims, whether they are to modulate the wound microenvironment, provide the

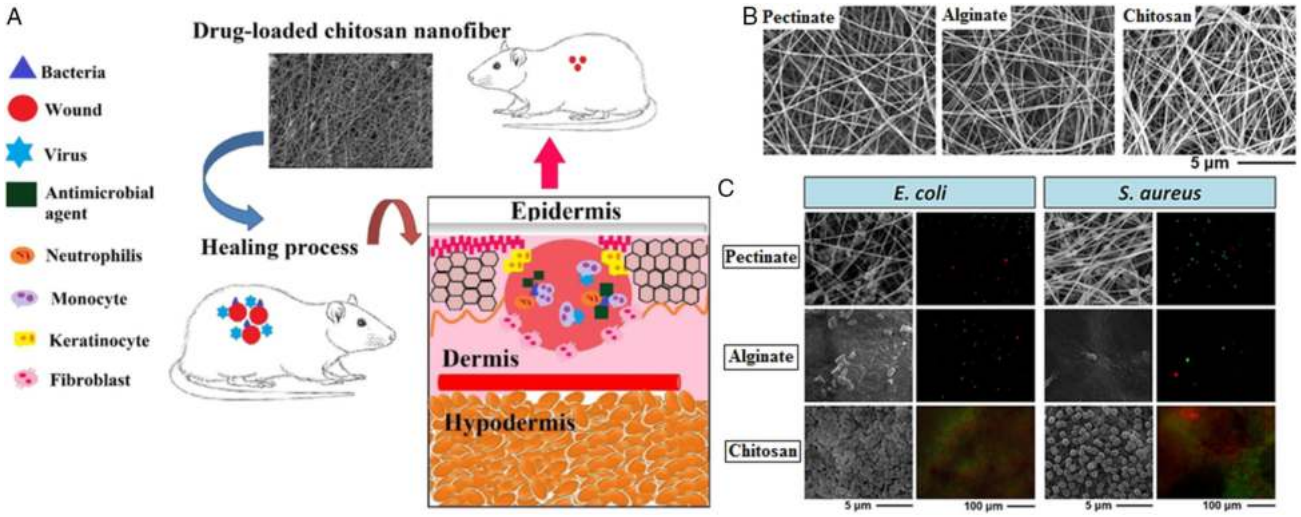

Figure 9. A) Representation of the healing process in a wound rat model. Reproduced with permission.[16] Copyright 2019, Elsevier. B) SEM images of various polysaccharide nanofiber mats and C) SEM and fluorescent images of bacteria on/in various nanofiber mats on plates. Reproduced with permission.[17] Copyright 2017, Elsevier.

best cellular scaffold, reduce scarring, or function as a delivery mechanism for cells or biologically active substances.[155] Polymer-based carbohydrate materials for wound dressing applications are now widely utilized in clinical practices, with positive results. In this context, CS, which has strong antibacterial properties, was identified as active material in a clinical trial to treat chronic periodontitis and wound healing (with or without AgNPs). An alginatecarboxymethyl cellulose–ionic silver dressing was recently clinically tested on 36 ulcer patients. The alginate–carboxymethylcellulose–Ag^+ dressing demonstrated an improved wound healing property.[156,165] Alginate-based dressings, like commercialized Askina Calgitrol Ag, is an alginate/silver wound dressing combined with the strong broad-spectrum antibacterial activity of Ag, and the improved exudate management characteristics of calcium alginate and polyurethane foam have been widely utilized in clinical studies.[156,166] Furthermore, hyaluronic acid possesses the biological characteristics described above and is commercially accessible as Hyalofill, including two products, Hyalofill-R for healing deep exuding wounds and Hyalofill-F for the healing acute and chronic exuding wounds. The addition of AgNPs to the dressing can improve antimicrobial properties in the wound bed and reduce inflammatory response.[156,167] Many kinds of polymers-based carbohydrate wound dressings incorporating AgNPs have been marketed. Aquacel Ag, a wound dressing containing carboxymethylcellulose combined with Ag^+, ALGICELL Ag, an Ag^+-incorporated alginate wound dressing, DynaGinate (consisting of calcium–alginate), Biatain Alginate Ag (consisting of alginate), ACTICOAT (containing alginate), and ALGISITE (containing calcium–alginate) are only a few of carbohydrate polymer-based marketed wound dressings.[156,167]

Alginate wound dressings have been demonstrated in clinical trials to improve wound closure and wound healing, resulting in fewer fibrotic lesions and better aesthetic appearances than traditional materials like cotton and viscose fibers.[168–173] The significant ability of alginate might be advantageous in surgical suture applications where quick wound closure, excellent wound healing, and low scar formation are desired therapeutic results.[174,175] Jäger et al.[176] used a collagen sponge scaffold for individuals with bone deficits. The patients' radiographic images revealed new bone growth in all of them. However, no bone repair was detected in two of the twelve individuals.[177] A clinical study using doxycycline-loaded PCL NFs for application in patients with chronic periodontitis was presented by Chaturvedi et al.[178]. First-order release kinetics have been shown for drug-coated NFs over a 11 day timeframe. When compared with the control group, the treatment group with SRP + doxycycline NFs showed superior improvement in probing depth, plaque index, and gingival index.[179] The same group published a clinical investigation using metronidazole-loaded PCL NFs for usage in patients with chronic periodontitis. When compared with the control group, the treatment group with SRP + metronidazole NFs showed superior enhancement in probing depth, gingival index, and plaque index.[179,180] Furthermore, a 3D electrospun NF scaffold for application in tissue restoration has been successfully patented.[181] As a result, electrospinning has much promise in biomedical applications as it is a reliable, consistent, scalable, and financially feasible process.[182]

4. Conclusions and Future Perspectives

Traumatic occurrences like thermal burns, lacerations, surgical incisions, cuts, or chronic wounds can affect skin structure and function (e.g., diabetic foot ulcers or pressure ulcers). When a considerable part of the skin is lost, early wound coverage is required to decrease water/blood loss, prevent bacterial invasion, and reduce the pain experienced by patients. In humans and animals, wound healing is a dynamic and complex process of repairing ruptured or damaged tissue, and bacterial colonization and biofilms on the wound surface can raise the risk of infection and

Table 3. Overview of synthetic and natural polymers-based electrospun membranes, with particular attention to their leading features.

Polymer	Advantages and limitations	Ref.
PCL	Cost-effectiveness, ease of the manufacturing process, biocompatibility, and great mechanical properties. Drugs have also been encapsulated in PCL beads for controlled release and targeted delivery of the drug. However, it has a slower degradation rate compared with PGA, PLA, and PLGA. Moreover, its hydrophobic nature impedes effective osteoblast cells attachment.	[1,41,147-149]
PLGA	Biodegradable, excellent biocompatibility, lower price, a well-defined structure, degradation kinetics, reliability, and good mechanical properties. PLGA can also be degraded by autocatalysis. The bulk of the polymer stays soaked in this acidic byproduct, autoaccelerating the degradation. Because they are homopolymers, PLGA degrades faster than PLA.	[49,50,150]
PGA	High mechanical properties, physiological compatibility, and nontoxicity. However, because PGA degrades quickly and is insoluble in many common solvents, PGA-based drug delivery methods have limited research applicability.	[150,151]
PVA	Biocompatible, biodegradable, water-soluble, and nontoxic; good physical and mechanical properties, noncarcinogenic, low cost, and film forming. Plasticizers such as water, glycerol, or potassium sorbate can be used to make PVA films more flexible. PVA, on the other hand, has no inherent antibacterial characteristics.	[57,148,152]
Cellulose acetate (CA)	Biocompatible polymers have the capacity to be recycled, cost-effectiveness, a simple mass production process, very soluble, biodegradable, nonirritating, nontoxic material, good mechanical properties, high chemical affinity with other chemicals, and regenerative characteristics, absorb exudates, retain moisture, and gelation. CA, on the other hand, has no antibacterial effect and hence cannot prevent wound infection.	[63,153,156]
PLA	Biocompatible polymer, biodegradability, and high bioresorbability. However, because it is not flexible, it must be combined with other polymers, like PEG as a plasticizer, to compensate for this shortcoming. Its applications are additionally limited by its strong polarity, limited thermal stability, and high density. PLA has various drawbacks, such as low cell adherence due to its hydrophobic characteristic and in vivo inflammatory reactions due to lactic acid, its degradation product. Furthermore, because of the hydrophobic methyl group in the backbone, PLA has a low degradation rate ranging from 10 months to 4 years.	[69,148,153,156]
PLLA	Glass transition temperature and degradability, as well as biodegradability, biocompatibility, and high elastic modulus. However, because of its hydrophobicity, PLLA does not create a favorable surface for cell attachment and spreading, which is required for skin cell proliferation. Furthermore, PLLA does not protect against infection because it has a limited effect against bacteria.	[78,153-157]
Collagen (Col)	Structural stability and good tensile strength. Collagen generated from animal tissues, on the other hand, has poor mechanical characteristics, a high degradation rate, and the risk of prior and viral contamination.	[6,83,149,158]
Elastin	Exceptional elasticity, biological activity, and long-term flexibility. However, elastin-based biomaterials are limited due to the protein's significant insolubility, which is caused by a high degree of covalent crosslinking.	[89,159]
Silk fibroin (SF)	Strong biocompatibility, acceptable mechanical properties, promising physiological characteristics, noninflammatory effects, and can be degraded completely by naturally occurring proteolytic enzymes. It does not, however, have antimicrobial characteristics.	[85-88,148]
Chitosan (CS)	Biocompatibility, nontoxicity, biodegradability, hemostatic, bacteriostatic, film-forming ability, low immunogenicity, and fungistatic properties. However, CS purity, origin, and molecular weight distribution are critical in terms of process characteristics and the nanofibrous mesh architecture. Antigenicity and the likelihood of disease transmission.	[6,100,149,160]
Alginate (Alg)	Biocompatibility, nontoxicity, nonimmunogenic, simply crosslinked. Alginate nanodevices have been intensely studied for controlled drug release purposes. Alginate dressings are highly absorbent, nonadherent, and generate highly hydrated gels in the presence of wound exudates. However, alginate dressings should not be used on dry wounds as their hydrophilicity can absorb wound bed fluid, causing the patient to experience a burning sensation.	[107,148,149]
Gelatin (Gel)	Biocompatible and biodegradable, low cost with low antigenicity. However, Gel has intricate processing and harvesting and it need to add a plasticizer to enhance their properties.	[6,148,160,161]
Hyaluronic acid (HA)	Antimicrobial, anti-adhesive, bioresorper, biodegradable, biocompatible, immunostimulator, lubricant, viscoelastic. HA also has hydrophilic character and good swelling properties. However, HA requires modification for stable crosslinking	[148,154,162-164]

physically hinder wound healing, leading to amputations. Smart and new dressing materials with antibacterial characteristics for speeding wound healing have received much attention in recent decades.[163,168–170] Electrospinning is now widely recognized as a simple, flexible, and cost-effective method to prepare nano- and microfibers that can be used in almost any research field, and it has emerged as one of the most promising methods for improving human quality of life through the development of tailored-made products for drug delivery systems, wound dressings, and tissue engineering in the last decade. In this regard, electrospun nanofibers are one of the most effective wound dressing products because they have morphological similarities to skin ECM, such as a large specific surface area and a porous nature that promotes homeostasis, exudate absorption, gas permeability, cell adhesion, migration, and proliferation with the goal of improving healing.[163,168–170]

In addition, considerable improvement has been made in advancing clinical treatments for wound care over the past few decades. Wound dressings made of nanofiber polymers with antibacterial effects and skin regeneration capabilities are good choices for preventing wound infection and speeding wound healing.[183–192] Antimicrobial agents have been applied to nanofibers to boost their antimicrobial activity. Antimicrobial substances, both inorganic and organic, have been used to achieve this aim. Metal, metal oxide NPs, and spatially silver NPs have recently been used to control wound infection. This article discussed recent advances in developing antimicrobial polymeric electrospun nanofiber meshes used as wound dressings. In addition, researchers have recently concentrated their efforts on creating antimicrobial nanofibers from synthesis and natural polymers, including PCL, PLA, PLLA, PLGA, PGA and CS, collagen, silk fibroin, elastin, alginate, gelatin, and hyaluronic acid. When it comes to achieving these outcomes, the integration of metallic silver, gold NPs, and metal oxides based on silver, zinc, copper, and iron is the most sophisticated way available. Because these nanometric inorganic compounds have demonstrated strong antibacterial behavior, and because they can also be modified or conferred with other relevant properties such as mechanical, magnetic, catalytic, and optical properties (among others), the possibility of developing multifunctional fibrous materials with a broader range of application areas is growing. As a result, despite the significant achievements of antimicrobial electrospun composite fibers, there is presently a need to assess their toxicity against additional microorganisms and better understand the influence of natural metabolites on the wound healing process, among other things. Finally, developing innovative electrospun nanofibers candidates from blended synthetic and natural polymers containing a combination of antibacterial agents and drugs or herbals for improving therapeutic performances and lower side effects is a mandatory prerequisite for wound dressing applications. However, it is necessary to conduct additional in vivo investigations to provide more realistic findings and medical projections in the future. In addition, enhancing the mechanical performances of antibacterial and biological properties of polymer-based nanofibers is essential, and it is another aspect of future studies. The investigations in this particular field can concentrate on the clinical potential of such dressings for developing suitable antibacterial biopolymeric nanofibers having a rapid rate of healing that helps avoid infection and unfavorable consequences in clinical applications.

Acknowledgements

The authors would like to thank the University Teknologi Malaysia (UTM), Norwegian University of Science and Technology, Islamic Azad University, Najafabad, and Isfahan University of Medical Sciences for providing this research facility.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

antimicrobial, electrospinning, nanofibers, polymers, wound dressing

Received: October 22, 2021
Revised: February 25, 2022
Published online:

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