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REVIEW



# Predictive design framework for electrospun pectin nanofibers in biomedical applications

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## ABSTRACT

Pectin, a structurally diverse plant-derived polysaccharide, is emerging as a distinctive platform for engineering bioinstructive nanofibrous scaffolds. Compared to other natural polymers commonly used in electrospinning, such as alginate, hyaluronic acid or collagen, pectin offers a unique combination of mucoadhesiveness, immunomodulatory potential, and fine-tunable molecular architecture governed by the balance of homogalacturonan and

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rhamnogalacturonan domains. However, its intrinsic polyelectrolyte behavior, low chain entanglement, and high aqueous solubility have historically constrained its use in nanofiber fabrication. Recent advances in chemical modification, solvent engineering, and post-spinning stabilization have enabled the generation of electrospun pectin fibers with controllable morphology, mechanical resilience, and degradation kinetics. This review introduces a predictive structure–property–function framework for the rational design of electrospun pectin nanofibers in biomedical applications. We classify molecular strategies into three groups (covalent, physical, and compositional) and evaluate how each of them affects fiber formation and downstream biological performance, with particular focus on immunological interaction, bioactive loading, and scaffold remodeling. In parallel, we identify translational bottlenecks including material variability, sterilization sensitivity, and regulatory misalignment of crosslinking chemistries. By integrating these factors into a design-informed scaffold logic, this review provides a roadmap for advancing electrospun pectin materials from laboratory prototypes to clinically viable platforms for regenerative medicine, wound healing, and localized therapeutic delivery.

**Key Words:** electrospinning; crosslinking; drug delivery; tissue engineering; wound healing; immunomodulation; polymerization

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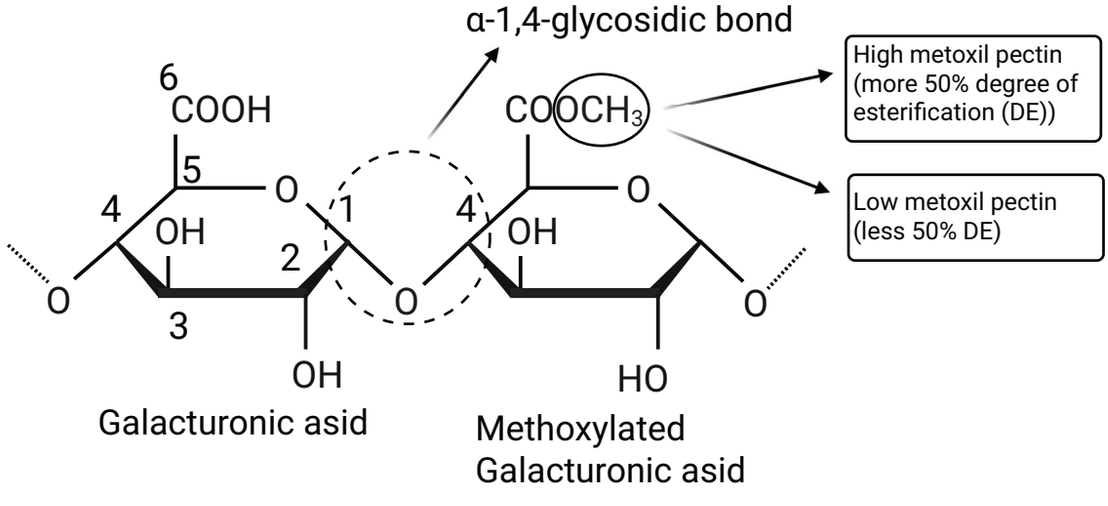
## Introduction

Natural polysaccharides are widely used for engineering degradable, immunocompatible scaffolds due to their hydrophilicity, mild gelation, and tunable chemistry. Pectin is a heterogeneous plant polysaccharide composed predominantly of α-1,4-linked D-galacturonic acid (Figure 1). It attracts interest for biomedical use due to its mucoadhesion, ionic responsiveness, and selective interactions with epithelial and immune tissues [1].

**FIG. 1.** Chemical structure of pectin



Depending on the number of carboxyl groups that can be esterified with methyl groups, pectins are classified by their degree of esterification (DE), also known as the degree of methoxylation. Pectins in which more than 50% of their carboxyl groups are esterified are classified as high-methoxylpectins. They require specific conditions for gel formation, such as a low pH (2.5–3.5) and the presence of soluble solids, primarily sucrose, and form gels primarily through hydrophobic interactions. In contrast, pectins in which less than 50% of their carboxyl groups are esterified are classified as low-methoxylpectins. They gel regardless of sugar content and are chemically more stable to moisture, heat, and pH than the aforementioned high-methoxylpectins. Low-methoxylpectins gel in the presence of divalent cations, typically calcium (Ca2+). Therefore, the degree of methoxylation is a critical parameter for pectin.

While traditionally limited to hydrogels or coatings, pectin has recently been electrospun into nanofibers, offering extracellular matrix-mimetic architecture, submicron porosity, and dynamic molecular exchange [2]. These features make it a promising candidate for regulating adhesion, inflammation, or localized delivery. Unlike more chemically uniform polysaccharides like alginate or hyaluronic acid, pectin's tunable ratio of homogalacturonan and rhamnogalacturonan domains allows for control over flexibility, hydration, and ion sensitivity. Its plant origin eliminates zoonotic risks, while its uronic-acid-rich surface enables immune-instructive signaling [3]. These traits make pectin not just an alternative, but a uniquely functional platform for electrospun biomedical scaffolds. However, rational design is limited by complex interdependencies between molecular structure, processability, and function.

Electrospinning pectin remains challenging due to its low chain entanglement, high charge density, and water solubility, which destabilize jet formation. Strategies to improve spinnability, such as periodate oxidation [1], methacrylation [4], and blending with carrier polymers like polyethylene oxide (PEO) or polyvinyl alcohol (PVA) [5], not only enable fiber production but also modulate degradation rate, mechanics, porosity, and biomolecule loading. Recent studies show that architectural features such as fiber diameter, orientation, and surface charge can direct immune and epithelial responses, including macrophage polarization and tissue integration [6, 7]. These data indicate that a predictive link between structural design and functional response is required.

Despite growing interest in pectin-based scaffolds, a design strategy that connects mechanism with function is still missing. Previous reviews have addressed pectin hydrogels [8], plant-derived wound matrices [9], and polysaccharide processing, but rarely connect chemical modification to biological function. Critical translational issues, including batch variability, sterilization, and the lack of good manufacturing practice (GMP)-compliant pectin, also remain underexplored. Furthermore, fiber-specific features, including anisotropic mechanics and controlled release, are sometimes interpreted as bulk hydrogel properties [1, 3, 6]. This gap limits clinical translation. This review addresses this point by outlining how molecular composition, processing parameters and scaffold performance can be analyzed within a single design framework.

To address these conceptual and translational gaps, we propose a predictive structure–property–function framework for the rational design of electrospun pectin nanofibers. We analyze how molecular engineering strategies (covalent modifications, crosslinking modalities, and compositional blending) influence electrospinnability and biological responsive. We further examine how

processing parameters such as solvent systems, ionic environment, and fiber assembly conditions shape nanofiber architecture, mechanical performance, and degradation behavior. These structural features are examined in relation to biological outcomes across key biomedical domains, including wound healing, drug delivery, and soft tissue regeneration. We also consider how polymer structure, fabrication parameters, and functional outcomes relate to each other. Finally, we identify major translational bottlenecks, such as the absence of GMP-grade pectin, sterilization constraints and uncertainty around crosslinkers regulation. These considerations provide a structured basis for advancing pectin nanofibers toward clinical use.

## Strategies for structural modification of pectin relevant to electrospinning

Effective electrospinning of pectin for biomedical use requires structural modification to overcome its native limitations, including low chain entanglement, high hydrophilicity and polyelectrolyte behavior, which impair fiber formation and mechanical stability. To address this, three groups of strategies are typically used. Chemical modifications target hydroxyl or carboxyl groups and change charge distribution, hydrophobicity or the ability to crosslink. Physical approaches rely on pH adjustment, thermal conditioning, or sonication to influence chain conformation or supramolecular organization. Compositional approaches include blending pectin with synthetic or natural polymers, proteins, or nanofillers to improve spinnability and function. The majority of modifications, with the exception of cross-linking, are implemented before electrospinning. These approaches are detailed in Table 1.

## Chemical modifications

The rational design of pectin-based nanofibers requires molecular modifications to mitigate their polyelectrolyte nature, low hydrophobicity, and limited functionality for crosslinking. One of the most effective strategies is periodate oxidation, which selectively cleaves the C2–C3 bond of galacturonic acid residues, introducing aldehyde groups capable of reversible imine bond formation. This modification proportionally reduces molecular weight while enhancing crosslinking potential through dynamic covalent interactions, improving chain flexibility and entanglement critical for electrospinning. Scaffolds with higher oxidation degrees (e.g., 50%) exhibit reduced fiber diameter, increased stiffness, and slower degradation under aqueous conditions [10], and further enable stiffness-mediated mesenchymal stem cells differentiation toward endothelial or smooth muscle phenotypes depending on matrix elasticity [1]. Aldehyde chemistry has also been used to drive Schiff base formation in injectable hydrogels for tumor-responsive drug delivery [28], and to control supramolecular condensation in freeze-dried constructs via hydrogen bonding and ice crystal modulation [11].

For stabilization post-electrospinning, adipic acid dihydrazide (ADH) is commonly employed to form hydrazone crosslinks with aldehyde-functionalized fibers. By tuning ADH concentration, pH, and reaction time, crosslink density and network properties can be precisely controlled, yielding scaffolds with tensile strengths up to 2.2 MPa, elongation above 60%, and water uptake exceeding 1200%, well suited for dynamically hydrated wound

**Table 1.** Physicochemical modification strategies and their structural consequences in pectin-based nanofibers

| Type of modification | Molecular target in pectin | Modification strategy | Mechanistic effect | Effect on nanofiber properties | References |
|---|---|---|---|---|---|
| Chemical | C2–C3 diols (GalA backbone) | Period ate oxidation + ADH crosslinking | Aldehyde groups form dynamic imine/ hydrazonebonds; tune crosslinking | Stronger, more stable fibers; degradation control; cell-instructive mechanics | [1, 10, 11] |
| | Carboxyl and hydroxyl groups | Methacrylation + UV curing | Photo-induced polymerization + thiol–ene click conjugation | Improved wet stability; spatial patterning and peptide/growth factor integration | [4, 12] |
| | Carboxyl groups | EDC/NHS amidation; ammonia/ amino acid coupling | Charge reduction + addition of amine moieties for biofunctionalization | Smooth morphology; tunable degradation; improved cell adhesion | [11, 13–15] |
| | GalA carboxyl groups (ionic) | Sequential $Ca^{2+}$ + ADH/ glutaraldehyde crosslinking | Ionic stabilization + covalent locking; regulates degradation | Enhanced tensile strength, swelling, and shape recovery in wet conditions | [11, 16] |
| Physical | Side chain density / DE / RG-I ratio | UAE | Cavitation-mediated partial scission; reduced DE; increased solubility | Homogeneous morphology; higher gel strength; better spinability | [17, 18] |
| | Anionic backbone and H-bond network | Acidic DMSO solvation and rehydration | Charge neutralization; conformational memory retained after rehydration | Improved spinning and functionalization compatibility | [19] |
| Compositional | Low entanglement polymer matrix | Blending with PEO / PVA | Improved viscosity and chain entanglement for stable jet formation | Bead-free fibers; high mechanical tunability; PEO removable post-spinning | [16] |
| | Surface interface and H-bond donors | Blending with gelatin, pullulan, chitosan | Enhanced viscoelasticity, bioadhesion, and electrostatic compatibility | RGD presentation; improved infiltration and immune modulation | [20–22] |
| | Polymer network + inorganic phase | Filler loading: Cu-MOF, AgNP, HA, $Fe_3O_4$ | Matrix reinforcement; controlled ion release; antimicrobial effect | Multifunctionality: angiogenesis, antibacterial, magneto-responsiveness | [23–26] |
| | π–π interaction and catechol groups | Hybridization with PDA | NIR-triggered heating; hydrogen bonding and π–π stacking | Photoresponsive antimicrobial action; tuning of swelling and mechanics | [27] |

**Note:** AgNP — Ag-based nanoparticles; ADH — adipic acid dihydrazide; Cu-MOF — Cu-based metal organic framework; DE — degree of esterification; DMSO — dimethyl sulfoxide; EDC — 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; HA — hydroxyapatite; NHS — N-hydroxysuccinimide; NIR — near-infrared; PDA — polydopamine; PEO — polyethylene oxide; PVA — polyvinyl alcohol; RGD — arginine, glycin and asparagine; UAE — ultrasound-assisted extraction; UV — ultraviolet.

environments [10]. In freeze-dried systems, ADH-mediated crosslinking further influences ice nucleation and porosity, reinforcing the impact of molecular design on final scaffold architecture [11].

Another effective strategy is methacrylation, which introduces photo-crosslinkable groups onto hydroxyl or carboxyl sites via methacrylic anhydride. Upon ultraviolet (UV) exposure, these groups undergo polymerization, forming dense covalent networks that improve aqueous stability and enable spatially controlled post-processing. Methacrylatedpectins, applied in dermal and

injectable constructs, exhibit tunable stiffness (20–70 kPa), suitable for soft tissue applications [29]. This chemistry also supports orthogonal thiol–ene conjugation with peptides or proteins under mild conditions, facilitating bioactive functionalization [19]. In dual-crosslinkable systems such as pectin methacrylate /gelatin methacryloyl hydrogels, methacrylation allows integration of ionic $Ca^{2+}$ bridges with UV-induced curing, yielding injectable scaffolds with effective hemostasis and porous architecture [4].

Amidation, typically via 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) coupling, converts carboxyl groups into amides, reducing surface charge and improving electrospinnability by minimizing electrostatic repulsion during jet formation. The incorporation of primary amine groups also enables post-spinning biofunctionalization, for example the immobilization of cytokines or integrin-binding motifs. Pectin scaffolds modified in this way promote fibroblast adhesion and proliferation, as well as cell infiltration in aligned fiber architectures [30]. Beyond enhanced biological performance, amidation with ammonia or neutral amino acids (e.g., alanine) has been shown to improve rheology, gel strength, and crosslinking efficiency by increasing hydrogen bonding and decreasing crystallinity [11, 14]. Additionally, amidated pectins exhibit strong flocculation capacity, with efficiency correlating to the degree of amidation, supporting their multifunctionality in both biomedical and environmental contexts [15].

Hybrid ionic–covalent crosslinking provides synergistic stabilization of electrospun pectin networks by combining rapid ionic interactions with long-term covalent fixation. Post-spinning treatment with $Ca^{2+}$ induces reversible “egg-box” complexes with galacturonic acid residues, offering immediate wet integrity, which can then be permanently reinforced via ADH- or glutaraldehyde-mediated covalent bonding. This sequential approach yields dual-crosslinked fibers with improved tensile strength, reduced degradation, and enhanced dimensional recovery under hydration cycles. These properties are relevant for mechanically active tissues such as oral mucosa or dermal wounds [16]. In freeze-dried systems, such hybrid crosslinking also modulates pore architecture by altering hydrogen bonding and ice crystal growth, leading to more structured and interconnected porosity [11]. These strategies exemplify how targeted molecular engineering can produce robust and responsive scaffolds tailored to demanding biomedical environments.

## Physical modifications

Physical modification techniques offer a structurally conservative yet functionally effective means of tailoring pectin’s macromolecular behavior for electrospinning. Unlike covalent derivatization, these approaches act at the supramolecular level, modulating chain conformation, intermolecular forces, and hydration behavior without altering the primary structure. This is useful in situations where regulatory requirements or material compatibility limitations restrict the use of chemical modification. Ultrasound-assisted extraction (UAE) is among the most impactful methods: it introduces localized cavitation, leading to partial cleavage of glycosidic bonds, reduced molecular weight, and disruption of side-chain aggregation, thus physical treatment leads to chemical modifications. These effects enhance solubility, viscosity, and entanglement. In sunflower pectin, UAE improved gel strength and storage modulus at lower $Ca^{2+}$ concentrations, indicating increased crosslinking efficiency [17]. Similar benefits were observed for *Actinidia*

*arguta* and *Cucurbita pepo*, where UAE higher viscosity, lower methylation (suggesting demethoxylation), and better gelation behaviour, which supports electrospinning [18].

Other physical levers such as pH modulation during extraction or processing influence the ionization state of galacturonic acid residues and the resultant chain conformation. Acidic environments (pH 2–3) protonate carboxyl groups, promoting coil-to-globule transitions, suppressing electrostatic repulsion, and enhancing intrachain hydrogen bonding. These changes increase solution viscosity and improve fiber formation. Microwave-assisted extraction at low pH yielded pectins with reduced crystallinity and broader surface morphology, facilitating uniform jetting and nanofiber uniformity [31, 32]. In contrast, pectins extracted at neutral or alkaline pH often retain extended, highly charged conformations that hinder chain entanglement and destabilize fiber jets. Thermal conditioning, including mild drying or controlled lyophilization, can further increase polymer packing density by rearranging hydrogen bonding patterns and removing excess water, thereby enhancing jet stability. For instance, orange peel-derived pectin subjected to sequential dehydration produced hydrogels with pseudoplastic behavior and dominant storage modulus — properties linked to improved electrospinnability and scaffold shape retention under physiological hydration [33].

An additional route involves solvent-mediated restructuring, particularly via dissolution in acidified dimethyl sulfoxide (DMSO). This system temporarily neutralizes anionic groups and disrupts intra- and interchain hydrogen bonding, enabling reversible conformational transitions. Upon rehydration, partial structural “memory” is retained, improving interchain association and promoting uniform fiber formation. Furthermore, DMSO provides a compatible reaction medium for subsequent chemical modifications, such as oxidation or methacrylation, supporting an integrated design strategy that combines physical and chemical tuning [19]. These physical approaches improve the reproducibility and performance of electrospun pectin while maintaining biocompatibility, which is important for further biomedical development.

## Compositional modifications

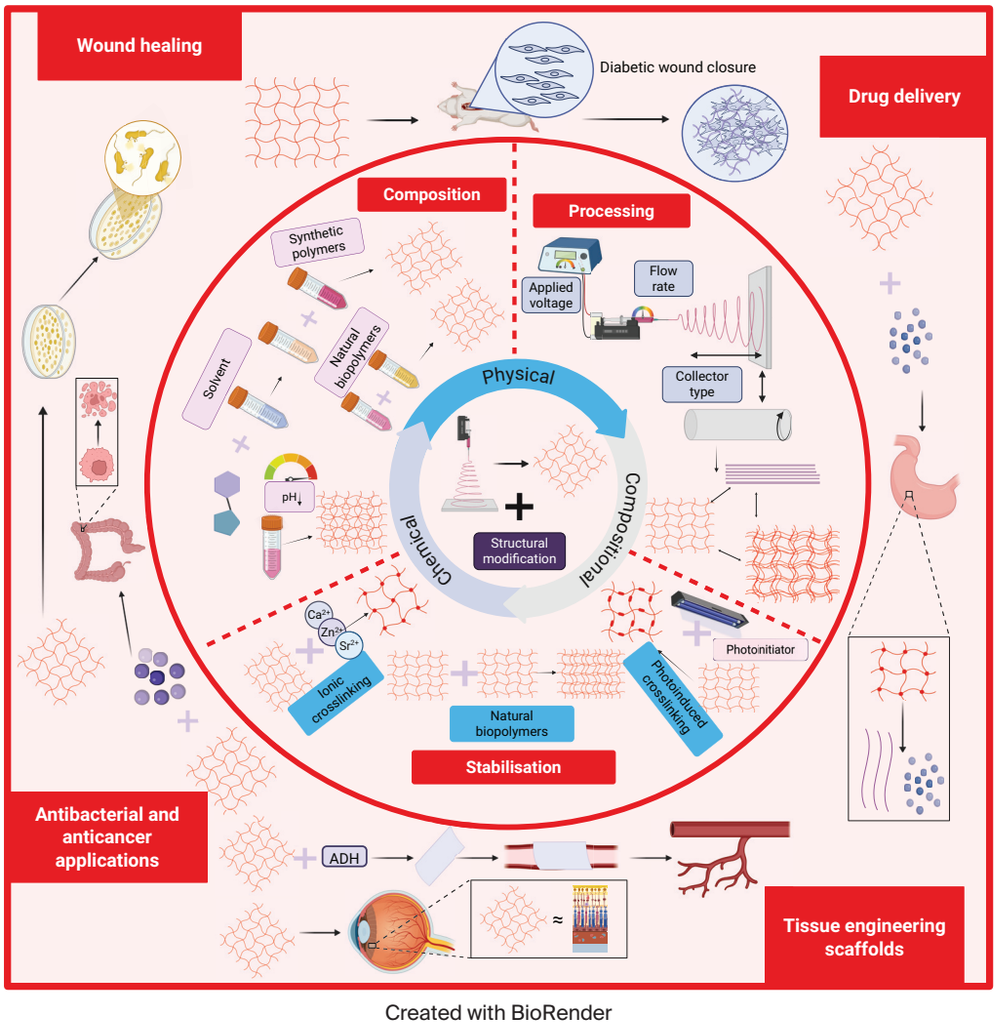
Compositional modification offers a modular strategy to overcome the intrinsic limitations of native pectin — such as poor chain entanglement, low viscoelasticity, and high hydrophilicity — by incorporating synthetic or natural polymers, bioactive agents, and nanofillers into electrospinning formulations. The most established approach is blending with synthetic carriers like PEO and PVA. PEO enhances entanglement and elasticity, while PVA improves hydrogen bonding and viscosity. Pectin/PEO blends containing as little as 10–35% PEO (v/v) enable the formation of bead-free, uniform fibers with tunable porosity and Young’s moduli up to 358 MPa, depending on source material and crosslinking strategy [16]. Notably, formulations with low PEO content permit selective post-spinning removal, yielding purer fiber matrices with tailored architecture.

Incorporation of natural biopolymers, such as gelatin, pullulan, and chitosan, introduces bioactivity and improves matrix–cell interactions. Gelatin has been employed both as a co-electrospinning component and as a post-spinning crosslinker, increasing fiber diameter, tensile strength, and cellular infiltration via arginine-glycine-asparagine (RGD) motifs and

balanced degradation [20]. Pullulan reduces solution surface tension and stabilizes jet formation by modulating ionic mobility, enabling finer fiber formation suitable for mucosal or nutraceutical applications [21]. Chitosan–pectin polyelectrolyte complexes exhibit pH-responsive swelling, protein adsorption, and immunomodulatory potential; PEC–Chi blends with up to 75% chitosan demonstrate reduced leukocyte adhesion and enhanced biofunctionality [22]. These blends improve not only electrospinnability but also downstream biological performance through controllable interfacial and rheological properties.

Beyond polymer–polymer systems, the addition of inorganic nanofillers expands the functionality of pectin-based fibers. Embedding Cu-MOFs into pectin/PEO scaffolds improves mechanical strength and imparts antibacterial and pro-angiogenic effects via sustained $Cu^{2+}$ release [23]. Similarly, incorporation of Ag-based nanoparticles, hydroxyapatite, and bioactive glass provides antibacterial, osteoinductive, or antioxidant properties depending on concentration and dispersion quality [24, 25, 34]. $Fe_3O_4$-nanoparticles introduce magnetic responsiveness, though excessive loading (>5 wt%) can compromise fiber cohesion due to aggregation [26]. In parallel,

**FIG. 2.** Schematic representation of the relationship between structure, properties, and functions, as well as representation of biomedical applications of pectin-based materials

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integration of photothermal agents such as polydopamine (PDA) enables near-infrared (NIR)-triggered antibacterial activity (>99.9% reduction of S. aureus) while reinforcing network stability via π–π interactions and enhanced hydrogen bonding [27]. Composite systems combining polymers and fillers, for example, pectin/gelatin/ADH-crosslinked matrices, provide combined control over degradation, water uptake and mechanical behaviour within ranges relevant to soft tissues [10]. Such designs require careful balancing of miscibility, electrostatic interactions, and nanoparticle compatibility to yield homogeneous, high-performance fiber architectures. Collectively, compositional modification enables multifunctional nanofibrous scaffolds tailored for wound healing, tissue engineering, and localized therapeutic delivery.

## Electrospinning strategies for pectin-based nanofibers

The successful fabrication of functional pectin-based nanofibers requires precise coordination between material properties and electrospinning parameters. While chemical, physical, and compositional modifications improve solubility, entanglement, and interfacial behavior, these alone do not guarantee stable fiber formation. Effective electrospinning demands a formulation strategy that balances viscoelasticity, surface tension, and charge distribution, along with process optimization of voltage, flow rate, and collector distance tailored to the physicochemical profile of the system. Fiber morphology and uniformity are further influenced by post-spinning stabilization methods such as ionic gelation or photo-crosslinking. As summarized in Figure 2, electrospinning of pectin is fundamentally a multi-parametric design process in which material formulation, processing conditions, and crosslinking converge to define scaffold architecture and biofunctionality.

## Solution engineering strategies for electrospinning of pectin-based systems

Electrospinning of native pectin is limited by low molecular entanglement, high charge density, and polyelectrolyte behavior in aqueous systems. Even at >4% (w/v), solutions exhibit low viscosity (<0.3 Pa·s) and high conductivity (>1.5 mS/cm), preventing stable jet formation. McCune et al. showed that unmodified pectin yields only droplets or fragmented filaments, with continuous spinning achievable only upon blending with ≥35% PEO (w/w) [13].

Synthetic polymers such as PEO, PVA, and polyethylene glycol (PEG) are widely used to restore entanglement and stabilize jets. Pectin–PEO blends (60:40 to 70:30 w/w) increase viscosity to 1.5–4.5 Pa·s, enabling uniform fibers of 130–200 nm at standard voltages and flow rates [13, 35]. PVA (87–98% hydrolyzed, >80 kDa) promotes hydrogen bonding and yields fibers up to 2.4 MPa in modulus [36], though often requires post-spinning removal. PEG, while less effective for entanglement, serves as a plasticizer or drug carrier. Hydrophobic polyesters like polycaprolactone and poly(lactic-co-glycolic) acidimprove mechanical properties but necessitate organic solvents incompatible with native pectin.

Natural polymers such as gelatin, chitosan, and pullulan add biofunctionality and influence solution properties. Gelatin enhances viscoelasticity

(G′ ~450 Pa), introduces RGD motifs, and improves fiber cohesion [20]. Chitosan forms electrostatic complexes with pectin, increasing pH-responsive swelling and structural stability [22]. Pullulan reduces conductivity by ~30%, promoting uniform fibers <150 nm and enabling gentle encapsulation of bioactives [21].

Solution electrospinnability is also sensitive to pH, ionic strength, and solvent composition. Acidification to pH 2.5–3.0 reduces ζ-potential and promotes coil compaction, improving jet stability and fiber homogeneity, particularly in rhamnogalacturonan-I-rich, low-methoxylpectins [31, 37]. Moderate salt addition (10–50 mM NaCl) screens electrostatic repulsion, but excess (>100 mM) can induce premature gelation. Solvent blends with 20–40% methanol or isopropanol help fine-tune interfacial tension and drying kinetics; e.g., methanol reduces fiber diameter (~150 nm) but increases surface porosity via peripheral phase separation [36]. For modified pectins, acidified DMSO enables dissolution up to 6% (w/v), shields ionic groups, and supports post-spinning chemistries such as Schiff-base or thiol–ene crosslinking [19]. However, its low volatility requires careful optimization of flow and humidity to avoid fiber fusion. Thus, precise control of solvent properties, including polarity, dielectric constant and evaporation rate, is important for adjusting fiber morphology and properties in pectin-based electrospun scaffolds.

## Processing–structure relationships in electrospun pectin fibers

Optimization of electrospinning parameters for pectin systems must account for polymer structure and chain flexibility. High-methoxyl, low-methoxyl, and rhamnogalacturonan-I–rich pectins differ in stiffness, hydration, and gelation, affecting their response to voltage, flow rate, and collector distance. Low-methoxyl variants with high charge density and rhamnogalacturonan-I content require greater collector distances (≥15 cm) to prevent premature mat densification [36], while oxidized or amidated pectins permit lower voltages (12–14 kV) and shorter jet paths due to increased hydrophobicity and crosslinking potential [19]. Solvent systems also influence behavior: DMSO enables gradual elongation but necessitates low humidity and reduced flow rates (<0.4 mL/h), whereas acidified aqueous blends tolerate higher flow but become unstable above 18 kV. As no universal regime exists, spinning conditions must be tailored to each formulation, linking molecular architecture to jet dynamics and fiber formation.

Fiber morphology in pectin-based systems reflects the interplay between solution properties, electrohydrodynamic forces, and solidification dynamics, all modulated by polymer chemistry. Pectin–PEO blends (70:30 w/w) produce uniform fibers (130–200 nm) under 15–18 kV and 0.6 mL/h, while higher flow or voltage induces beads and ribbon defects [13]. Gelatin incorporation into oxidized pectin improves circularity and diameter uniformity via enhanced hydrogen bonding and slower relaxation [20]. Solvent volatility further shapes morphology: DMSO promotes dense, smooth fibers through gradual evaporation, while ethanol–water blends yield microporous structures via phase separation [19, 37]. Collector design influences fiber architecture: rotating drums generate aligned nanofibers, whereas static collectors produce isotropic mats. Alignment effects are well established for electrospun polymers, although pectin-specific mechanical data under controlled orientation have not yet been reported.

The type of pectin influences network architecture: low-methoxyl pectins form more compact networks, whereas rhamnogalacturonan-I–rich pectins form less compact and more heterogeneous structures because their intermolecular cohesion is lower. Architectural parameters such as orientation, interfiber spacing, and porosity govern both mechanical properties and biological response. Aligned fibers enhance tensile strength and promote directional mesenchymal stem cells migration [1], while random mats offer higher porosity and greater drug loading. Porosity is influenced by solvent behavior (more compact in DMSO and more porous in ethanol [19, 37]) and by chemical modifications, including oxidation, which promotes inter-fiber crosslinking and increases mesh density. Gelatin-rich blends improve elasticity and allow more compliant deformation [20].

These findings highlight the absence of a universal electrospinning regime for pectin-based systems. Unlike synthetic polymers with predictable rheology, pectin formulations vary with source and modification, necessitating precise control of voltage, flow, humidity, and solvent conditions. Importantly, fiber morphology is not a passive outcome but a key determinant of mechanical performance, cell interaction, and release dynamics. Considering the relationship between processing and structure allows adjustment of scaffold architecture, from dense and crosslinked meshes for controlled delivery to more open and aligned structures for tissue regeneration. This range shows that pectin can be electrospun into different scaffold types. Mastery of these interdependencies is critical for application-specific translation.

## Post-spinning stabilization and crosslinking strategies for pectin nanofibers

Although electrospun pectin fibers offer tunable morphology and nanoscale architecture, they are intrinsically unstable in aqueous environments due to their hydrophilic and soluble nature. Unlike synthetic polymers with crystalline or hydrophobic domains, pectin lacks sufficient cohesion to resist swelling or dissolution, limiting its use in biomedical contexts without further stabilization. Post-spinning crosslinking, which may be ionic, covalent, or photoinduced, is required to provide water resistance, mechanical stability and control of degradation.

Unlike pre-spinning modifications (e.g., oxidation, methacrylation), these strategies act directly on the fiber network, influencing inter-fiber adhesion and pore retention. Covalent stabilization via Schiff-base chemistry has been widely applied: Zheng et al. showed that ADH-crosslinked oxidized pectin scaffolds maintained tensile strength >2 MPa, >1200% water uptake, and degradation half-times >14 days [10]; Cui et al. reported reduced mass loss in PBS (Phosphate-Buffered Saline) (<20%) and increased modulus (1.2 → 2.1 MPa) [16]. Similar results were obtained in antibiotic-loaded systems, achieving both sustained drug release and structural robustness [38]. These findings underscore that crosslinking is not merely reinforcing but defines the mechanical and functional identity of pectin-based scaffolds.

Ionic crosslinking with $Ca^{2+}$, $Zn^{2+}$, or $Sr^{2+}$ offers a rapid, biocompatible means of stabilizing pectin fibers via ‘egg-box’ junctions formed with galacturonic acid residues. However, such reversible interactions may degrade under physiological conditions. To enhance durability, dual-crosslinking strategies have been developed: Shi et al. combined $CaCl_2$ treatment with glutaraldehyde fixation in pectin–gelatin fibers, improving tensile resilience and hydrolytic

resistance [20]. Belousov et al. demonstrated that tuning methoxylation in $Ca^{2+}$-gelled low-degree of esterisation pectin ionogels modulates G′ across ~4–870 Pa, highlighting the versatility of purely ionic systems [39]. Photoinitiated crosslinking offers an orthogonal approach, particularly for methacrylated pectins. Upon UV exposure with photoinitiators (e.g., Irgacure 2959, LAP), pendant vinyl groups polymerize into inter-fiber covalent networks. Dong et al. showed UV-crosslinked scaffolds with compressive moduli >30 kPa and stability in proteolytic media over 3 weeks — metrics aligned with soft tissue needs [4].

Polymers like gelatin and PDA further enhance performance: gelatin provides reactive amines and RGD motifs, while PDA improves bonding and introduces photothermal antimicrobial function under NIR light [27]. Choice of crosslinking must align with application: ionic systems suit transient scaffolds; covalent and photoinduced strategies are preferable for load-bearing or long-term platforms. Crosslinking influences stiffness, degradation, and ligand presentation. This means that crosslinking acts not only as structural reinforcement but also as an important factor in controlling the functional behaviour of biomaterials.

## Biomedical applications of electrospun pectin-based nanofibers

Electrospun pectin nanofibers combine nanoscale architecture, physicochemical adaptability, and bioresponsive behavior, enabling their use across diverse therapeutic settings. While formulation and processing determine structural integrity, biomedical utility depends on matching physiological demands, including moisture retention, enzymatic degradation, cell adhesion and bioactive delivery.

Thanks to inherent biofunctionality and molecular compatibility, pectin scaffolds have been explored for wound healing, drug delivery, tissue regeneration, and antimicrobial or anticancer therapy [7, 40, 41]. Figure 2 summarizes these modular applications and their structural design logic. Subsequent sections detail the relationships between fiber architecture, material behavior, and therapeutic function.

## Wound healing

Electrospun pectin-based nanofibrous scaffolds are increasingly recognized as multifunctional platforms for wound healing, capable of integrating mechanical protection, moisture regulation, redox buffering, and immunomodulatory activity into a single biomaterial construct. Structurally, pectin's carboxyl-rich backbone facilitates water uptake and hydrogel-like behavior under physiological conditions, while blending with co-polymers such as PEO, sulfonated polyimides, gelatin, or zein enables tailoring of fiber morphology, swelling capacity, and tensile strength. Mirhaj et al. developed bi-layered scaffolds composed of cellulose microfibers and pectin–soy protein–pomegranate peel nanofibers, achieving swelling ratios above 900%, pore diameters between 450–650 nm, and tensile strength up to 3.57 MPa. These values fall within the range reported for native dermal tissue [6]. These matrices provided effective exudate management and vapor transmission (~1250 g/$m^2$/day), while promoting re-epithelialization and granulation in full-thickness wound models.

In parallel, Fiorentini et al. reported zein–pectin–vitamin C microfibers that exhibited antioxidant activity in HaCaT keratinocytes, reduced intracellular reactive oxygen species by >50%, and downregulated pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in ultraviolet B (UVB)-inflamed murine skin [3]. These redox effects translated into improved collagen I expression and accelerated wound closure. Similar outcomes were observed by Gao et al., who embedded dihydromyricetin in pectin/chitosan/PVA membranes via cyclodextrin complexation; the resulting scaffolds showed high mechanical integrity (modulus ~2.2 MPa), sustained antioxidant release, and >89% closure in diabetic wound models by day 14 [7].

In addition to oxidative stress modulation, anti-inflammatory functionality has been engineered through encapsulation of phosphatidylcholine liposomes and antibiotics. Schulte-Werning et al. developed pectin–PEO nanofibers loaded with chloramphenicol-containing liposomes that suppressed nitric oxide production and TNF-α expression in LPS-activated macrophages, while maintaining fibroblast viability and barrier integrity [5]. These immunoregulatory effects were accompanied by stable mechanical performance (σ = 4.2 MPa) and sustained fiber integrity upon hydration.

These studies demonstrate that electrospun pectin scaffolds can be engineered to adjust structure and function and to reproduce microenvironmental conditions relevant to wound repair, including hydration control, matrix stability, oxidative balance, and inflammation resolution. These findings indicate that such scaffolds can be applied in both acute and chronic wound settings. Multiple preclinical studies in both *in vitro* and *in vivo* models show that specific compositional and structural features of pectin-based matrices, for example network density, the type of crosslinking or the presence of particles, influence functional outcomes such as wound closure, granulation tissue formation and antimicrobial activity (Table 2).

**Table 2.** Structure–function outcomes of pectin-based materials in preclinical wound healing models

| Material / Structure | Biological model | Size | Key properties | References |
|---|---|---|---|---|
| Electrospun nanocomposite fibers gelatin-PCL/PVA-Pectin | *S. aureus* and *P. aeruginosa* | - | The inhibitory effect on S. aureus and P. aeruginosa was 8.4 and 22.6% respectively. Mats exhibited excellent blood and cell compatibility and stimulated cell migration *in vitro* | [41] |
| Hydrogel: pectin + Na-/Zn-alginate particles | Human fibroblasts (PCS-201-012) | - | Release efficiency >86% within 5 h; supports fibroblast proliferation | [42] |
| Nanocomposite hydrogel: $TiO_2$–chitosan–pectin | Rats (140–180 g), full-thickness wounds | 2×2 cm | Wound closure 99.1% by day 16; advanced epidermis/dermis structure | [43] |
| Pectin–honey hydrogel | Rats (225–250 g), 2×2 cmwounds | 2×2 cm | Complete wound healing by day 23; hair follicles present | [44] |
| Hydrogel: AgNPs/pectin/ polyacrylic acid | Rats (180–220 g), circular wounds, 8 mm | 8 mm | 90% closure by day 14; regeneration with follicular structures | [45] |
| GSNO-loaded pectin–alginate powder dressing | Mice (7 weeks), circular wounds, 8 mm | 8 mm | Reactive NO release; 6-log reduction of MRSA, 90% closure by day 10` | [46] |
| Alginate-Pectin hydrogel | Rats (Wistar), circular wounds, 8 mm | 8 mm | Angiogenesis stimulation; 99% closure by day 21 | [47] |
| Composite film: pectin–alginate–HA | Mice (ICR, 7–8 weeks), circular wounds, 8 mm | 8 mm | Controlled drug release over 12 h; antibacterial efficacy maintained | [48] |
| Phosphorylated pectin hydrogel | Mice (5–6 weeks), wounds 7 mm | 7 mm | Granulation resolved by day 14; 89% closure, hair follicle regeneration | [49] |
| Electrospun oxidized pectin–gelatin scaffold | Rats (140–180 g), wounds 2×2 cm | 2×2 cm | 99.3% closure by day 12; scar-free epithelialization | [50] |

**Note:** AgNPs — Ag-based nanoparticles; GSNO — S-nitrosoglutathione; HA — hyaluronic acid; MRSA — Methicillin-resistant; Staphylococcus aureus

## Drug delivery

Electrospun pectin-based nanofiber systems have garnered significant attention as advanced platforms for controlled drug delivery due to their high surface area, tunable porosity, and capacity to stabilize and release sensitive therapeutic agents under physiologically relevant conditions. The intrinsic mucoadhesiveness, pH-sensitivity, and hydrophilic nature of pectin provide a versatile framework for achieving both rapid and sustained release kinetics depending on the formulation strategy.

In one representative study, Bernardi et al. incorporated cloxacillin into polycaprolactone: pectinelectrospun membranes reinforced with faujasite (FAU)-type zeolite, producing nanofibers with high mechanical integrity ($\sigma = 3.1 \pm 0.3$ MPa), increased hydrophilicity (contact angle 97°), and controlled drug release over 229 hours in phosphate buffer at pH 5.5, achieving plateau concentrations up to 6.18 mg/L [51]. The zeolite acted not only as a structural filler but also as a modulator of antibiotic retention and release, while maintaining antimicrobial efficacy against S.aureus via 28 mm inhibition halos. Similarly, Wei et al. developed pectin–ethylcellulose core–shell nanofibers for colon-targeted lactoferrin delivery, where the outer pectin emulsion shell acted as a pH-responsive gatekeeper, delaying protein release in simulated gastric fluid and achieving complete release in the colonic environment within 3–10 hours, depending on pectin content [52].

For probiotic delivery, Nawaz et al. encapsulated *Lactobacillus acidophilus* into PVA–pectin fibers, achieving 82.9% encapsulation efficiency and ≥7 log CFU (Colony-Forming Unit)/mL viability retention after simulated gastrointestinal digestion, demonstrating that the fibrous matrix offered superior protection against acidic and bile salt stress [53]. The drug release capabilities of pectin nanofibers have also been enhanced by incorporation of antioxidant or anti-inflammatory phytochemicals: Guo et al. demonstrated sustained release of dihydromyricetin from pectin/chitosan/PVA membranes over 72 h, promoting wound closure in diabetic models via redox signaling modulation [7], while Fiorentini et al. achieved reactive oxygen species scavenging and cytokine suppression in burn models using zein–pectin–vitamin C microfibers [3].

The morphology of electrospun fibers, including fiber diameter, pore structure, and network density, together with physicochemical parameters such as ζ-potential and hydrophilicity, strongly influenced diffusion rates and matrix–payload interactions. Schulte-Werning et al. further demonstrated that pectin/PEO scaffolds embedding chloramphenicol-loaded liposomes could sustain antibiotic release over 48 hours while suppressing nitric oxide production in activated macrophages [5].

Taken together, these studies underscore the adaptability of pectin-based nanofibers as delivery vehicles across dermal, gastrointestinal, and mucosal interfaces, supporting therapeutic strategies that demand localized, temporally controlled, and cell-compatible drug administration.

## Tissue engineering scaffolds

Electrospun pectin-based nanofibers have garnered increasing attention as biointeractive scaffolds for tissue engineering owing to their intrinsic biocompatibility, hydrated extracellular matrix-like architecture, and tunable physicochemical properties.

In vascular tissue models, Li et al. demonstrated that scaffolds fabricated from oxidized pectin and stabilized via ADH crosslinking exhibited oxidation-dependent stiffness gradients (0.12–0.29 MPa) and swelling ratios exceeding 1000%, enabling lineage-specific differentiation of mesenchymal stem cells toward endothelial or smooth muscle phenotypes through matrix-guided mechanotransduction [1]. Complementing this, McCune et al. employed oligochitosan as a nonionic crosslinker, yielding nanofibers with enhanced aqueous stability, positive surface charge, and cytocompatibility, thereby promoting adhesion and proliferation of preosteoblasts — highlighting the potential of pectin matrices for osteogenic applications [13].

In epithelial reconstruction, Lin et al. reported that chitosan–pectin hybrid nanofibers supported robust keratinocyte stratification under air–liquid interface culture, with increased tensile strength (~2.8 MPa), reduced fiber diameter (~160 nm), and sustained hydration capacity, while preserving tight junction integrity and progenitor marker expression [54]. In the ocular domain, Chan et al. incorporated 10–20% pectin into polyhydroxybutyrate nanofibers to mimic Bruch's membrane ultrastructure, significantly enhancing wettability, mechanical compliance, and ARPE-19 cell adhesion, with preservation of epithelial phenotype and cytoskeletal organization [2]. Moreover, Tavakoli et al. devised a bilayer scaffold comprising an electrospun pectin/poly (acrylic acid)/simvastatin basal layer and a platelet-rich fibrin-infused upper layer, which synergistically accelerated angiogenesis and tissue remodeling in dermal wound models [55].

Collectively, these studies underscore the adaptability of pectin nanofibers as instructive microenvironments capable of directing cellular fate and tissue-specific functionality across diverse applications, including vascular, epithelial, osseous, and retinal regeneration — without reliance on supraphysiological stiffness or exogenous growth factors.

## Antibacterial and anticancer applications

Electrospun pectin-based nanofibers have demonstrated significant potential as localized therapeutic platforms for both antimicrobial and anticancer applications due to their inherent biocompatibility, high surface-area-to-volume ratio, and capacity for controlled release of active agents within pathological microenvironments.

In antimicrobial settings, Bernardi et al. developed hybrid polycaprolactone–pectin nanofibers reinforced with 2.5 wt% FAU-type zeolite and loaded with sodium cloxacillin. These composite mats (polycaprolactone:pectin:FAU–cloxacillin) exhibited enhanced mechanical strength (3.1 ± 0.3 MPa), increased hydrophilicity (contact angle 97°), and controlled cloxacillinrelease up to 229 h in phosphate buffer (pH 5.5), achieving peak drug concentrations of 6.18 mg/L. The bactericidal activity against *S. aureus* was confirmed by inhibition zones up to 28 mm, indicating that FAU facilitated both sustained antibiotic release and structural integrity under physiological conditions [51]. Similarly, Guo et al. demonstrated that antioxidant-loaded pectin/chitosan membranes embedding dihydromyricetin produced dual antimicrobial and anti-inflammatory effects, suppressing oxidative stress while promoting wound healing in diabetic murine models [7].

From an oncological perspective, Wei et al. engineered multilayered ethylcellulose–pectin coaxial nanofibers for colonic delivery of lactoferrin. By modulating pectin content in the hydrophilic shell phase (5–20%), they

achieved colon-specific release of lactoferrin within 3–10 hours under fermentation-simulated conditions, with over 95% release efficiency. Importantly, released lactoferrin retained its biological activity, demonstrating dose-dependent suppression of HCT116 colorectal cancer cells via upregulation of apoptosis-associated proteins and downregulation of cell cycle markers in MTT (methyl thiazolyl tetrazolium assay) and Western blot assays [52].

These findings suggest that microstructural tuning of pectin-containing scaffolds not only enables diffusion-governed, environment-responsive delivery but also preserves molecular activity under harsh conditions such as gastrointestinal transit or infected wound environments. Moreover, pectin-based scaffolds co-loaded with polyphenols or flavonoids have exhibited synergistic reactive oxygen species scavenging and antibacterial effects, as demonstrated in UVB-burn and LPS-induced inflammation models using plant-derived antioxidant-loaded nanofibers [3].

Collectively, these studies highlight that compositional and architectural control over pectin-based nanofibers enables development of multifunctional drug-delivery systems that combine sustained bioactive release, barrier function, and targeted modulation of microbial or tumor cell behavior in a broad spectrum of biomedical applications.

## Translational challenges and future directions

The structural heterogeneity of pectin, which reflects both the botanical origin of the material and the variability of industrial processing, is a major limitation for its qualification as a biomedical-grade scaffold material. As a mixture of homogalacturonan and rhamnogalacturonan regions with varying degrees of methyl esterification, acetylation, and branching, pectin exhibits significant batch-to-batch variability in molecular weight, charge distribution, and gelling capacity [36]. These compositional differences, strongly influenced by the choice of extraction protocol (acidic, enzymatic, ultrasound-assisted), translate into unpredictable rheological behavior of spinning solutions and fluctuating electrohydrodynamic stability under high-voltage fields.

Consequently, nanofibers fabricated from such materials often display inconsistent diameters, pore structures, and alignment, which directly affect degradation kinetics, drug release profiles, and cellular interface geometry [1, 10]. Mechanistically, this undermines the reproducibility of scaffold performance, while functionally it complicates regulatory validation, particularly in clinical contexts that demand high levels of batch comparability and mechanistic predictability. The immune-modulatory behavior of pectin scaffolds, including effects on macrophage polarization, dendritic cell activation and cytokine secretion, is sensitive to nanoscale features of fiber topography and surface chemistry. These effects become difficult to control in the absence of defined and standardized input materials.

To address these limitations, there is a pressing need to develop source-agnostic pectin “fingerprints” that integrate compositional, viscoelastic, and immunological descriptors into a predictive, quality-by-design framework. A consolidated overview of these translational constraints and proposed engineering strategies is summarized in Table 3.

Beyond compositional variation, sterilization represents a critical translational bottleneck. Electrospun pectin nanofibers, particularly those crosslinked ionically or via Schiff base chemistry, are highly susceptible to hydrolytic and oxidative degradation during conventional sterilization

**Table 3.** Key translational barriers and engineering-based strategies for electrospun pectin nanofibers

| Barrier | Structural and mechanistic origin | Functional/clinical impact | Engineering-based solution | References |
|---|---|---|---|---|
| Material heterogeneity | Variability in DE, RG-I content, molecular weight due to source/extraction | Inconsistent fiber formation, degradation rates, immune profile | Molecular fingerprinting; source-agnostic specifications; batch QC protocols | [12, 37] |
| Sterilization incompatibility | Hydrolyzable glycosidic bonds, ionic crosslinks; high water content | Scaffold collapse, loss of biofunction, altered immunogenicity | Use of covalent/photo-crosslinking; validation of low-temp sterilization (e.g., peracetic acid) | [6] |
| Cytotoxic crosslinkers | Residual glutaraldehyde, EDC/NHS; undefined degradation products | Inflammation, fibrosis, rejection; regulatory failure | Bioorthogonal, enzymatic or UV-initiated chemistries with GMP-compliant reagents | [16] |
| Immunological unpredictability | Surface charge, fiber topography, uronic acid exposure | Variability in macrophage response, poor tissue integration | Immuno-informed scaffold design; TLR profiling; cytokine mapping; in vitro-in vivo correlation | [3, 7] |
| Lack of design–regulatory integration | Empirical formulation; no traceability of structure–function link | Delayed or failed clinical translation | Structure–function modeling; integration of QC, sterilization, immuno-compatibility into early design stages | [56, 57] |

**Note:** DE — degree of esterisation; EDC — 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; GMP — good manufacturing practice; NHS — N-hydroxysuccinimide;QC — Quality Control;RG-I — rhamnogalacturonan-I; TLR — Toll-like receptor; UV — ultraviolet.

procedures such as autoclaving or gamma irradiation. These methods disrupt labile glycosidic bonds, denature hydrogen bonding networks, and induce chain scission or pore collapse, resulting in irreversible loss of scaffold architecture and mechanical integrity [6]. Additionally, exposure to reactive oxygen species or ionizing radiation can generate surface neoepitopes or alter surface energy in ways that inadvertently trigger inflammatory cascades. Since these physicochemical changes may escape detection by bulk characterization techniques, they pose hidden risks for *in vivo* deployment. . The development of sterilization-compatible design strategies (for example covalent network stabilization, dry-state formulations, or vapor-phase sterilization using agents like peracetic acid or supercritical $CO_2$) is needed to maintain scaffold function and meet clinical requirements while maintaining immunological safety [57].

Another major concern relates to chemical crosslinking. Widely used agents including glutaraldehyde, EDC/NHS, and dialdehydes have been shown to enhance fiber cohesion by promoting the formation of imine, hydrazone, or amide linkages, but they also introduce residual cytotoxic compounds and uncontrolled reaction byproducts that impair scaffold biocompatibility [16]. These chemical residues can disrupt redox homeostasis, induce apoptotic or necrotic responses, and interfere with native protein adsorption, resulting in delayed healing or fibrotic encapsulation *in vivo*. Furthermore, such reagents are rarely GMP-compliant, and their undefined degradation pathways and lack of validated residual assays limit their regulatory acceptability. To advance pectin scaffolds toward clinical use, it is therefore imperative to prioritize the development of safer and more controlled crosslinking strategies, including bioorthogonal, enzymatically cleavable, or photoinitiated chemistries that operate under mild, aqueous conditions while enabling precise tuning of mechanical performance and degradation kinetics.

Bridging the gap between laboratory research and clinical translation requires a shift from empirical formulation to integrative design logic. Despite

their promise, electrospun pectin nanofibers remain underutilized clinically due to the lack of standardized pipelines linking synthesis, processing, and function. Key scaffold features, for example stiffness, porosity or ligand presentation, should be included in models that help predict biological responses such as macrophage polarization or matrix remodeling. With advances in materials informatics and organotypic models, such translation-oriented modeling is now feasible [51], enabling the alignment of material design with regulatory and therapeutic goals.

## Conclusions

Electrospun pectin nanofibers have progressed from an electrohydrodynamically unstable polysaccharide system to a promising class of bioinstructive scaffolds enabled by molecular design and supramolecular control. Specific chemical modifications such as oxidation, amidation, and methacrylation, together with processing choices such as solvent selection, fiber alignment or post-spinning stabilization, determine structural and mechanical properties of pectin-based nanofibers. These engineered features directly influence key biological outcomes, including immunomodulation, tissue integration, and localized therapeutic delivery.

By integrating these multiscale relationships, the proposed structure–property–function framework offers a predictive logic for tailoring pectin nanofibers toward targeted biomedical applications. This approach moves beyond empirical formulation, providing a rational basis for scaffold design grounded in mechanistic understanding. Pectin's responsiveness to ionic, enzymatic, and topographical cues, together with its bioavailability and regulatory potential, supports further development toward clinical use.

However, critical challenges remain, including the lack of GMP-grade pectin, difficulties in sterilization, and limited regulatory acceptance of certain crosslinkers. Overcoming these barriers will require not only compositional and processing innovation, but also integration of immuno-engineering principles, scalable fabrication platforms, and rigorous *in vivo* validation. Advancing electrospun pectin scaffolds from experimental constructs to translationally viable systems will depend on the continued alignment of material science with clinical and regulatory imperatives.

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