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Original Article

Chitosan-Based Electrospun Nanofibers for Wound Healing: A Systematic and Bibliometric Synthesis of Material Design and Biological Performance

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Abstract

Background: Chronic wound pathogenesis is associated with infection, inflammation, oxidative stress, and poor tissue regeneration, creating a major clinical challenge. Electrospun nanofibers, especially using chitosan, may be promising therapy with various advantages.
Objective: This research investigated design strategies and methodological factors affecting the therapeutic efficacy and translational potential of chitosan-based electrospun nanofibers for wound healing.
Methods: Advances in the research field, formulation characteristics, production specifications, biological efficacy, and comparability between studies were evaluated through a systematic analysis of 23 studies and a bibliometric analysis of 186 articles published between 2015 and 2025.
Results: The annual growth rate of publications is 29.24%, indicating growing interest in the methods of multifunctional wound-dressing methods. This allows evaluation of different studies to understand the characteristics of chitosan for electrospinning. Most studies employed single-layer nanofiber scaffolds incorporating medium- to high- molecular weight chitosan, with varying copolymer, bioactive, and crosslinker compositions, as well as electrospinning parameters, particularly applied voltage and flow rate. However, differences in production processes, biological assessment methods, and wound models limited the comparability of the studies. Healing outcomes were more dependent on mechanism-based approaches that addressed the underlying causes of injuries.
Conclusion: The results demonstrate that differences in manufacturing conditions, material composition, and biological assessment can strongly affect the interpretation across studies.

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INTRODUCTION

Chronic wounds are wounds that fail to heal through the systematic stages of healing within a three-month period. The increasing burden of chronic wounds is a global public health problem with huge clinical, economic, and societal implications. These injuries affect nearly 10.5 million Medicare beneficiaries in the United States, or almost 2.5% of the population, with an estimated annual cost of $22.5 billion.[1] Significantly, this burden is growing: epidemiological data demonstrate a significant rise in prevalence in the last decade in Western countries; for example, venous ulcers and diabetic foot ulcers increased by 101% and 93%, respectively, in the United Kingdom between 2012-2013 and 2017-2018.[2] With an aging population, the increasing prevalence of diabetes worldwide, and the ongoing evolution of antibiotic-resistant bacteria, sophisticated wound care systems are not just good; they are a health essential.

The pathophysiology of impaired chronic wounds is complex and differs according to the type of wound. In diabetic wounds, arguably the most clinically challenging and intensely investigated type, hyperglycemia and ongoing inflammation promote the overproduction of reactive oxygen species (ROS), leading to oxidative stress and sustained inflammatory signaling that impedes healing.[3] High superoxide levels in the blood of diabetics, dermal fibroblasts, and wound tissue, and prolonged pro-inflammatory macrophage polarization compromise fibroblast function and extracellular matrix reconstruction. Hyperglycemia also disrupts important signaling pathways, such as Rho GTPase,

PI3K/Akt, TGF-β/Smad, and Wnt/β-catenin, leading to compromised growth and migration abilities of key cell types including keratinocytes, fibroblasts, endothelial cells, and immune cells.[4] Cumulatively, these changes are detrimental to wound healing and result in chronic, hard-to-heal states. The microbial factor exacerbates this problem: *Pseudomonas aeruginosa* is always the second most prevalent pathogen in chronic wounds worldwide, after *Staphylococcus aureus*, and their frequent co-occurrence favors the development of robust polymicrobial biofilms that are poorly addressed by traditional, single-target therapies.[5]

Traditional wound dressings, including gauze, films, and foams, are inherently limited in addressing these complexities as they provide only passive physical protection without actively influencing the biochemical milieu of the wound. Furthermore, resistance to antibiotics and, in some cases, inadequate management of moisture are increasingly diminishing their effectiveness. Electrospun nanofibers, on the other hand, are a promising platform for next-generation wound dressings. These materials are highly porous, have a large surface area, and are structurally similar to the native extracellular matrix (ECM). This allows for proper regulation of exudate, protection from microbial ingress, and support for cellular respiration, adhesion, and proliferation.[6]

Among the various polymers studied, chitosan has been demonstrated to be one of the most promising biomaterials, owing to its intrinsic biocompatibility, biodegradability, antibacterial efficiency, and hemostatic ability.[7] However, the rigid molecular architecture and low spinnability require the addition of water-soluble co-polymers to increase the chain entanglement and enable the fabrication of continuous nanofibers via electrospinning. The structural role of chitosan is evidenced by the improvement in the mechanical integrity of the fiber mats produced at higher concentrations. Chitosan has antimicrobial activities because its positive amino groups are attracted to the negative charges on the walls of bacterial cells and break down the membrane. High molecular weight chitosan interacts with proteins on the outer membrane and inhibits the uptake of nutrients into the cell. Low molecular weight chitosan can penetrate the cell and interfere with nucleic acid and protein production.[8]

Although numerous studies have reported positive results across a variety of wound models, complex variations in material composition, manufacturing techniques, incorporated bioactive, and biological evaluation have limited cross-interpretation of biological performance. Previous assessments have been oriented to specific aspects of this field such as manufacturing processes, electrospinning parameters, and drug delivery approaches. However, a holistic quantitative model combining compositional, physicochemical, antibacterial, and biological efficacy has not yet been achieved.[9] To fill this gap, the present systematic review critically reviews 23 studies on chitosan-based electrospun nanofibers for wound healing. The present study aimed to elucidate the research landscape and evaluate the design, properties, and biological function of chitosan-based nanofibers for wound healing through integrated bibliometric mapping and systematic review. The approach was intended to identify emerging research in the field while pinpointing the compositional and processing factors most consistently linked to the biological outcomes.

METHODS

The present study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.[10] A bibliometric analysis was conducted combined with a systematic review to gain comprehensive insight into the use of chitosan-based nanofibers for wound healing. Bibliometric analysis is helpful in monitoring the evolution of the discipline, especially regarding publishing trends, keyword usage, and collaboration among researchers. The systematic review was conducted to critically evaluate the material composition, electrospinning parameters, physical characteristics, antibacterial efficacy, and in vitro/in vivo wound healing properties of the selected studies, thereby capturing compositional and processing factors related to the biological outcomes.

Study Search and Selection Strategy

A systematic search in the PubMed and Dimensions databases was conducted to get relevant publications. The study encompasses publications from 2015 to 2025, original research articles, in English, and publicly accessible. The subsequent inquiry was utilized throughout both databases: ("nanofiber" OR "nanofibers") AND ("electrospinning" OR "electrospun" OR "electronspin") AND "chitosan" AND ("wound healing" OR "wound dressing"), with the search confined to the titles and abstracts of articles. After a preliminary review of articles in both databases, entries were imported into reference management software to remove duplicates. The manual evaluation procedure entailed two reviewers working independently, who reconciled any differences through dialogue. The complete procedure for research discovery and selection is illustrated in the PRISMA 2020 flowchart.

Risk of Bias Assessment

Risk of bias in the in vivo studies was assessed using a SYRCLE framework modified for wound-healing models (diabetic, excision, and burn wound), with each item rated as low, high, or unclear risk across the domains of selection (random allocation to groups, comparability of baseline wound characteristics, concealment of the randomization method), performance (random housing of animals, blinding of investigators applying the dressing), detection (random selection of animals for evaluation, blinding of assessors measuring wound closure, and analyzing histology), attrition (completeness of the final dataset and reporting of reasons for animal exclusion), and reporting (consistency between planned and reported outcomes). Methodological quality of the in vitro and material studies was assessed based on the completeness of reporting of fabrication parameters (humidity and temperature during electrospinning, quantification of residual toxic crosslinker such as glutaraldehyde), antibacterial assay design (appropriate negative and positive controls, minimum triplicate replication for ZOI, MIC, CFU, or OD measurements), and cellular assays (confirmation of cell confluence prior to scratch assay or MTT/CCK-8 testing, blinding of assessors during quantitative image analysis).

Bibliometric Analysis

All 186 articles chosen from PubMed and Dimensions underwent bibliometric evaluation. Metadata from both sources (in .txt format from PubMed and .xlsx format from Dimensions) were integrated into a single database using the "merge collection" functionality in Biblioshiny (version 5.0), an intuitive web interface derived from the R package bibliometrix.[11] Descriptive and statistical analyses of bibliometric data, along with visualizations, were conducted using Biblioshiny. Additional investigation of keyword co-occurrence within the corpus of literature was conducted utilizing VOSviewer (version 1.6.20).[12] The consolidated database generated with Biblioshiny served as the input for the analysis. The resulting visualizations were downloaded in PNG format. The foundational data were saved in Excel file format (.xlsx).

Data Synthesis

Data synthesis involved an integration of results derived from bibliometric analysis and systematic review. Bibliometric analysis was used to describe the research environment at a macro level, including the annual pattern of publications, the geographic distribution of scholarly production, the identification of the main journals, and the most cited publications. Network-oriented evaluations, such as keyword co-occurrence and co-authorship mapping, were used to clarify the conceptual framework of the discipline and the collaborative dynamics underlying it. The combination of these approaches links the experimental results with general scientific trends and makes possible the identification of methodological gaps, research biases, and emerging directions, providing a more analytical and forward-looking perspective on the development of chitosan-based nanofiber systems for wound healing.

Along with that, the systematic review facilitated a more profound comprehension of chitosan as the primary polymer for electrospinning, along with other polymers or bioactive substances contributing to the formation of nanofibers. The principal factors examined included nanofiber composition, electrospinning settings, physical characteristics of nanofibers, antibacterial efficacy, and wound healing performance. Bibliometric results were combined with the outcomes of the systematic review to gain a more profound understanding of the topic at hand. To address cross-study variability in outcome reporting, wound healing efficacy was standardized utilizing measures of percentage of improvement over control (%IOC) [1] and relative improvement index (RII) [2]:

$$\%IOC = \%Treatment - \%Control \quad [1]$$

$$RII = \frac{\%Treatment - \%Control}{(100 - \%Control)} \times 100 \quad [2]$$

Graph-Based Data Extraction

Graph-oriented data extraction was performed to increase the completeness of the dataset used in the systematic review. Quantitative values not explicitly given in the text were deducible from the graphs presented in the articles. The data were extracted by the Plot Digitizer program (version 2.6.8). Most of the figures were examined at 300% magnification.

Validation was performed using data points with explicitly given numerical values considered as definite references. To assess precision, these data points were directly compared to values obtained using Plot Digitizer to remove any ambiguity in terms of self-derived or extracted values. The extraction of 10 confirmed data points showed excellent accuracy with relative percent difference (RPD) of 0.94%, mean absolute error (MAE) of 0.34, and mean

absolute percent error (MAPE) of 0.93%. These results indicate that the difference between reported and digitized values is small. Full validation results are shown in **Supplementary Table S1**.

RESULT AND DISCUSSION

Study Search and Selection

The identification and selection of studies were carried out strictly following the PRISMA 2020 statement to ensure that the data set obtained was sufficient in quantity and methodology to evaluate the application of chitosan-based nanofibers in wound healing. 186 papers were selected for bibliometric analysis. Of these, 23 publications were included in the systematic review. The decision to retain a larger number of documents during the bibliometric assessment was made to allow for the identification of emerging trends and neglected topics. Narrowing the bibliometric dataset would have limited the mapping to the narrower scope of development of the study field. On the other hand, the systematic review was limited to a smaller set of studies because investigating chitosan-based nanofibers required studies to report sufficiently detailed and comparable data. The approach of combining bibliometric analysis with systematic reviews seems to allow researchers to address many aspects. The bibliometrics carry out a general analysis of the trends in the evolution of the discipline, while the systematic reviews carry out a detailed examination of specific elements. The approach to select the papers used in this research is shown in **Figure 1**.

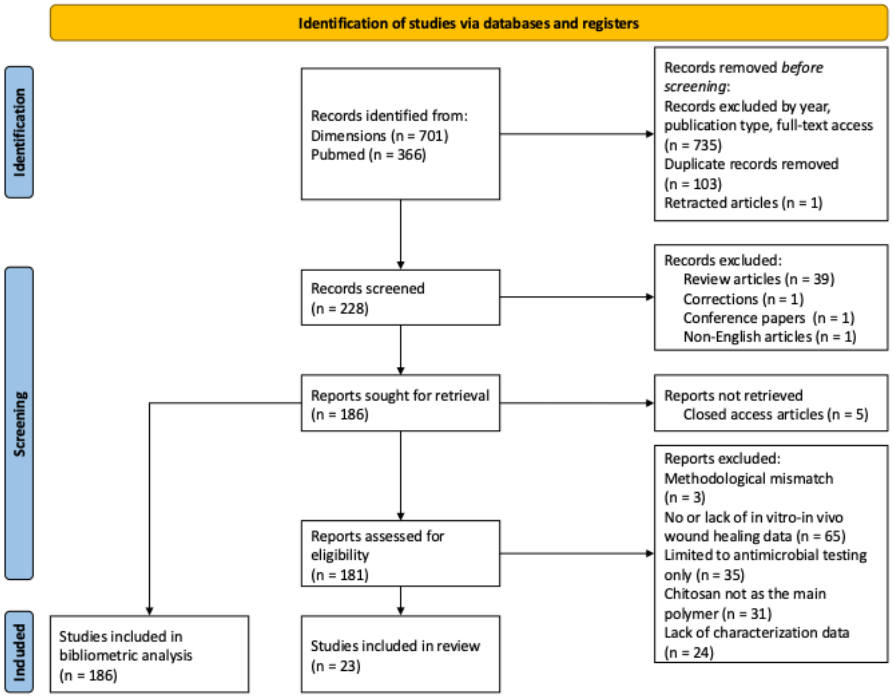


Figure 1. PRISMA Flowchart

Risk of Bias Assessment

Overall, the risk-of-bias assessment indicated that most studies demonstrated low risk in domains supported by clearly reported experimental procedures, particularly antibacterial testing, where the consistent use of positive controls and biological replicates strengthened the reliability of the findings. However, several domains were predominantly rated *Unclear*, largely reflecting reporting gaps rather than demonstrable methodological flaws. Environmental electrospinning parameters, initial cell confluency, and blinding of cellular outcome assessment were rarely reported, limiting verification of their potential influence on study outcomes. For studies employing glutaraldehyde crosslinking, the absence of quantitative verification of residual aldehyde groups represented a more substantive uncertainty because residual toxic crosslinker could potentially confound cytotoxicity results. Similarly, *Unclear* ratings in some in vivo domains, such as random housing, reflected insufficient reporting of methodological details despite otherwise controlled experimental conditions. Collectively, these findings suggest that the principal limitation across the literature is incomplete methodological transparency, while the adoption of independent pathological evaluation in some in vivo studies indicates emerging attention to reducing assessment bias.

Bibliometric Analysis Results

1. Overview of Analyzed Publication

The scientific field is growing continuously, as shown by the increase in the number of publications every year. Publications grew at an average annual rate of 29.24% from three publications annually in 2015 to 39 publications annually in 2025. This scientific trend predicts that the number of scientific publications will be 43 papers per year in 2027. Research into chitosan nanofibers for wound healing is expected to reach its peak in terms of the expansion of the publication rate, signifying the advancement of this field. However, saturation does not diminish its relevance, given the high citation rate of nearly 32 citations per document. One possible cause may be a shift of interest away from research aiming with problems relevant to the subject matter under discussion, to work dealing with practical applications. This is particularly pertinent as it is based in the developing and multidisciplinary areas of tissue engineering and advanced wound dressing technologies.[13,14]

2. Analysis of Sources

The analysis of the sources aims to understand the publishing environment and to evaluate the dissemination of scientific literature about chitosan-based nanofibers for wound healing. To this end, it was necessary to analyze the journals that contribute to the development of the scientific field in question according to Bradford's Law, to determine the number of core journals, which are characterized by a disproportionate impact on the evolution of the research topic.[15] The study revealed that *Polymers* was the most active and significant core journal, with the highest number of publications: 17 articles. The main collection of journals also includes *International Journal of Molecular Sciences*, *International Journal of Nanomedicine*, and *Journal of Nanobiotechnology* (seven articles each), *ACS Omega* and *Pharmaceutics* (six articles each), *RSC Advances* and *Scientific Reports* (five articles each), and *Carbohydrate Polymers* (four articles). The key distinction between *Polymers* and other important journals is the concentration of scientific contributions in few sources, and this is especially important when looking for relevant information. But this supremacy must be taken with caution. Three of the top ten journals are published by MDPI, which is known for its open-access publishing model. Therefore, the importance of a given journal could be in the editorial guidelines and publication methodologies, rather than in the theme of the journal.[16]

3. Analysis of Authors

Analysis of authors was performed to ascertain their degrees of publication output and citation impact within the research field. Valeriia Korniienko (Sumy State University, Ukraine), Li Yiyang (Qingdao University, China), and Zhang Miqin (Seattle University, United States) were identified as the authors with the most productivity, with a total of four works. This signifies a consistent focus among researchers on electrospun nanofibers in biomedical contexts. Despite elevated individual productivity, the collaboration among the authors does not appear as cohesively integrated and synergistic as expected in this rapidly evolving field. **Figure 2** illustrates disjointed research collaboration, characterized by clusters of minor interconnections lacking a cohesive global network, especially among the previously stated authors (pink and blue cluster). This indicates that investigations in this domain are primarily carried out inside specific research groups.

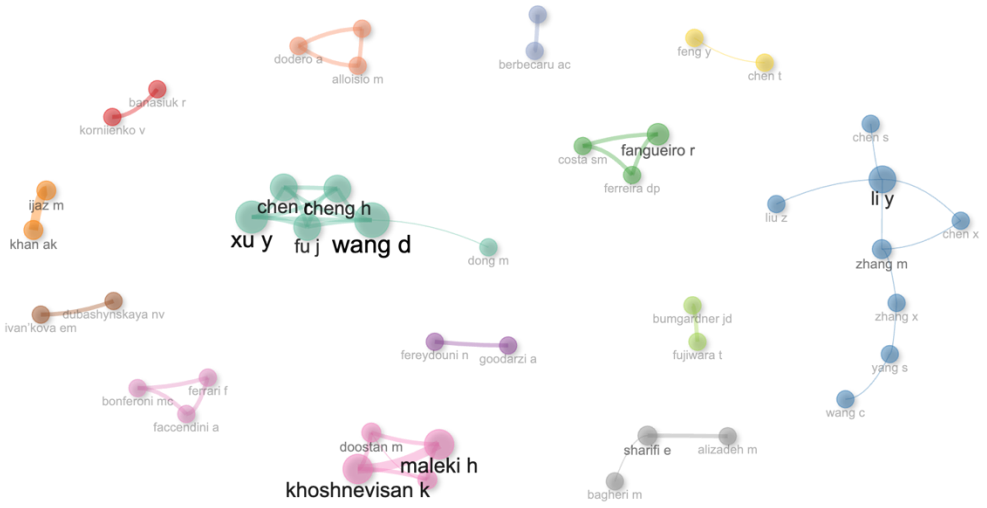


Figure 2. Co-Authorship Network

The geographical distribution of publishing output also supports the co-authorship finding with a substantial imbalance among nations. The authors were from Iran and China have a notably higher research productivity than the other nations: Türkiye, Pakistan, the United States, Indonesia, Czech Republic, India, and Egypt. There may be several structural factors that contribute to the limited international cooperation. Iran's geopolitical problems could have repercussions on global partnerships.[17] By contrast, China appears to have a robust research ecosystem that provides incentives for local collaboration.[18] The findings are seen as a major obstacle that does not permit further research and effective progress of studies, especially for chitosan nanofibers in wound healing.

4. Analysis of Keywords

The co-occurrence network (**Figure 3**) enables to classify the research area of chitosan-based nanofibers for wound healing into three major research clusters: materials and bioactive, clinical and biological activity, and physical characteristics. Cluster 1 (red) and Cluster 5 (purple) are related to materials and bioactive field, including words such as *nanofibers*, *tissue scaffolds*, and *biocompatible materials*. Cluster 2 (green), the largest cluster, and Cluster 4 (yellow) represent the clinical and biological activity research area, characterized by keywords such as *chitosan*, *antibacterial agents*, and *wound infection*. Finally, clusters 3 (blue) represents the physical characteristics of chitosan-based nanofibers, with terms such as delayed-action preparations and tensile strength. Detailed information on the identified keywords and their relevance to the systematic review in this study are summarized in **Table 1**.

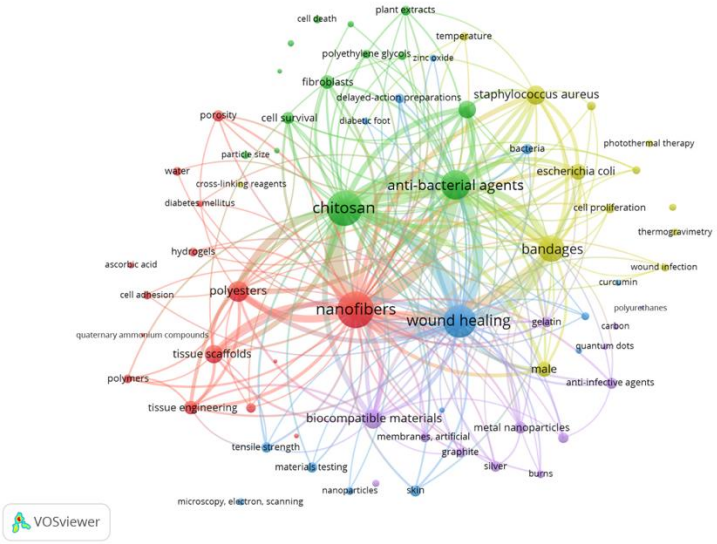


Figure 3. Co-Occurrence Network

Table 1. Keyword Clusters and Their Correspondence to the Systematic Review

No	Cluster	Selected Keywords	Themes	Corresponding Findings to Systematic Review
1.	Red	Nanofibers; Tissue engineering; tissue scaffolds, polymers	Material design and engineering	Consistent with all 23 studies that used chitosan as main polymer for nanofiber engineering
2.	Green	Chitosan; anti-bacterial agents; fibroblast; cell survival	Intrinsic biological properties of chitosan	Consistent with all 23 studies reporting medium- to high- MW chitosan responsible for antibacterial and cell adhesion properties.
3.	Blue	Wound healing; delayed-action preparations; material testing; tensile strength	Physical characteristics of chitosan-based nanofibers	Consistent with 14 of 23 studies reporting fiber diameter near the natural fibril collagen diameter and better mechanical properties.
4.	Yellow	Bandages; *Escherichia coli*; *Staphylococcus aureus*; wound infection	Antibacterial activity of chitosan-based nanofibers	Consistent with 16 of 23 studies reporting good antibacterial activity of chitosan-based nanofibers.
5.	Purple	Biocompatible materials; artificial membrane; metal nanoparticles; quantum dots	Biocompatibility and bioactive incorporation	Consistent with 22 of 23 studies reporting incorporation of different bioactive material in chitosan-based nanofibers.

The most frequent and related keywords, such as *chitosan*, *nanofibers*, *wound healing*, *antibacterial agents*, and *bandages,* were found to be widely used, which reveals that the main research area in the field is the investigation of chitosan nanofiber-based wound bandages with antibacterial properties. Meanwhile, other developing topics have been identified, such as the integration of bioactive substances,[19,20] the application of photothermal therapy,[21,22] the incorporation of metal-based materials,[23,24] and the development of multifunctional materials.[25] The comparatively lower frequency of these topics compared with the main ones indicates the emergence of new trends in the field. There are both fundamental and emerging topics, which points to a shift in the main research area to specialized and new topics. This result confirms the trends observed in the previous part of the study.

Study Characteristics of Included Study in Systematic Review

Table 2. Study Characteristics Included in Systematic Review

Ref	Scaffold	Bioactive Agent	In Vitro		In Vivo	
			Cell Line	Assay	Animal	Wound
19	NM	Lawsone	NHFC	MTT+SCR	N/A	N/A
26	NM+S	N/A	L929	MTT+SCR	N/A	N/A
27	NM+S	*Cissus quadrangularis*	NIH/3T3	WST-1+SCR	N/A	N/A
28	NM	Graphene nanosheets	NHFC	MTT+SCR	N/A	N/A
29	NM	*Tragopogon graminifolius*	N/A	N/A	Wistar rats	EX
25	NM+H	Ursodeoxycholic acid + carbon dots (on hydrogel)	L929	MTT+SCR	N/A	N/A
30	NM	Metformin + Pioglitazone HCl	L929	MTT	SD rats	DB
31	NM	Erythromycin	NIH/3T3 NHFC	MTT SCR	N/A	N/A
21	NM	MXene-infused microgels	L929	CCK-8+SCR	SD rats	DB+IN
32	CS	Dexpanthenol	HNFF-P18	MTT	Albino mice	EX
24	NM	Silver@curcumin nanoparticles	L929	MTT	Kunming mice	PC
33	NM	Ursolic acid	L929	CCK-8	Mouse	DB
34	NM	*Zingiber officinale* + *Thymus vulgaris*	N/A	N/A	Wistar rats	IN
35	CS	Levofloxacin + Quercetin	NIH/3T3	MTT	Wistar rats	BN
23	NM	Bromelain + Silver nanoparticles	L929	MTT	Wistar rats	BN
36	NM	TMP+ TMP-loaded chitosan tripolyphosphate nanoparticles (TMPNP)	HFFF2	MTT	Wistar rats	IC
37	CS	PDGF-impregnated eugenol microemulsion-based silver nanoparticle	NIH/3T3	MTT	Wistar rats	DB
38	NM	*Achillea wilhelmsii*	HDF	MTT+SCR	N/A	N/A
39	NM	Collagen extracted from chrome-tanned shaving dust	Vero	Qual.Cytotox.	Swiss mice	IC
40	NM	Zinc nitrate hexahydrate + fucoidan	L929	MTT+SCR	N/A	N/A
41	NM	Graphene oxide-polyethyleneimine + $LaCl_3$	HSF	CCK-8+SCR	N/A	N/A
22	NM	Polyaniline + S-nitrosoglutathione	L929	CCK-8+SCR	SD rat	DB+IN
20	NM	Anemoside B4	L929	CCK-8	BALB/c mice	DB

Information:

NM : Single-layer nanofiber mat
NM+S : Nanofiber + sponge
NM+H : Nanofiber + hydrogel
CS : Core-shell nanofiber mat
PEO : Polyethylene oxide
PCL : Polycaprolactone
GEL : Gelatin
PVA : Polyvinyl alcohol
PLGA : Poly(D, L-lactic-co-glycolic acid)
NHFC : Normal Human Fibroblast Cells
L929 : National Collection of Type Cultures "Loose" clone 929
NIH/3T3 : National Institutes of Health/3-day transfer, inoculum 3× 10^5 cells
HNFF-P18 : Human Neonatal Foreskin Fibroblast - Passage 18
HDF : Human Dermal Fibroblast
HSF : Human Skin Fibroblasts
PU : Polyurethane
PCEC : Poly (caprolactone)–poly (ethylene glycol)–poly (caprolactone)
HTCC : Hydroxypropyl trimethyl ammonium chloride chitosan
MTT : 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide
CCK-8 : Cell Counting Kit-8
SCR : Scratch in vitro assay
SD : Sprague-Dawley rat
EX : Excision wound
DB : Diabetic wound
IN : Infected wound
PC : Puncture wound
BN : Burn wound
IC : Incision wound

A total of 23 papers were included (**Table 2**) focusing on chitosan-derived electrospun nanofibers in wound healing applications. In 17 of the 23 studies, the major scaffolds were developed as single-layer nanofiber mats, demonstrating the simplicity and versatility of this approach. Other investigations used advanced scaffolds that have

been relatively underexplored: core-shell nanofiber mats (3 of 23), nanofiber-sponge composites (2 of 23), and nanofiber-hydrogel composites (1 of 23). Polyvinyl alcohol (PVA) was the predominant co-polymer in 13 of 23 studies, while polyethylene oxide and gelatin were used in 5 of 23 studies each. Only one study used chitosan alone, highlighting the current limitations in its standalone use. The scope of investigations involved a wide range of treatment modalities, including natural extracts, conventional pharmaceuticals, metal-based nanoparticles, carbon nanomaterials, and combinatorial approaches. Evaluation of wound healing was performed by in vitro and in vivo experiments, in which 21 of 23 studies contained in vitro data and 14 of 23 studies contained in vivo data. However, the heterogeneity of test methods, cell lines, and wound models restricts the comparability of studies. In vivo studies were performed in different types of wounds: excision (1 of 14), diabetic (6 of 14), infected (3 of 14), and burn wounds (3 of 14); incision, excision, and puncture were reported in one study each. Despite these advances, the field remains largely at the proof-of-concept stage. The dominance of basic scaffold designs and the limited mechanistic investigation of multifunctional systems represent major deficiencies. Further, the use of small animal models and lack of focus on scalability and clinical validation restrict translational capabilities. Collectively, these findings emphasize the necessity for more cohesive, mechanistic, and clinically relevant approaches to fully realize the potential of chitosan-based nanofiber systems.

Material of Chitosan Nanofiber

Table 3. Desired Chitosan Nanofiber Composition

Ref	Chitosan		Co-Poly		Crosslink	Desired Conc. (%)		
	DD (%)	MW (kDa)	Name	MW (kDa)		CHI	Co-Poly	Bioactive
[19]	NR	(low)	PEO	600	N/A	3†	4†	1†
[26]	75–85	190–310	PCL	80	N/A	15†	5‡	N/A
[27]	77.5	(medium)	PEO	NR	GN	2‡	NR	NR
[28]	75–85	(medium)	GEL	NR	GA	3‡	25‡	0.15‡
[29]	85	270	PVA	72	N/A	3‡	~14‡	50‡
			PEO	NR			2‡	
[25]	NR	600–800	GEL	NR	N/A	8‡	30‡	N/A
[30]	NR	190–310	GEL	NR	GA	2.5‡	20‡	M: 40^
			PCL	~80			20‡	P: 12^
[31]	98	72	PVA	NR	N/A	3‡	10‡	2‡
[21]	95	NR	GEL	NR	N/A	30	70	N/A
[32]	76	600	PVA	72	GA	0.5‡	5‡ (core)	6‡
							4.5‡ (shell)	
[24]	≥75	150	PEO	900	N/A	3†	3‡	2†
[33]	75–85	160	PVA	146	N/A	0.5‡	0.5‡	0.2‡
[34]	75–85	190–300	PVA	72	GA	2‡	10‡	5†
								5†
[35]	76	NR	PEO	NR	N/A	3‡	2‡ (core)	L: 10‡
			PLGA	45			20‡ (shell)	Q: 5‡
[23]	85	(medium)	PCL	80	N/A	2	14‡	B: 1‡
								SNP: 1‡
[36]	75–85	(medium)	PCEC	NR	GA	3†	NR	TMP: 0.2†
			PU					
[37]	≥75	NR	PVA	89–98	GA	3‡	10‡	9‡
[38]	75–85	50–190	PVA	72	N/A	2‡	10‡	10‡
[39]	>90	150	PVA	115	N/A	2†	10†	10†
[40]	75–85	50–190	N/A	N/A	N/A	10‡	N/A	NR
[41]	NR	350	PVA	145	GA	4†	16†	GO: 2 (mg/mL)
								La: 12.5 (mmol/L)
[22]	≥95	50	PVA	~67	GA	15	80	Pa: 5 (mg)
			HTTC				5	G: 15 (mg)
[20]	75–85	160	PVA	146	N/A	~0.67‡	2‡	0.2‡

Information:

DD	: Degree of deacetylation	L	: Levofloxacin
MW	: Molecular weight	Q	: Quercetin
kDa	: kilo Dalton	B	: Bromelein
Co-Poly	: Copolymer	SNP	: Silver nanoparticles
Conc.	: Concentration	TMP	: meso tetrakis (N-methyl pyridinium-4-yl) porphyrin tetratosylate salt
CHI	: Chitosan	GO	: Graphene oxide
NR	: Not reported	La	: Lanthanum(III) chloride
N/A	: Not applicable	Pa	: Polyaniline
GA	: Glutaraldehyde	G	: S-Nitroglutathione
GN	: Genipin	†	: w/w or wt%
M	: Metformin	‡	: w/v
P	: Pioglitazone hydrochloride		

The compositional data from the 23 investigations (**Table 3**) show consistent design principles that are not limited to material selection, providing a deeper understanding of the structure-property-function relationship of wound healing biomaterials. The prevalence of medium- to high-molecular weight chitosan (100–800 kDa) appears to be a design feature rather than a coincidence. Higher molecular weight results in increased chain entanglement, solution viscosity, and mechanical robustness of electrospun nanofibers. It also enhances the density of cationic charges on the surface, which allows the nanofibers to exhibit intrinsic antibacterial properties and facilitates cell adhesion via electrostatic interactions with negatively charged bacterial membranes and proteoglycans on the cell surface.[42,43]

Correspondingly, the degree of deacetylation (DD) within the range of 75–85% across studies indicate a functional tradeoff between solubility and bioactivity. An increased degree of deacetylation enhances the cationic charge and antibacterial activity but reduces water solubility, whereas a lower degree of deacetylation reduces both antimicrobial activity and cell-material interactions.[44,45] The observed outlier (DD ≥95%) is an example of intentional design where highly deacetylated, quaternized chitosan (HTCC) was intentionally selected to increase charge density, facilitating a synergistic antibacterial-photothermal effect.[22] This highlights the point that DD selection acts as a functional parameter instead of a nominal material descriptor.

Structural integrity versus biocompatibility is a major compromise in crosslinking methodologies. Glutaraldehyde (GA) is used in 6 of the 7 crosslinked systems, which promotes effective imine bond formation, leading to improved water resistance and mechanical strength.[46] However, the cytotoxicity thought to arise from residual aldehyde groups that were unreacted was largely overlooked, since no study quantified the residual GA concentrations.[47] This gap is a major limitation for clinical translation and regulatory approval. On the other hand, genipin (GN) has been investigated in a single study and represents a more biocompatible option, but it is underexploited, likely due to its slower crosslinking kinetics and related processing difficulties.[27]

The selection of co-polymers reveals distinct functional roles that are often neglected in comparison studies. Polyethylene oxide (PEO) is used routinely at low concentrations (2–4% w/v), primarily as a processing aid to improve spinnability and reduce bead formation, without significantly impacting biological activity.[48] Alternatively, gelatin is incorporated to incorporate bioactive elements that promote integrin-mediated cell adhesion, showing a purposeful biomimetic strategy. Polyvinyl alcohol (PVA) is widespread, while it is good to increase mechanical properties and fiber formation, it shows a reliance on a limited number of materials that might stifle innovation.

The most sophisticated formulations, in particular the core–shell structures, represent the epitome of rational design in the dataset.[32,35,37] Sethuram and Chandrasekaran[37] have prominently incorporated various functional elements, such as chitosan, PVA, eugenol microemulsion, silver nanoparticles, and platelet-derived growth factor (PDGF) into a hierarchical structure that simultaneously addresses hemostasis, infection control, inflammation modulation, and angiogenesis. These spatially structured, multifunctional systems exemplify the transition from empirical formulation to systems-level design and may serve as a benchmark for future progress.

Electrospinning Method and Setting

The data obtained from the electrospinning parameters (**Supplementary Table S2**) demonstrated significant mechanistic relationships between the processing conditions and the characteristics of the resultant nanofibers that ultimately impact the biological efficacy. The primary method in 20 of the 23 studies was conventional single-needle electrospinning, which supports the inverse relationship between applied voltage and fiber diameter. The highest voltage applied (30 kV) resulted in the finest fibers (64.3 ± 17.1 nm),[30] and the nanofibers obtained at 15–18 kV were in the range of 127–270 nm. This result is consistent with the well-known fact that a stronger electrostatic force leads to higher jet elongation and whipping instability, which reduces the nanofiber diameter.[49] The three coaxial electrospinning studies employed significantly lower flow rates (0.13–0.6 mL/h) than the blending systems (~0.5–1 mL/h), underscoring the importance of a stable concentric Taylor cone.[32,35,37] High flow rates in coaxial systems may destabilize the core-shell interface, leading to poor compartmentalization and failure of the controlled release capabilities that justify the higher structural complexity.

Humidity and temperature are important environmental factors that are often neglected. Relative humidity (RH) was reported in 5 of the 23 studies (25-60% RH). RH mainly affects solvent evaporation and fiber solidification, that is essential for porosity, cell migration, and bead formation.[50] In addition, temperature was only reported in 9 of the 23 studies (25–37 °C), which is important, especially in heat-sensitive bioactive stability. Sethuram and Chandrasekaran[37] employed electrospinning at 37 °C for a system containing platelet-derived growth factor (PDGF), which raised concerns about potential temperature-induced denaturation, which minimally investigated experimentally. The absence of

humidity and temperature affected study replication and differentiation between solution factors and environmental factors, since similar formulations may result in different fiber properties under specific environmental conditions. Informing environmental factors explicitly will improve consistency and clarity of nanofiber manufacturing results.

Physical Characterization of Chitosan Nanofiber

The physical characterization results (**Supplementary Table S3**) indicate partial achievements and design constraints in the chitosan electrospun nanofiber scaffold. Physical attributes do not appear to be closely related to biological outcomes. The diameter range of the fiber was 64.3 to 395 nm. About 14 of 23 studies were close to the size of natural collagen fibrils (100-300 nm in diameter), which helped the cell to adhere and move via integrin cluster and formation of focal adhesion. But the connection between physical characteristics and biological outcomes seems a somewhat inconsistent. The best in vivo healing (RII=91.0%) was reported by Liu et al.[24] with sub-100 nm fibers (65.35 nm, while Tavallaei et al.[38] showed a significant in vitro migration (%IOC=+38 pp), although their fiber diameter was the largest (395 nm). These findings indicate that fiber diameter alone does not adequately explain biological performance, suggesting that wound-healing efficacy reflects the combined effects of scaffold characteristics, material composition, incorporated bioactive, and release behavior.

Mechanical characterization emphasizes the inherent trade-off between biological efficacy and structural robustness. The materials had high absorbency and swelling capacity (2716%) but very low tensile strength (0.002 MPa), which limited their clinical application since the tensile strength of real skin is between 2.5 and 30 MPa.[27,51] Conversely, materials with tensile strength of 12.9 MPa and Young's Modulus of 51 MPa showed better mechanical properties than native skin (2.5–30 MPa), which may be due to the rigidity of the scaffold material.[26,51] Although the design was compelling, none of the in vivo investigations evaluated the tension of the wound edge, tissue deformation, or flexibility of the scaffold. This underscores a major limitation in the assessment of therapeutic relevance, as mechanical properties are often characterized, but their relevance to wound site adaptation and interaction with mechanically active tissue is never evaluated.

Surface wettability has been shown to be remarkably consistent in many studies, with most studies reporting contact angle measurements within the ideal range of 40–80°. However, Lv et al.[33] reported very hydrophilic nanofibers (CA ≈ 0°), while Hashemi et al.[32] demonstrated extremely hydrophobic nanofibers (CA = 140.9°), indicating more design trade-offs in fabrication of chitosan nanofibers. It is expected that the highly hydrophilic nanofiber will promote rapid fluid absorption and better cell attachment, while also degrading faster to achieve the desired result. This phenomenon partly explains the continuous release pattern observed in Lv et al.,[33] where the embedded medicines start to release after the first rapid expansion of the scaffold.

Most of the studies investigated showed a considerable consistency in the drug release patterns, with the biphasic profile being identified in all of them, except for Tujjohra et al.[39] which documented only an initial release phase. This profile should lead to optimal in vivo results due to rapid killing of germs in the initial phase and progressive administration of antibiotics thereafter.[35,52] The even release of drugs is a property of the structure of the chitosan nanofiber matrix, not a consequence of particular bioactive compounds.

Antibacterial Activity of Chitosan Nanofiber

Understanding more than inhibition data can be gained by examining the antibacterial results of 16 studies with a focus on methodological variation, control selection, and bacterial grouping as shown in **Table 4**. A common trend in zone-of-inhibition (ZOI) assays is often better efficacy against Gram-positive than Gram-negative bacteria, with few exceptions. This can be explained by the structure of Gram-negative bacteria. The membrane of Gram-negative bacteria consists of lipopolysaccharide that limits susceptibility to the mechanism of electrostatic disruption of the membrane characteristic of chitosan.[53] Thus, efficacy of systems relying primarily on the intrinsic cationic nature of chitosan may be limited against clinically relevant Gram-negative pathogens such as *Pseudomonas aeruginosa*.[37]

Among the systems assessed, NIR-responsive substances exhibited the most developed antibacterial mechanisms.[22,41] For example, Xie et al.[22] observed a reduction of MSSA from 1.2×10^{8} to 8.9×10^{5} after NIR irradiation, corresponding to a 2.13-log reduction. This points to the potential of photothermal-assisted antibacterial strategies. However, the requirement of external irradiation limits its practicality and may prevent its application in normal clinical settings. Fu et al.[21] found an important inconsistency where the bacterial counts of the treated samples were similar to the controls, but significant progress was made in vivo wound healing. This inconsistency suggests that biomaterials may promote wound healing through mechanisms other than direct bactericidal activity, such as immunomodulation or promotion of angiogenesis.

In addition, the drug-loaded nanofiber systems demonstrate minor but meaningful improvements in antibacterial efficiency. The minimum inhibitory concentration of erythromycin encapsulated in nanofibers was two-fold lower than that of the non-encapsulated drug, indicating the advantages of targeted and sustained drug delivery in improving therapeutic efficacy.[31] In sum, these findings show that research in this area has moved from the simple determination of basic antibacterial efficacy to more complex problems such as antimicrobial spectrum, biofilm interaction, and mode-of-action-specific activity.

Table 4. Antibacterial Activity of Desired Chitosan Nanofiber Formula

Ref	G(+) Bacteria	G(-) Bacteria	Units	Antibacterial Activity		Control	
				G(+)	G(-)		
19	*S. aureus*	*E. coli*	ZOI	19*	15*	Imipenem (G+)	: 24*
						Tetracycline (G-)	: 29*
26	*S. aureus*	*E. coli*	OD	0.09*	0.08*	Filter paper (G+)	: 0.1*
						Filter paper (G-)	: 0.1*
27	*S. epidermidis*	*E. coli*	ZOI	1±0.1 (DL)	1.62±0.08 (DL)	Amoxicillin (G+)	: 11
						Amoxicillin (G-)	: 8
28	*S. aureus*	*E. coli*	CFU	212*	223*	Blank (G+)	: 1476*
						Blank (G-)	: 465*
25	*S. aureus*	*E. coli*	%INH	51	41	Gentamicin (G+)	: 82*
						Gentamicin (G-)	: 78*
31	*S. aureus*	*E. coli*	MIC	1	4	Erythromycin (G+)	: 2
						Erythromycin (G-)	: 8
21	*S. aureus*	*E. coli*	CFU	$9.8 \cdot 10^8$*	$2.1 \cdot 10^8$*	Blank (G+)	: $10.4 \cdot 10^8$*
						Blank (G-)	: $1.8 \cdot 10^8$*
24	*S. aureus*	*E. coli*	OD	0.12	0.15*	Blank (G+)	: 1.27*
						Blank (G-)	: 1.35*
34	*S. aureus*	*E. coli*	ZOI	18±3		Free NF (G+)	: 0
						Free NF (G-)	: 0
23	*S. aureus*	*E. coli*	ZOI	21±1	25±2	Free NF (G+)	: 0
						Free NF (G-)	: 0
36	*S. aureus*	*E. coli*	%INH	D: 32.1* L: 79.5*	D: 31.1* L: 81.2*	PU/PCEC NF (G+) L:4.2*	: D:5.2*
						PU/PCEC NF (G-) L:2.1*	: D:4.2*
37	*S. aureus*	*P. aeruginosa*	ZOI	21.02*	21.04*	Free NF (G+)	: 3.02*
						Free NF (G-)	: 2.06*
39	*B. subtilis*	*E. coli*	ZOI	30±2.1	23±1.0	Free NF (G+)	: 28±1.8
						Free NF (G-)	: 20±1.5
40	*S. aureus*	*E. coli*	ZOI	16.3*	17.5*	Positive control (G+)	: 22.6
						Positive control (G-)	: 21.2
41	*S. aureus*	*E. coli*	%INH	NIR(-): 92.7 NIR(+): 97	NIR(-): 88.45 NIR(+): 99	Free NF (G+) Free NF (G-)	: -: 24* +:15* : -: 11* +:15*
22	MSSA	*E. coli*	CFU	NIR(-): 1.2×10^8 NIR(+): 8.9×10^5	NIR(-): 4.17×10^7 NIR(+): 1.26×10^6	Free NF (G+) Free NF (G-)	:-+: 4.07×10^8 :-+:9.55×10^7

Information:

(+)	: Gram positive	%INH	: Antibacterial activity (%)
G(-)	: Gram negative	MIC	: Minimal inhibitory concentration (μg/mL)
S. aureus	: *Staphylococcus aureus*	CFU	: Colony forming unit
S. epidermidis	: *Staphylococcus epidermidis*	DL	: Double-layer nanofiber
B. subtilis	: *Bacillus subtilis*	D	: Treated in dark condition
MSSA	: Methicillin-susceptible *Staphylococcus aureus*	L	: Treated in light condition
E. coli	: *Escherichia coli*	NIR(-)	: Treated without near infrared light
P. aeruginosa	: *Pseudomonas aeruginosa*	NIR(+)	: Treated with near infrared light
ZOI	: Zone of inhibition (mm)	NF	: Nanofiber
OD	: Optical density	*	: Data extracted using Plot Digitizer

Wound Healing Activity of Chitosan Nanofiber

The findings of in vitro and in vivo studies show a clear yet non-linear relationship between cytocompatibility, functional processes, and overall efficacy of wound healing in chitosan-based electrospun nanofiber systems as shown in **Table 5**. The in vitro data (cell viability in 21 of 23 studies and scratch assay in 9 of 23 studies) generally indicate significant cytocompatibility (≥86% viability), but this should be considered a basic prerequisite rather than a reliable predictor of therapeutic efficacy. Those causing supra-normal proliferation (>100% of control) are more informative and indicative of true mitogenic activity, but exhibit highly variable migration results, from significantly enhanced to little or

even inhibitory effects.[26,32,36,38] Crucially, this variation is often a result of methodological limitations, such as ceiling effects in control groups or the inability of two-dimensional scratch assays to accurately represent the behavior of structurally complex three-dimensional scaffolds, rather than inherent deficiencies in the materials themselves.

Table 5. In Vitro Wound Healing Assay of Desired Chitosan Nanofiber Formula

Ref	Viability (% at 24 h)	Wound Closure (%, time)	IOC (points)	RII (%)
[19]	91*	98 (24 h)	+10	83.3
[26]	158±14 (3 d)	23±5 (24 h, DL)	+7	8.3
[27]	105*	15* (48 h, DL)	+4	4.5
[28]	102*	97 (48 h)	-3	N/A
[25]	100	~40 (24 h)	-9	-17.6
[31]	86	~100 (48 h)	+39	100.0
[21]	95*	45* (12 h)	+14	20.3
[38]	114.4	79 (24 h)	+38	64.4
[40]	76*	63* (72 h)	+39	51.3
[41]	~90	79* (24 h)	+1	4.5
[22]	93	84.30±4.38 (3 d)	+23.12	59.6

Information:
IOC : Improvement Over Control
RII : Relative Improvement Index
h : hour(s)
d : day(s)
DL : Double layer nanofiber
N/A : Not applicable
* : Data extracted using Plot Digitizer

In contrast, in vivo results (**Table 6**) show consistent positive effects in multiple wound models, with wound closure improvement ranging from +9.6 to +49 percentage points (%IOC) and RII values ranging from 39.3 to 100%. These findings suggest that functional efficacy is more reliably demonstrated at the tissue level, where mechanisms such as angiogenesis, inflammatory control, and extracellular matrix remodeling act together synergistically. Sethuram and Chandrasekaran[37] achieve optimal efficacy (RII = 100%) by combining pro-angiogenic (PDGF), anti-inflammatory (eugenol), and antibacterial (AgNPs) properties. On the other hand, simpler formulations that target the key pathological mechanisms, such as oxidative stress and inflammation in diabetic wounds, can result in similar outcomes.[33,34] This indicates that a focus on disease-specific mechanisms may be more relevant than structural or compositional complexity. Therefore, successful scaffold design needs to move towards mechanism-based, context-tailored techniques that integrate multiple functional characteristics, rather than focusing on isolated material properties or one-dimensional optimization.[54]

Table 6. In Vivo Wound Healing Assay of Desired Chitosan Nanofiber Formula

Ref	Wound Size (mm^2)	Wound Closure (%, time)	IOC (points)	RII (%)	Collagen Deposition
[29]	400	49 (14 d)	+33	39.3	High
[30]	~50	76.3 ±3.4	29	55.0	High
[21]	~79	87* (14 d)	+16	55.2	High
[32]	~79	92.3±2.5 (14 d)	+9.6	55.5	High
[24]	~28	97.0 (12 d)	+30.2	91.0	High
[33]	~79	~100 (18 d)	+16.4	100	High
[34]	~314	98.0 (14 d)	+21.6	100	High
[35]	~314	97* (21 d)	+24	88.9	High
[23]	~79	73* (7 d)	+21	43.8	N/A
[36]	~314	99* (21 d)	+15	93.8	N/A
[37]	~400	100 (30 d)	+49	100	High
[39]	~314	100 (14 d)	+17	100	High
[22]	~79	91* (14 d)	+18	66.7	High
[20]	~79	97.8 (12 d)	+26.4	92.3	HIgh

Information:
IOC : Improvement Over Control
RII : Relative Improvement Index
d : day(s)
N/A : Not applicable
* : Data extracted using Plot Digitizer

Gap Research and Future Perspectives

Recent studies on electrospun chitosan nanofibers for wound healing reveal a great variety of methodologies, limiting the comparability and reproducibility of results and the comprehensive understanding of their therapeutic effects. Critical fabrication parameters such as humidity or temperature in electrospinning and quantification of residual crosslinker after crosslinking are merely reported. Furthermore, different methods of antibacterial testing are used, such as zone of inhibition, minimum inhibitory concentration, colony-forming unit counting, and optical density. The duration of drug release testing varies widely from hours to weeks, making direct comparison across studies challenging. Although clinical investigations of chitosan-based wound dressings have been reported, the available evidence remains insufficient to determine how specific material and fabrication characteristics of electrospun systems influence clinically relevant outcomes. Such limitations suggest that the majority of the chitosan-derived electrospun nanofiber technologies are at lower Technology Readiness Levels at the laboratory validation level only, reflecting that future studies should focus on mechanism-oriented and wound-specific designs while providing sufficient information on fabrication conditions, material characteristics, biological evaluation, and safety-related parameters to enable meaningful comparison and assessment of clinical relevance.

Systematic consistency is required to bridge the gaps in wound healing research with electrospun chitosan nanofibers. More consistent reporting of key fabrication parameters and clearer reporting of biological outcomes would facilitate cross-study comparisons while allowing manufacturing strategies to remain formulation- and application-specific. In future design, attention should be paid to the development of mechanism-oriented multifunctional systems to target the complex pathogenic mechanisms of infection, inflammation, hypoxia, and oxidative stress in chronic wounds. Innovative stimuli-responsive and electroactive wound dressings capable of promoting macrophage polarization and allowing controlled release of therapeutics, and theranostic systems for the combination of antimicrobial therapy and real-time wound assessment, such as pH-responsive fluorescence, are highly promising for enhancing the therapeutic efficiency and facilitating clinical translation.

Limitation

This review is comprehensive but has some limitations. In this study, Biblioshiny was used to consolidate records from different databases into a single dataset. The initial discrepancies in metadata across databases were due to differences in field formats and citation styles; although the records were manually curated, some inaccuracies may remain. Second, many studies were excluded at the screening phase due to the lack of data on physical characteristics, antibacterial efficacy, and in vitro and/or in vivo wound healing outcomes simultaneously. This restriction reflects the patchy nature of the literature available at present, rather than overly stringent criteria, but does limit the representativeness of the final sample of 23 studies included.

The varied ways the research was presented made the comparative evaluation a challenging task. The comprehensive nature of both physical and antibacterial synthesis was restricted by the infrequent reporting of key parameters, including scaffold porosity, pore size, degradation characteristics, and antibacterial activity against clinically relevant resistant strains (e.g., MRSA). Other sources of bias were also found. Publication bias is likely to affect the number of beneficial %IOC and RII results. The lack of blinded assessment in the histological analysis may be a potential risk for performance bias. The numerical data obtained from the software PlotDigitizer have been validated with an average inaccuracy of about 1 %, but any digital information has some amount of measuring ambiguity.

CONCLUSION

The present study has adopted a combination of bibliometric mapping and systematic review to map the research landscape and relationships between the structure, properties, and functionalities of chitosan-based electrospun nanofibers for wound healing. The bibliometric analysis showed a stable growth pattern with regional concentration and fragmentation of collaborations. Keyword clustering suggested a transition toward specialized multifunctional applications, especially when considering photothermal therapy and addition of metal nanoparticles. A systematic review of 23 studies emphasizes the significance of molecular weight (100–800 kDa) and degree of deacetylation of chitosan (75–85%), choice of copolymer (predominantly PVA), and cross-linking agent (predominantly glutaraldehyde), and electrospinning parameters for desirable mechanical properties, better antibacterial efficacy (especially for Gram-positive bacteria) and better in vitro/in vivo wound healing effects.

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I Gede Adi Wiguna: Conceptualization, Methodology, Writing - Original Draft; **Ni Nyoman Rupiasih**: Conceptualization, Methodology, Writing - Review & Editing; **Tambunan Matthew Valentino**: Investigation, Data Curation, Writing - Original Draft; **Eka Indra Setyawan**: Supervision, Validation, Writing - Review & Editing.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

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