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Antibacterial activity of chitosan-based electrospun membranes: applications, challenges, and future trends

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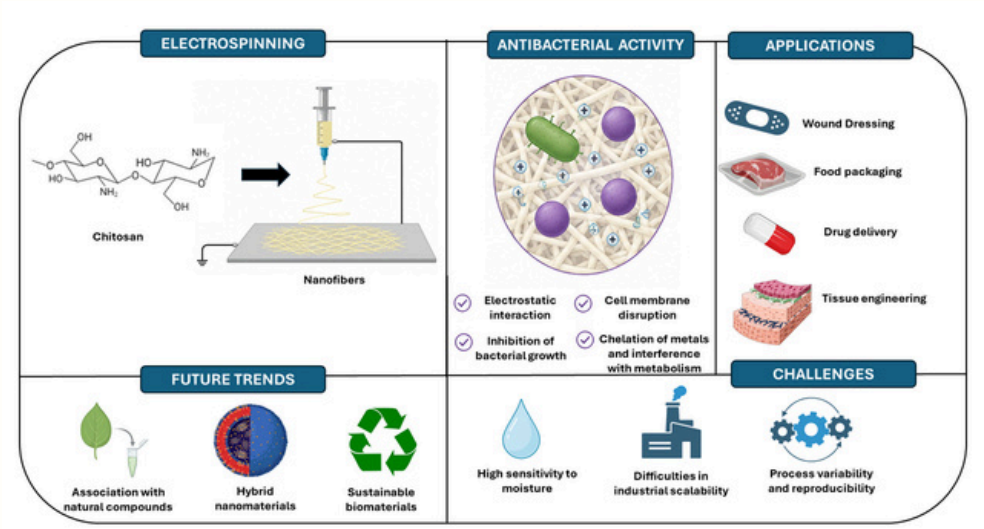

Abstract: Chitosan is a polysaccharide with promising industrial and biomedical applications, owing to its intrinsic electrostatic interactions with negatively charged cells, providing outstanding antimicrobial activity. For use in fiber structures, several parameters must be controlled by incorporating additives to achieve desirable porosity and surface area for wound-dressing applications, such as polymer templates, metal nanoparticles, and functional groups as crosslinking agents. These compounds provide adequate control over porosity and absorptivity, which can be combined to achieve desirable conditions for gas exchange and microbial capture in the resulting electrospun fibers. In this review, the potential and bottlenecks for the scalability and industrial application of chitosan-based biomedical fibrillar prototypes are discussed, underscoring the relevance of toxicological assays in elucidating their potential across several areas, including food packaging, smart dressings, controlled-release systems, and antimicrobial coatings.

Keywords: Electrospinning, wound healing, polymers, silver nanoparticles, nanofillers

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Introduction

The development of biomaterials with intrinsic cationic behavior is beneficial for several adsorptive applications, including the electrostatic removal of negatively charged structures from surfaces. Chitosan is a cationic polysaccharide obtained by deacetylation of chitin; its positive charge favors electrostatic interactions with the bacterial surfaces, increasing membrane permeability, leading to leakage of cellular contents, and inhibiting the synthesis of bacterial mRNA/proteins. In addition, as additional advantages for chitosan are the role as a metal chelator, the formation of barrier films, and the generation of oxidative stress in combination with nanoparticles or photoactive agents, which represent effective mechanisms that can reinforce the antibacterial effect [1; 2]. Strategies to broaden the spectrum and antimicrobial activity involve the controlled release of the active agent, improvement in the stability of associated chemical compounds, reduction of toxic effects, and the modulation of the physical-mechanical properties, which are based on the formulation of hydrogels, electrospun nanofibers, and composites incorporating silver nanoparticles, metal oxides, or antibiotics with the use of chitosan as a host [3 ; 4].

Despite these advantages, there are significant technical challenges for the extensive use of chitosan as a standard building block for biomaterials, such as its limited solubility at physiological pH, the variability of antimicrobial activity according to the degree of deacetylation and molecular weight, the potential cytotoxicity associated to additives (e.g., at high concentrations of metallic nanoparticles), and gaps in predictive models that correlate in vitro performance with clinical efficacy, representing barriers to standardization and regulatory approval. Furthermore, diverse protocols for determining inhibitory concentration, release tests, and biofilm activity hinder direct comparisons [5–7].

This review presents a critical evaluation of chitosan-formulated biomaterials by discussing mechanisms of action, performance against microorganisms, biofilm behavior, and structural factors that influence their antibacterial activity, and by outlining recent advances and emerging directions in the development of chitosan-based antimicrobial biomaterials to meet current and future demands.

Chitosan: structure and applications

Chitosan is a natural biopolymer obtained from the alkaline deacetylation of chitin, whose structure (see Fig. 1) is composed of D-glucosamine and N-acetyl-D-glucosamine units linked by β-(1→4) bonds. Primarily derived from the exoskeletons of crustaceans such as shrimp, crabs, and lobsters, it has been considered an abundant, low-cost, and environmentally sustainable material. The presence of free amino groups confers a cationic character on chitosan in acidic media, as well as high chemical reactivity, film-forming capacity, and biocompatibility, biodegradability, low toxicity, and broad-spectrum antimicrobial activity. These characteristics make chitosan highly versatile and promising for applications across different areas, including controlled drug release, wound dressings, food preservation, and wastewater treatment, thereby consolidating its role as a material of interest in multidisciplinary fields [8; 9].

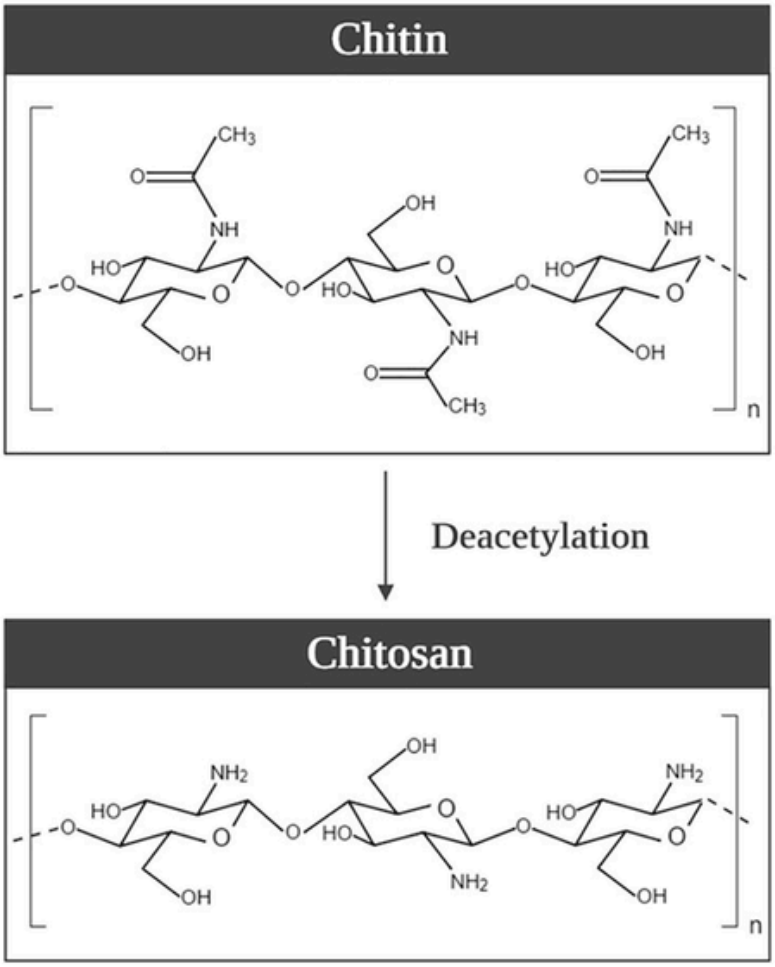

Figure 1. Scheme of the deacetylation process for converting chitin to chitosan. Reproduced from [10]. Published under a Creative Commons CC-BY license

The deacetylation of chitin preserves the original polysaccharide structure (as shown in Fig. 1) while substituting acetyl groups with amino groups. The degree of deacetylation is directly related to the proportion of glucosamine units in the polymer chain and influences parameters such as solubility, charge density, crystallinity, and molecular weight. Furthermore, the hydroxyl groups at positions C-3 and C-6 play a critical role in intermolecular interactions, thereby enhancing solubility in aqueous media and enabling chemical modifications. The combination of the degree of deacetylation and structural properties affect the physicochemical properties of chitosan and its antibacterial activity [11; 12]. All these properties must be carefully controlled to provide for the production of multifunctional biomembranes, as discussed below.

Chitosan Membranes: preparation and properties

The diversity of chitosan's physicochemical properties, such as its polyelectrolytic nature, enables electrostatic interactions with negatively charged species and facilitates the incorporation of active compounds [13; 14].

Despite having moderate mechanical strength, their stability in aqueous environments and wear resistance can be improved by chemical interactions with other compounds, such as glutaraldehyde, or by forming composites with polymers such as poly(vinyl alcohol) [15; 16;17].

When disposed as a biomembrane, the biological activity of chitosan can be enhanced by incorporating metal nanoparticles (e.g., silver nanoparticles) or natural bioactive compounds, thereby promoting additional mechanisms of mi-

crobial damage and growth inhibition. However, the magnitude of the observed antibacterial effect critically depends on the membrane processing method, the influence of incorporated additives, underscoring the importance of standardizing assay protocols [18;19].

The preparation of chitosan membranes involves a wide range of methodologies. The simplest and most effective method is solvent evaporation, commonly performed by dispersing chitosan in acetic acid, homogenizing it, and controlling the drying rate to form a film. This method facilitates the incorporation of plasticizing agents (such as glycerol), nanofillers, and drugs being widely used for the development of packaging and dressings, despite intrinsic limitations in controlling porosity and mechanical resistance [20].

One of the most critical parameters in this process is the molecular weight of the chitosan. As reported in Ref. [14] chitosan with low, medium, and high molecular weights, in native and glycerol-plasticized forms, was evaluated for its potential to modulate properties such as water sorption, degree of swelling, mechanical strength, and ion exchange capacity.

To optimize the mechanical and chemical properties of the resulting membranes, several studies evaluate the influence of the chemical associations of chitosan with polymers, enabling the optimization of mechanical resistance and the reduction of solubility. Due to their good biocompatibility, associations with cellulose or glass fibers are favored, thereby adjusting permeability and mechanical stability, properties frequently required for applications in filtering membranes [15,21,22]. However, control over the degree of porosity and swelling of the structure has been favored in fibrillar structures. Alternatively, the production of highly porous membranes by electrospinning has attracted attention in the literature due to the advantages of fibrillar structures, as follows.

Electrospinning of chitosan: Properties and Preparation Approaches

The electrospinning technique has been widely used due to its various functional and structural advantages, including a high surface area-to-weight ratio, high porosity, low density, and tensile strength of the modified membranes [23].

The solution flow rate, field intensity, and the distance between the spinneret tip and the collector are among the factors that affect the fiber morphology. A higher intensity electric field increases the electrostatic forces acting on the jet, promoting the formation of finer fibers. However, low field intensity results in crimped or thicker fibers due to incomplete elongation [24,25]. The flow rate of the polymer solution can affect fiber size and shape; higher flow rates increase pore size and fiber diameter, leading to ribbon-like fibers. Furthermore, fiber diameter varies with polymer concentration and higher-molecular-weight polymers [26].

In addition, the fiber and network structures are mutually dependent on the polymer solution's conductivity and viscosity (as shown in Figs. 2a-2c for SEM images of samples prepared at increasing conductivity and in Figs. 2d-2f for samples prepared at increasing viscosity). The mixture of polymers with reduced conductivity allows the formation of more homogeneous fibers without thickening or spheres (Fig. 2c). However, the low viscosity of the polymer mixture results in spindle-shaped spheres rather than fibers (Fig. 2d). In contrast, high viscosity produces larger fibers due to polymer chain entanglement (Fig. 2f) [27]. The application of an electric field also affects fiber morphology: higher fields produce cylindrical fibers, while lower fields form flat, ribbon-like structures [28].

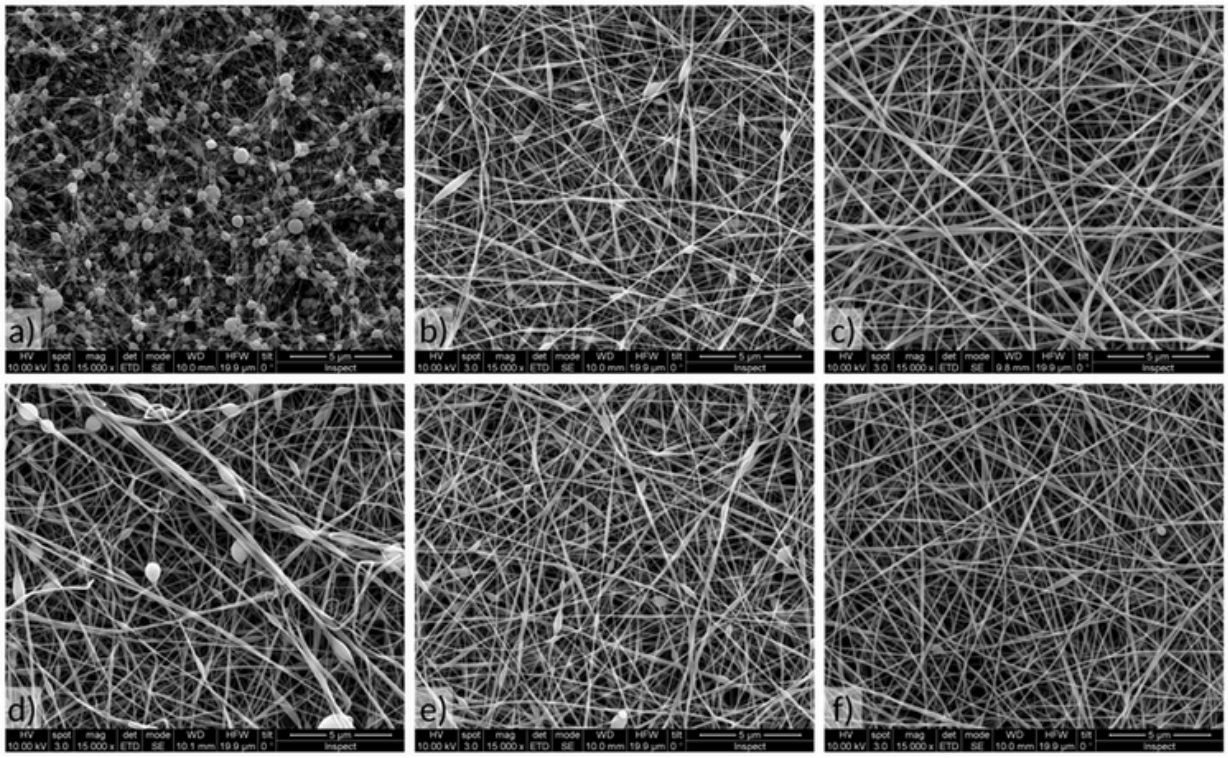

Figure 2. Evaluation of the effects of increasing conductivity (from a to c) and increasing viscosity (from d to f) on the morphology of PVA/CSM fibers from SEM images. Reproduced from Ref. [27]. Published under a Creative Commons CC-BY license.

Also, the use of additives (polymers, crosslinking agents, and metal nanoparticles) represents a central strategy for achieving desirable properties in chitosan-based electrospun fibers.

Polymer Additives

The cationic nature of chitosan represents a critical issue for the production of electrospun fibers due to a delicate balance among several factors, including strong electrostatic interactions between polymer chains at very high or very low viscosity, the polymer's molecular weight, and the acidic media. Therefore, different polymers have been considered as co-spinning agents [29,30]. Poly (vinyl alcohol) (PVA), for example, has been considered an important component in chitosan fiber production, since its interaction with chitosan reduces repulsive interactions between polycations, thereby decreasing polymer entanglement and favoring fiber production [31]. It is worth noting that PVA is a standard biocompatible polymer [32] with numerous applications in bio-based products such as implants, fibers, pharmaceuticals, cosmetics, and films, with negligible influence on bioactive fillers.

In addition, the formation of PVA-chitosan composite films improves mechanical properties compared with pure chitosan films, with increased elongation and tensile strength [33]. The PVA/CS ratio affects the resulting fiber diameter: a reduction in chitosan content reduces the solution's viscosity and, consequently, the surface charge, thereby decreasing the number of ejected fillers and surface repulsion and increasing fiber diameter. Furthermore, a higher PVA-to-chitosan ratio produces uniform fibers with a smooth surface and a low concentration of beads or imperfections [34].

Also, the inherent antioxidant properties of CS, derived from its reactive functional groups, were enhanced by the inclusion of PVA. Electrospun nanofibers (NF) showed superior antioxidant activity compared to cast films (CF). This increase may be related to the high surface area/volume of NF, which provides more active sites available to neutralize free radicals [35].

Polycaprolactone (PCL) has also been used in the production of food packaging under combination with CS via electrospinning [36,37], ena-

bling the production of a biodegradable and antimicrobial material incorporating curcumin nanoparticles with a 94.69% encapsulation efficiency. The effect of concentration on the overall response was evaluated, with optimal performance at 15% PCL and 1.0% CS, which exhibited good tensile strength. Furthermore, the inclusion of 1.0% NPs improved thermal stability and water-vapor barrier properties, and provided antioxidant and antibacterial activities [38].

Also, the combination of gelatin/chitosan polymer solution yields fibers with a smooth surface, whereas at a low solution viscosity, it produces defects (beads) [39]. Similarly, the use of poly (ethylene oxide) (PEO) in electrospinning chitosan yields dense nanofiber networks with uniform diameters, free of spindles, beads, or other imperfections, making this method a standard for fiber formation [40].

Totito et al. [41] reported the production of composites of chitosan with polyethylene terephthalate (PET) polymer and PET-based plastic waste. The composite fibers showed greater water solubility than unmodified PET fibers and better durability than pure CS fibers. Furthermore, it was reported that the best solvent for electrospinning chitosan was a 7:3 mixture of trifluoroacetic acid (TFA) and dichloromethane (DCM), containing 7% by weight of CS-TFA/DCM [41].

Metallic nanoparticles as additives for electrospun fibers

Silver nanoparticles (AgNPs) have been widely explored due to their intrinsic properties favoring their encapsulation in chitosan fibers [42]. In this context, mesoporous silica decorated with AgNPs with a smooth, spherical surface has been incorporated into chitosan polymer solution [43]. Morphological and structural analyses indicated that the fibers produced retained silver within their structure and increased the mechanical properties of the fibers, also favoring their biocompatibility and regenerative efficacy when applied in wounds [43].

Several methodologies for doping nanofibers with AgNPs have been reported [44] including a method that gradually coats PEO/CS fibers with AgNPs via in situ synthesis (ISS) through chemical reduction. Following the ISS of AgNPs, the fibers exhibited a significant change in their intrinsic hydrophobicity, thereby altering the material's wettability by increasing the contact angle [44]. Furthermore, the wet-chemical process can be used to enable layer-by-layer electrospinning of chitosan/polycaprolactone (CS/PCL) and AgNPs. The synthesized fibers retained a porous structure, exhibited high biocompatibility, balanced hydrophilicity, and antibacterial activity against multiple bacterial strains, a characteristic achieved through the release of silver ions under incubation [42].

In addition, experimental design software has been used to optimize parameters that affect fiber formation. After determining the ideal conditions for feed rate, PVA/CS mixing ratio, and applied electric field, ZnO with star and pyramidal rod morphologies were added to the electrospinning solution. Also, the effects of NPs with different morphologies in biomedical applications are reported, with pyramidal rod-shaped NPs conferring improved mechanical strength on the fibers than star-shaped NPs. Furthermore, incorporating ZnO into PVA/CS nanofibers significantly increases their thermal stability and confers antibacterial and wound-healing activities, particularly for pyramidal rod-shaped NPs[45]. Fig. 3a shows that the incorporation of ZnO-NPs into CS/PVA fibers was able to reduce the average diameter from 200 nm to less than 150 nm, in comparison to pure CS/PVA fibers (Fig. 3b). The ZnO-NPs were homogeneously distributed along the nanofibers, that exhibited good cell viability, efficient antibacterial activity, and low toxicity [46].

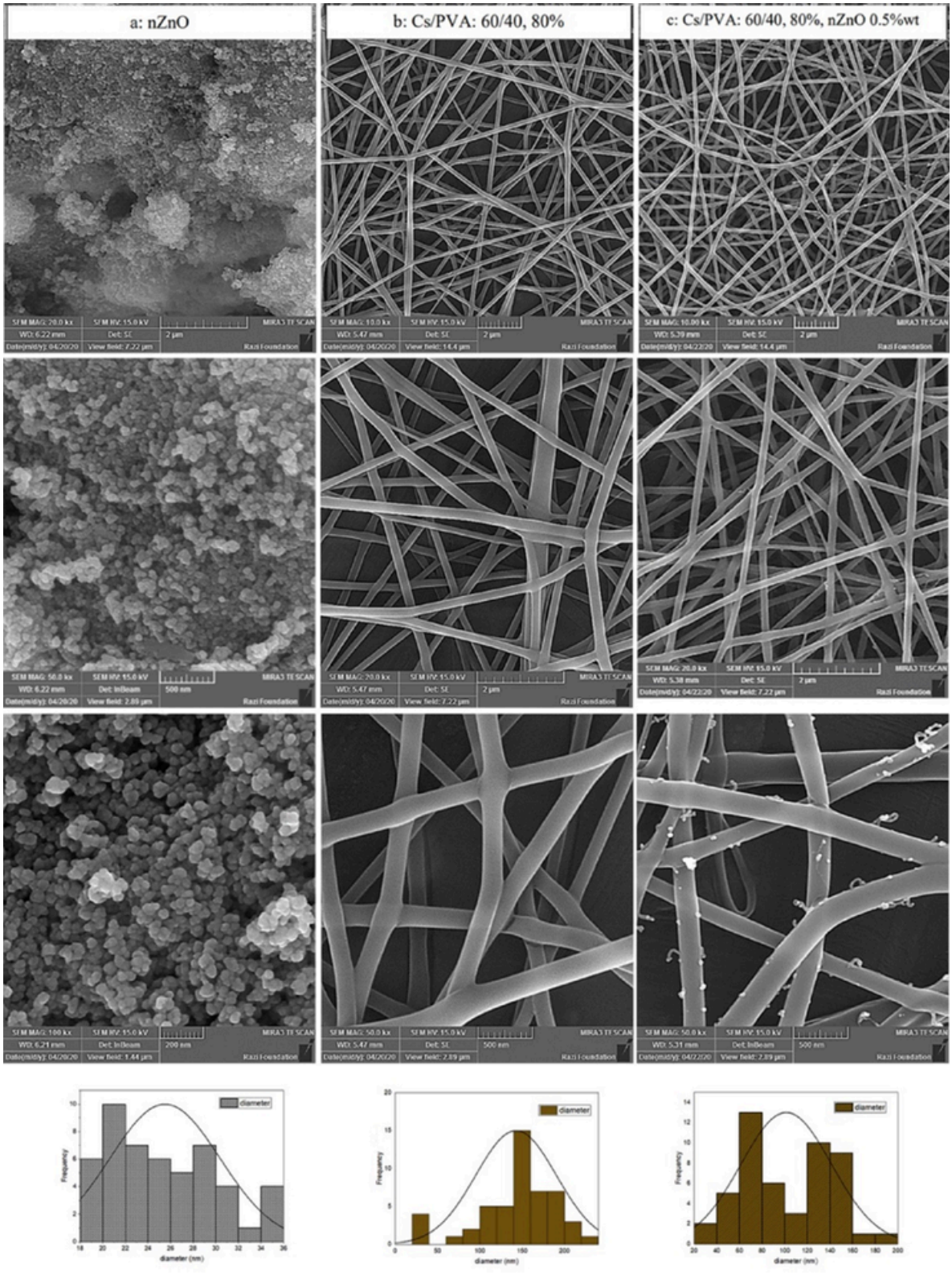

Figure 3 - FE-SEM images of ZnO nanoparticles (column a), Cs/PVA fibers (column b), and Cs/PVA/ZnO nanoparticle composite (column c) at different magnification levels with the corresponding diameter distribution of components. Reproduced from Ref. [46] Published under a Creative Commons CC-BY license.

Crosslinking agents

An important strategy to improve several properties of electrospun nanofibers is the addition of crosslinking agents [47]. Modifications to chitosan fibers by incorporating crosslinking agents enhance stability and mechanical properties, thereby improving functionality for biomedical applications [48]. Higher water contact angles were reported to electrospun CS/PVA membranes encapsulating sodium Y (NaY) zeolites, by the use of 1,1' -carbonyldiimidazole (CDI) as a green crosslinker, resulting in membranes of CDI-CS/PVA/NaY. CDI-crosslinked results in the reduction in amine and hydroxyl groups, properties that make them suitable for water filtration applications (Figure 4A). As shown by the authors, the CDI-CS/PVA/NaY membrane exhibits the lowest swelling rate due to the crosslinking, which reduces water absorption and increases stability, optimizing the membrane's performance (Fig. 4B). The crosslinking process of the CDI-CS/PVA/NaY membranes conferred structural stability and high permeability, making them ideal for use in applications that require durability and high-water vapor transmission (WVTR) (Fig. 4C), as well as minimal degradation/mechanical deformation (Fig. 4D)[49].

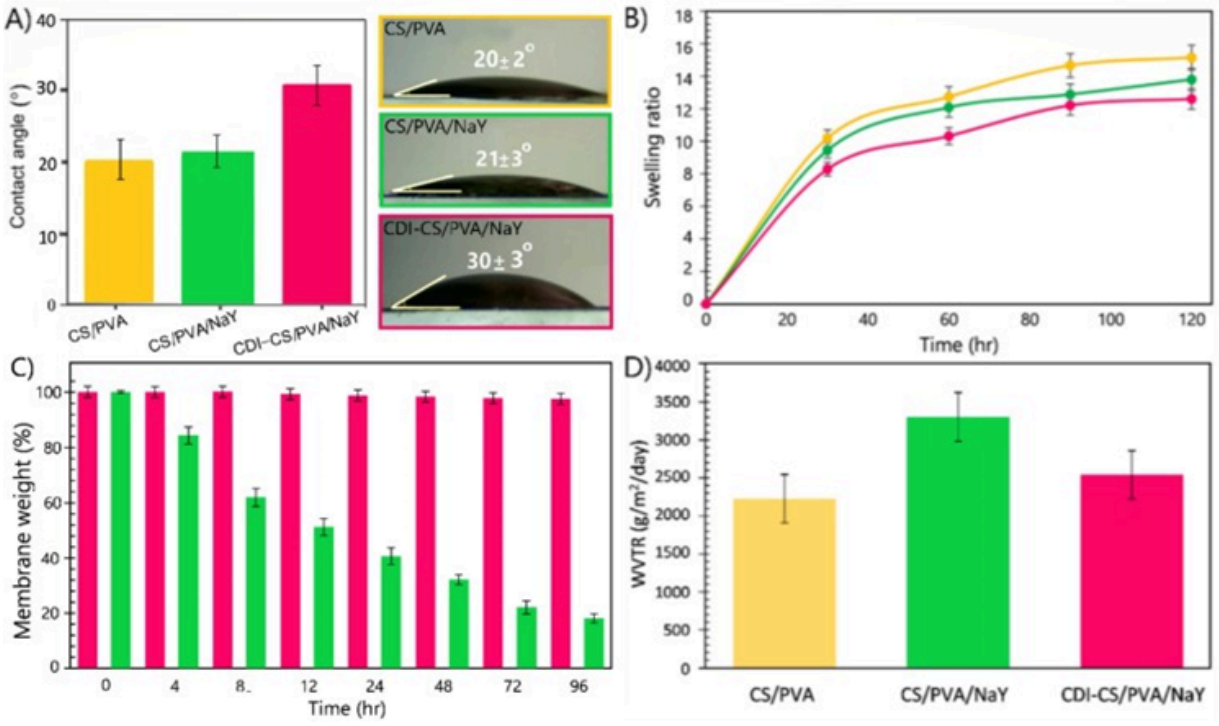

Figure 4 - Evaluation of properties of chitosan-based membranes: A) Water contact angle, B) Swelling ratio, C) Water vapor transition rate, and D) Membrane stability with CS/PVA shown in yellow, CS/PVA/NaY in green, and CDI-CS/PVA/NaY in pink. Reproduced from Ref. [49] Published under a Creative Commons CC-BY license.

Regarding biomedical applications, the wettability of electrospun fibers is an issue to be critically considered. Studies show that cross-linking with 1,4-butanediol diglycidyl ether (BDDE) in a solution of chitosan, polycaprolactone, and kappa-carrageenan polymers reduced the water contact angle, thereby improving wettability. This capacity may be associated with several factors, including changes in chain interactions, the ring-opening reaction of epoxides, and the formation of new hydroxyl groups that generate new covalent bonds as well as for polysaccharides [50]. On the other hand, other crosslinking agents, such as genipin, prevent the rapid degradation of CS+PCL fibers in aqueous environments, making crosslinking essential to maintain the integrity of the nanofibers [48].

In tissue-engineering assays, biomimetic nanofibrous scaffolds were produced using polyelectrolyte mixtures of chitosan (CS), alginate (AL), and PVA as a viscosity-modulating agent. The crosslinking the scaffolds by freeze-thaw processes with ethyl-dimethyl-aminopropyl carbodiimide (EDC) and N-hydroxy-succinimide (NHS) improved the structural stability of the materials and provided high thermal stability [51]. Carboxymethylcellulose has a negative electrical charge, acting as ionic crosslinking agent. Studies with carboxymethylcellulose and carboxymethyl chitosan nanofibers have demonstrated the formation of narrow-diameter nanofibers. Furthermore, recent studies indicate that the materials produced enhanced antibiofilm activity and osteoblastic cell survival [52].

In addition, the amino group of chitosan can be used for crosslinking with various agents, including glutaraldehyde (GA) [53]. Ejegu et al. proposed incorporating discopodium penninervium (DP) leaf extract into chitosan-polyvinyl alcohol (CS-PVA) structures. Prolonged crosslinking with GA provides fiber reinforcement, enhances biodegradability, and maintains a hydrophilic surface, which promotes cell adhesion and wound exudate absorption [54].

Antibacterial activity of chitosan-based structures: mechanisms

The prevailing antibacterial mechanisms of chitosan are reinforced by a wide range of interactions with microorganisms that can occur extracellularly, intracellularly, or both [55]. These polycationic interactions arise from the presence of amino acid groups, such as lipopolysaccharides (Gram-negative bacteria) and teichoic acids (Gram-positive bacteria) [56 ; 57].

In general, the antibacterial activity has been attributed to three distinct processes, with electrostatic interactions being the most evident: positively charged NH_3 groups are favored at pH < 6.3, thereby enabling glucosamine to interact with bacterial cell membranes [58,59]. Through electrostatic and hydrophobic interactions, chitosan derivatives adsorb negatively charged bacteria, promoting accumulation in the cell wall and leading to membrane degradation, cytoplasmic material leakage, and bacterial death [60].

The second mechanism is affected by the molecular weight of the chitosan: it has been reported that low- and high-molecular-weight chitosan differ in their mechanisms of action. Low-molecular-weight chitosan easily penetrates the bacterial cell wall, binds to bacterial DNA, inhibits mRNA synthesis, and blocks DNA transcription [61].

The hypothesis is based on the possibility of penetration of low-molecular-weight chitosan through the bacterial cell wall, being, however, considered as a secondary process, since it has been discussed in the literature the prevailing role of chitosan as a membrane disruptor in comparison with a penetrating material. Regarding the discussion of the influence of chitosan MW on antibacterial performance, Másson[62] evaluated data reported in the literature for MIC, reaching a desirable fitting for a bilinear relationship, providing the critical molecular weight to reach maximum antibacterial performance. As a result, the author hypothesized that the central mechanism was cell membrane disruption. Regarding dependence on MW, it is considered that the polymer chain must reach a critical length to interact effectively with the cell membrane.

The third mechanism is based on the activity of chitosan as a metal chelator involved in vital bacterial processes, inhibiting nutrient absorption and modifying bacterial cell permeability [63], being this process favored by the ability of unprotonated amine groups to donate electrons to metal ions.

Figure 5 illustrates the mechanisms underlying chitosan's antibacterial activity, highlighting electrostatic interactions, DNA binding, metal chelation, and transcriptional and translational inhibition.

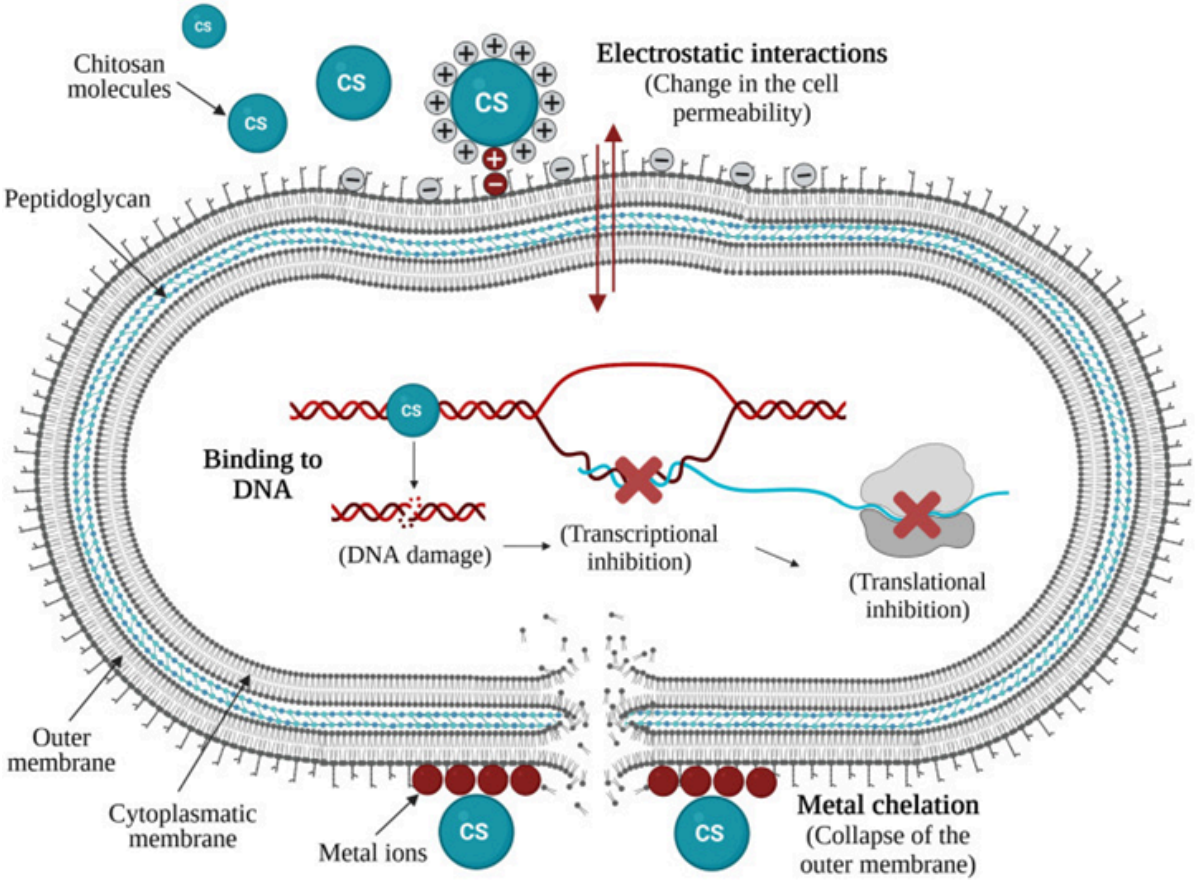

Figure 5 - Schematic representation of antibacterial mechanisms of action of chitosan based on electrostatic interactions between its cationic groups and anionic components of the bacterial membrane; chelation of essential metal ions; direct binding to DNA; and inhibition of protein synthesis processes. Reproduced from [10]. Published under a Creative Commons CC-BY license

Given the dynamic profile of the mechanisms underlying the antibacterial activity of chitosan, several factors can influence its activity, which may be related including the biological or physicochemical conditions inherent to microorganisms (species and cell viability), and the reaction medium (pH, temperature, presence of cations)[60].

The pH of the medium is a primary requisite of chitosan's inhibitory activity against microorganisms. The acidic/basic environment controls chitosan's solubility and modulates the polymer's surface charge. This charge modulation affects the electrostatic interactions, enabling or avoiding chitosan molecules from binding and exerting their antimicrobial effects [64; 65].

Pristine chitosan is soluble in acidic solutions with a pH below 6, but insoluble in aqueous or alkaline media or in organic solvents, and its anti-microbial activity is more effective at ambient pH below its pKa [; 66,67]. Regarding the influence of molecular weight, although some papers indicate that low-molecular-weight structures or their oligomers exhibit more potent activity against bacteria than high-molecular-weight polymers. Másson suggests that optimal performance is achieved at specific molecular weights, such as 50-90 kDa [62].

The bacterial species also directly influence the optimal chitosan molecular weight, with distinct behaviors observed in Gram-negative and Gram-positive bacteria. Some studies report that the polymer's low molecular weight is more effective at inhibiting Gram-negative bacteria, whereas high molecular weight is associated with better activity against Gram-positive species [68; 69].

One hypothesis is that low-molecular-weight chitosan molecules can more easily penetrate the

cell walls of Gram-negative bacteria. On the other hand, high-molecular-weight chitosan could primarily act as an external barrier, impairing nutrient uptake by microbial cells. However, reduced-molecular-weight chitosan has also been reported to exhibit superior antimicrobial efficacy against Gram-positive microorganisms, characterizing distinct processes and an explanation for the optimal performance at intermediate values of chitosan MW [68,70].

Regarding the Degree of Deacetylation (DD) [71], Yu et al. [72] observed an increase in the overall activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli* and *Salmonella typhimurium*, with pronounced activity at a DD of 90%. This hypothesis was also reinforced by Amor et al. [73], who reported that chitosan with a higher degree of deacetylation exhibited strong antibacterial activity against *Listeria innocua*, *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhimurium*, and *Pseudomonas aeruginosa*.

Wound dressing applications

CS fibers have several characteristics that make them suitable alternatives for wound healing. Ahmadabad et al. [74] demonstrated that CS and gelatin fibers balance evaporation and moisture retention, thereby keeping the wound site moist and allowing healing and cellular activity to occur without causing fluid accumulation or excessive dehydration [74]. Another functionality is the ability of CS and PLGA fibers to release Zn ions, which can increase the biological activity of Zn^{2+}, suggesting their therapeutic potential [75].

Associations with extracts and green materials have been considered to prevent toxicity issues and improve the biocompatibility of CS fibers. Fibers produced from PVA/CS with extracts of ginger (*Zingiber officinale*) and thyme (*Thymus vulgaris*) accelerated the healing of infected skin wounds and prevented bacterial growth. In addition, epithelial structures were reconstituted mainly with the development of collagen fibers 76. PCL/PVA-CS fibers were synthesized incorporating ethanolic extract of *Tridax procumbens L.* leaves (PCL/PVA-CS/Tp) and returned anti-inflammatory activity and regenerative activity in both laser radiation wounds and punch wounds [77].

Curcumin has been incorporated into the materials to enhance wound-healing activity in a bilayer dressing, with chitosan-polyacrylic acid (QCs-PAA) fibers forming the top layer and curcumin in the bottom layer. This material exhibited antibacterial activity against Gram-positive and Gram-negative bacteria, leading to a significant increase in blood vessel thickness and number, thereby contributing to angiogenesis [78]. Abaza et al. [79] produced zein-methylcellulose fibers loaded with curcumin (ZeinMCNPs), in which an increase in activity is observed in comparison with pure CS fibers. The composites contributed to collagen deposition, increased neovascularization, and re-epithelialization [79].

Several other formulations were produced, including CS fibers coated with 2-formylphenylboronic acid and containing a high concentration of norfloxacin. The nanofibers promoted granulation tissue formation and epithelialization, reduced inflammation and leukocyte count, and lowered levels of inflammatory cytokines 80. A fibrous membrane of PCL-CS-CI was developed through an inclusion complex by altering β-cyclodextrin as an oryzanol carrier, in which the CIs enhanced drug delivery, exhibited antibacterial activity, high air permeability, and wettability. PCL-CS-CI promoted reductions in inflammatory factors and enhanced re-epithelialization capacity [81].

Chitosan (CS) has also been explored as an alternative for healing chronic diabetic wounds, as these wounds are difficult to treat and often resistant to conventional therapies. Fan et al. [82] developed hydroxybutyl chitosan sponges grafted with thioctic acid that significantly accelerated healing in diabetic wounds, promo-

ting angiogenesis and neurogenesis at the lesion sites through symbiosis between blood vessels and nerves [82]. Given the complexity of diabetic wounds and their high incidence of bacterial infections, levofloxacin was encapsulated in CS and PCL fibers. The adhesive behavior promoted controlled drug release, with an initial peak, considered essential for antibacterial efficacy, followed by a slower release phase [83]. A detailed description of chitosan-based experimental systems, along with their corresponding activities, advantages, and limitations, is summarized in Table 1.

Table 1. Chitosan-based bioactive nanofibers: analysis of system types, biological functionalities, and technological constraints.

Reference	System	Activity	Advantages/limitations
84	Silk Fibroin (SF)/Chitosan (CS)	Skin tissue regeneration and repair	Hydrogen bonds between SF and CS promoted the formation of β-sheets, increasing crystallinity, decreasing the mass loss rate/larger fiber diameter of SF/CS scaffolds, and reducing the typical high specific surface area and solubility.
85	Acetoacetylated polyvinyl alcohol (AAPVA), chitosan (CS), and carbon quantum dots.	Wound dressings	Maximum tensile strength of approximately 10 MPa and excellent structural integrity / Features include limited thermal reinforcement.
86	Oryzanol/β-cyclodextrin (IC) inclusion complexes in polycaprolactone-chitosan (PCL-CS) fibers	Grape preservation.	The addition of CS and IC increased conductivity and decreased fiber diameter. The PCL-CS-IC fiber membrane exhibited the greatest thickness and the worst air permeability of the membranes.
87	Poly(ε-caprolactone) (PCL), chitosan (CS) and tigecycline (Tig)	Drug release and antibacterial wound healing	Chitosan and tigecycline effectively improve wettability/ PCL layers reintroduce hydrophobicity.
54	*Extract of Discopodium penninervium (DP) leaf in chitosan-polyvinyl alcohol (CH-PVA) structures*	Wound dressings	Lower DP concentrations and shorter crosslinking times resulted in smaller water contact angles (WCA), indicating greater wettability and lower hydrophobicity. Increasing DP concentration and crosslinking time led to a progressive increase in WCA, reflecting lower moisture retention and potentially altered cellular interactions.
88	CS/PEO nanofibers (solution blow spinning)	Antibacterial, antioxidant, wound healing.	High breathability, high antibacterial activity (>99.99%), good water stability, promotes cell proliferation, and accelerates healing / Low processability of pure chitosan; requires combination with PEO.
89	PCL/CS nanofibers with curcumin (electrospinning + electrospray)	Antibacterial, antioxidant, controlled drug release, wound healing.	High porosity, controlled release, improved cell proliferation and healing (including in infected wounds) / Low solubility of curcumin; nanoencapsulation is necessary for better bioavailability.
90	CS/PEO/CNC nanofibers with acacia extract (electrospinning)	Antibacterial, antifungal, sustained release, tissue regeneration.	Biocompatibility, low cytotoxicity, continuous release of the active ingredient, and improved mechanical and thermal properties / Optimization of formulation and electrospinning parameters is necessary.
91	CS/PEO nanofibers with propolis (electrospinning)	Antibacterial and antibiofilm	Effective against Gram-positive and Gram-negative bacteria, antibiofilm activity, and biocompatible / Lower efficacy against some bacteria (e.g., P. aeruginosa); dependent on propolis concentration.
92	CS/PEO nanofibers with rosmarinic acid (electrospinning)	Antibacterial, antioxidant, wound healing (especially in diabetes)	Sustained release, improved tissue regeneration, increased collagen production, and wound contraction. / Low bioavailability of isolated rosmarinic acid; requires incorporation into a carrier system.

Challenges in Scalability, Industrial Production, and Future Prospects

The development of electrospun chitosan-based fibers incorporating bioactive compounds has advanced significantly in recent decades; however, the industrial-scale adoption of this technology and its use in pharmaceutical, biomedical, and food applications still depend on addressing technical, regulatory, and economic challenges. Understanding these limitations and identifying strategic paths for innovation are fundamental to guiding future research and shaping the next steps.

One of the main challenges is the difficulty of electrospinning pure chitosan, owing to its polycationic nature, low solubility in volatile solvents, and inadequate rheological behavior. Studies show that chitosan often requires the presence of auxiliary polymers, such as PEO or PVA, to form continuous and stable fibers [93,94].

However, the use of these secondary polymers can compromise chitosan's biodegradability or alter its expected bioactive properties, requiring the development of more sustainable hybrid systems or green solvents that enable the electrospinning of chitosan in its purest form [95]. Thus, the standardization of electrospinning conditions remains a significant issue.

Regarding production strategies, the low efficiency of traditional single-needle electrospinning systems constitutes a central bottleneck. Scaling strategies, such as multi-needle configurations, needleless electrospinning, and Nanospider™-type technologies, have demonstrated promising advances. Needle-less electrospinning offers higher production rates and overcomes problems such as needle clogging and the low scalability of traditional methods. By eliminating needles, nanofiber uniformity is improved. Liquid-free, high-voltage surface technologies, such as Nanospider™, are ideal for industrial use due to their minimal solvent use, which enables continuous production, compatibility with various polymers, and optimization of external parameters [1,96,97].

Despite the favorable biocompatibility of electrospun chitosan fibers, incorporating additional fillers, such as metallic nanoparticles or residual solvents, requires in-depth toxicological studies to assess safety and regulatory compliance. Gholizadeh et al. evaluated the production of electrospun chitosan fibers loaded with mesoporous silicon nd decorated with AgNPs for diabetic wound treatment. MTT tests demonstrated that relative concentration of AgNPs above 7% results in a burnt release of Ag^+ ions, causing mitochondrial dysfunction and a decrease in cell viability to 58%[98].

In addition to the tests on the release and migration of these components into food, their potential for bioaccumulation and degradation behavior in the environment also need to be considered. The absence of standardized risk assessment protocols and specific guidelines for nanomaterials is the main factor hindering regulatory approval and large-scale commercial adoption of these new materials [99,100]. The prospects indicate that progress in the field will depend on integrating materials science, microbiology, process engineering, and sanitary regulations to develop safe, efficient, and scalable products.

Conclusion

Chitosan fibers obtained by electrospinning, pure or combined with other natural or synthetic polymers and functionalized with bioactive compounds, represent a highly promising strategy for developing advanced materials with antimicrobial properties. The nanofibrous architecture resulting from the electrospinning process confers a high surface area, controlled porosity, and a morphology favorable for interactions with microorganisms and reactive species, thereby enhancing the efficacy of chitosan and the incorporated bioactive agents.

Furthermore, the cationic nature of chitosan facilitates electrostatic interactions with microbial membranes, whereas antioxidant compounds can complementarily neutralize free radicals and protect the material and the surrounding environment. The tunable parameters, such as polymer composition, degree of deacetylation, molecular weight, and electrospinning conditions, enable modulation in the physicochemical, mechanical, and functional properties of fibers, thereby expanding their application spectrum. In this context, studies that contribute to advances in formulation techniques, structural characterization methods, and biological and functional evaluation are increasingly necessary to improve the performance of these systems and enable their application in areas such as active food packaging, smart dressings, controlled-release systems, and antimicrobial coatings, consolidating these technologies as innovative, sustainable, and high-value-added solutions.

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