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Advances in nanofiber technology for biomedical application: A review

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Abstract

The application of nanofiber technology in the biomedical field has garnered significant interest due to its potential to revolutionize areas such as tissue engineering, wound healing, and antimicrobial treatments. This paper provides a comprehensive review of the recent advancements in nanofiber technology, particularly focusing on electrospinning and 3D printing methods that enable the fabrication of scaffolds mimicking the native extracellular matrix. These technologies have facilitated the development of nanofibers with high surface-to-volume ratios, adjustable porosity, and enhanced mechanical properties, tailored to meet specific biomedical needs. Despite their promising features, challenges such as the optimization of pore size for effective cell infiltration and the mechanical robustness required for hard tissue regeneration remain. The review also explores the evolution of sustainable polymers from natural resources, highlighting their potential to create biodegradable and biocompatible scaffolding materials. Future directions emphasize the need for cross-disciplinary collaboration to overcome current limitations and scale production from laboratory to industrial levels. The ongoing research and development efforts aim to refine the properties of nanofibers to achieve optimal performance in clinical applications, underlining the dynamic and evolving nature of this field.

Keywords: Nanofiber Technology; Electrospinning; Tissue Engineering; Biodegradable Polymers; Clinical Applications

1. Introduction

Over the past century, the rise in polymer utilization has spurred advancements in techniques for producing polymer fibers, meeting the stringent performance demands across various industries and modern applications [1]. Among these developments, nanofibrous materials—1D structures with diameters between 50.0 to 500.0 nm and length-to-diameter ratios exceeding 1:200—have emerged from polymer solutions or melts. Due to their substantial surface area, porosity, and adjustable pore sizes, nanofibers offer significant advantages over bulk materials, particularly in mimicking the extracellular matrix and human tissue structures, which is crucial for organ and tissue regeneration [2,3,4]. Nanofibers are extensively used in medical applications such as bone and nerve tissue engineering, vascular and skin tissue reconstruction, leveraging their unique properties for innovative solutions [4]. Among various fabrication techniques, electrospinning is prominent for creating nanofibers ranging from 3.0 nm to over 5.0 mm in diameter, utilizing electrostatic forces to form layers from polymer solutions. This process accommodates both natural and synthetic polymers [5].

Advancements in this field also include integrating natural and synthetic polymers with ceramics and exploring core-shell fiber geometries to enhance the mechanical properties of electrospun membranes. These enhancements address mechanical strength, wettability, and toxicity [6]. Furthermore, the conditions under which electrospinning occurs, such

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as polymer solution concentration, voltage, and solvent type, can be finely tuned to optimize fiber diameter and material porosity [7,8,9]. As the fiber diameter increases, so does the membrane porosity, enhancing its utility.

The distinctive characteristics of nanofibers have expanded their use beyond biomedical applications to include air filtration, water treatment, cosmetics, textiles, and active materials in photonics and electronics [1,10]. This broad spectrum of applications underscores the growing interest and continuous innovation within the field of nanofibrous materials. The development of petroleum-based polymers has significantly impacted society, offering properties like easy preparation and low cost. Yet, the environmental burden of these non-degradable materials has become a pressing issue, as they contribute substantially to pollution and are not aligned with sustainable practices [11]. The quest for sustainable alternatives—both natural and synthetic—is driven by the need for materials that are biodegradable, recyclable, and safely disposable.

In modern life, polymers are ubiquitous, found in textiles, electronics, healthcare products, and packaging, among others. Sadly, about 95% of these polymers, derived from seemingly inexhaustible sources like ethylene and propylene, do not degrade in the environment [12-14]. Historically, the production of these polymers did not consider their environmental impact, leading to significant waste accumulation, which makes up about 10% of total municipal waste. This waste severely contaminates various ecosystems, from mountains to oceans [15-17]. The field of biomaterials is divided into biocompatible and biodegradable materials. While bio-inert materials like metals and traditional polymers have long been used in medical applications, they remain in the body indefinitely unless surgically removed. Conversely, biodegradable materials are designed to break down into non-toxic components after fulfilling their functional purpose, such as scaffolds in bone regeneration that dissolve once healing is complete [18].

Research is increasingly focused on sustainability across various fields, from economics to materials science. This shift is driven by a global push towards using renewable resources for polymer synthesis and designing biomaterials that degrade within a pre-determined timeframe. The biomaterials market is experiencing rapid growth, with expectations to double from 105 billion USD in 2019 to 206 billion USD in 2024, reflecting a compound annual growth rate of 14.5%. Meanwhile, the production of polymers has surged from 2 million tons in 1950 to 380 million tons in 2015, yet bio-based and biodegradable polymers still represent a small fraction of this volume [19-20].

Recent advancements in nanofiber technology have demonstrated their potential in wound care. For instance, Darabi et al. (2024) highlighted the development of GO/AgNW-aided starch/PVA nanocomposite mats, emphasizing their superiority over conventional bandages by providing an excellent environment for wound healing through sustained release of ciprofloxacin[21] . Similarly, the work by Ziabari et al. (2024) on bilayer nanofibers loaded with Malva sylvestris extract showcased enhanced wound healing applications through prolonged extract release, ensuring a sustained therapeutic effect [22]. These studies underline the significant strides being made in the field, illustrating the pivotal role of sustainable nanofibers in advancing wound care solutions.

The integration of nanotechnology in wound care has led to the development of innovative materials that significantly enhance healing processes. Among these, sustainable nanofibers are particularly noteworthy due to their ability to mimic the extracellular matrix, supporting cell attachment and proliferation, and facilitating sustainable medical applications. Recent studies highlight the dynamic capabilities of these materials in wound management. For instance, Sen et al. (2024) explore smart nanofibrous hydrogel dressings that not only aid in infection control but also adapt to the wound environment, offering real-time diagnostics and therapeutic interventions [23]. Similarly, Singh et al. (2024) discuss the development of airbrushed nanofibers with a bioactive core and antibacterial shell, tailored for enhanced wound recovery and infection prevention [24]. Firdous et al. (2023) reviews the advances in transdermal delivery systems using biomaterial-based strategies that include nanofibers for the sustained release of antimicrobial peptides, demonstrating significant potential in managing complex wounds [25]. Celebioglu and Uyar (2023) present a green synthesis approach for polycyclodextrin/drug inclusion complex nanofibrous hydrogels, emphasizing their pH-dependent drug release capabilities essential for effective wound care [26]. Moreover, Prabhu et al. (2023) provide insights into how nanomaterials, particularly nanofibers, are transforming wound management through enhanced drug delivery and healing efficacy [27]. These studies collectively underscore the crucial role of sustainable nanofibers in advancing wound care solutions, aligning with both environmental sustainability and clinical efficacy.

Tissue engineering aims to develop scaffolds that act as temporary replacements for the native extracellular matrix (ECM), facilitating the regeneration of specific tissues. This field integrates advancements in biomaterial sciences and cellular transplantation to create bioartificial tissues for repairing various types of tissue damage, such as skin [28], cartilage [29], bone [30], nerve [31], and vascular tissues [32]. Despite numerous efforts over the past three decades to produce small-diameter vascular grafts for clinical use, many have not met the necessary standards for application, prompting a shift towards cell-based methods that more closely mimic the ECM [33].

Electrospinning plays a crucial role in scaffold fabrication, offering micro- and nanoscale topography that is conducive to tissue repair and regeneration. Electrospun nanofiber scaffolds (ENFSs) mimic the ECM's porous network, which is essential for cellular growth and organ development. These scaffolds must be biocompatible, highly porous, and capable of gas exchange while possessing the mechanical strength to support bioactive molecule transfer for cell adhesion, growth, and migration [34,35,36].

Additionally, tissue engineering scaffolds aim to replicate the native extracellular matrix (ECM) and must possess essential qualities such as biodegradability, non-immunogenicity, cost-effectiveness, and ease of fabrication. Electrospun nanofibers are particularly notable in this context for their high surface area-to-volume ratio and porosity, which support effective nutrient exchange and cellular interactions vital for tissue regeneration. The adaptability of nanofibers is enhanced through surface functionalization techniques, allowing for the integration of bioactive molecules that promote specific cellular responses critical for repairing various tissues. Functionalization of nanofibers can be achieved via pre-treatment, where modifiers are mixed with spinning materials before electrospinning, or post-treatment, which involves modifying the surface of already formed nanofibers. These methods ensure that nanofibers are optimized for targeted applications, such as bone, nerve, vascular, and skin tissue regeneration [37]. This versatility not only meets the diverse requirements of different tissue types but also maximizes the effectiveness of the scaffolds in enhancing tissue repair and regeneration.

While numerous reviews have documented the use of electrospun nanofibers across various specialized areas, this article aims to shed light on the most innovative and promising research directions involving electrospun nanofibers within several domains of biomedical science. It will also discuss recent advancements, identify prevailing challenges, and outline future prospects in the utilization of these nanofibers, particularly focusing on their sustainable applications. This analysis is intended to assist researchers in bridging the existing gaps in the application of electrospun nanofibers in explored biomedical fields, enhancing both the sustainability and efficacy of these materials.

1.1. Nanofibers Fabrication

Numerous techniques are available for producing nanofibers, including methods like melt spinning [38], air jet spinning[39], template synthesis[40], drawing[41], electrospinning [39-42] (which includes random, aligned, and core-shell nanofibers), self-assembly[43], centrifugal spinning[44], and phase separation[45]. Of these, electrospinning stands out as a cost-effective and straightforward approach for creating nanofibers from a vast array of polymers in both nano- and micro-scale dimensions [46]. The electrospinning process utilizes an electric field to transform a polymer solution or melt into fibers [47]. Electrospun nanofibers are distinguished by their high surface-to-volume ratio, dense pore structure, and superior surface adhesion, making them highly useful across various applications [48-50]. The specific morphology of electrospun nanofibers is influenced by the choice of material and the processing conditions used [51]. (Table 1)

Table 1 Influencing Factors on the Structure of Electrospun Polymer Nanofibers [51]

Parameters	**Effect on Fiber Morphology**
Solution Parameters	
↑ Molecular weight of polymer	↓ Beads and droplet formation Formation of irregular shape with larger pores
↑ Polymer concentration (viscosity)	↓ Bead formation ↑ Fiber diameter (within optimal range)
↑ Solution conductivity	↓ Uniform bead-free fibers Fiber diameter with broad diameter distribution
↑ Solvent volatility	Generation of pores on the surface fiber (microtexture)
Processing Parameters	
↑ Applied voltage	↑↓ First fiber diameter, after that with bead formation
↑ Distance between tip and collector	(working distance) ↓ Fiber diameter Bead formation occurs in too short or too far distance Minimum distance is required for uniform fibers generation
↓ Feed rate/flow rate	↓ Fiber diameter Bead formation with very high feed rate
Ambient Parameters	

↑ Temperature	↓↓ Fiber diameter and viscosity
↑ Humidity	Generation of circular pores on the fibers
↑ Air velocity	↑ Fiber diameter

1.2. Electrospinning

Electrospinning is an effective, economical, and flexible method for producing nanofiber layers with diameters ranging from 3.0 to over 5.0 nm. This process utilizes a high-voltage electric field to elongate droplets of injected polymer solutions [52,53,54,55]. The applied high voltage encourages the interaction between charged polymer precursors and external electrical fields, leading to the creation of polymer nanofibers (PmNFs) [52], as shown in Figure 1. The high-voltage power source, which can deliver several tens of kilovolts [53], allows the resulting nanofibers to exhibit distinctive properties such as increased surface areas and both inter- and intra-fibrous porosity. This technology is widely used to develop one-dimensional (1D) continuous polymeric materials and 1D nanocomposites or inorganic materials [54].

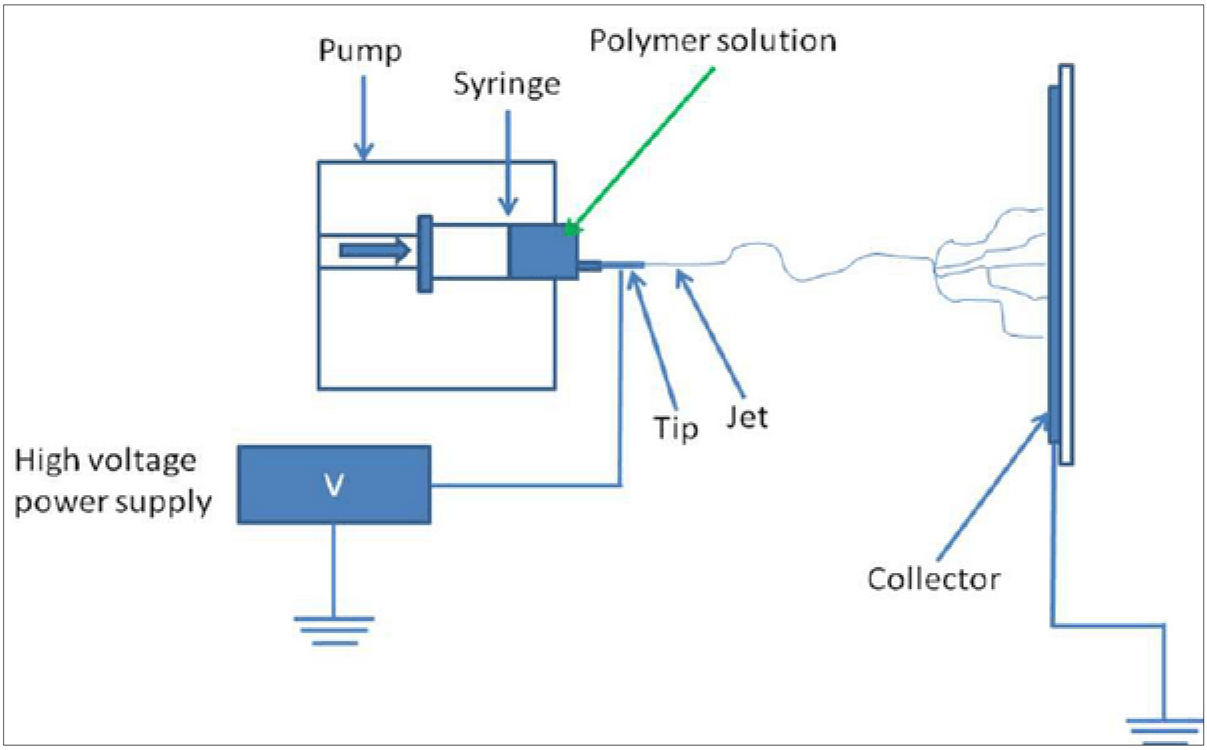

Figure 1 Electrospinning process [55]

1.3. Nanofiber Applications

Nanofibers exhibit unique features such as a high aspect ratio, extensive porosity, and the capability to integrate active substances at a nanometric scale, benefiting various industries like semiconductors [55], protective materials [56, 57], water treatment [58], clean energy [59], and enzyme immobilization [60], along with biosensor immunoassays [61]. Particularly in the biomedical sector, their use spans drug delivery systems, tissue engineering, and wound care [62, 63], where they enhance functionality, such as efficient drug dispersal in wound dressings due to their porous nature, and tissue compatibility in engineering applications [64, 65].

1.3.1. Applications in biomedical field

In the realm of medical applications, nanofibers mimic the nanoscale fibrous composition of human tissues like bone, skin, and collagen, driving research in biomedical engineering [66]. Their properties are akin to the extracellular matrix, making them suitable for various medical uses, including implants, drug delivery systems, and biomimetic devices. Specifically, nanofibrous materials facilitate controlled drug release and targeted delivery through specially designed membranes [67].

1.3.2. Bone cell proliferation

Bone cell proliferation is complex and limited by defects that impede self-regeneration. In the past decade, various bionanomaterials have been developed to create porous scaffolds that replicate the structure of the natural extracellular matrix (ECM) [68,69,70]. These scaffolds are crucial in the replacement and regeneration of damaged bone tissues.

Two types of hybrid scaffolds made of collagen/polycaprolactone (PCL) and gelatin (Gel)/PCL, both with a 70:30 ratio, were electrospun to culture bone marrow endothelial progenitor cells (BEPCs) [68]. BEPCs adhered better and showed reduced expression of inflammatory markers like interleukin (IL)-1 on these scaffolds compared to glass slides used as controls. Additionally, polyurethane (PU)/Nylon 6 (N6) blended with gelatin (Gel) formed dual non-woven nanofibrous scaffolds, which enhanced osteoblast proliferation due to their biomimetic properties and high wettability [69].

Gelatin nanofibers have gained attention for their eco-friendly properties and positive effects on tissue cell adhesion, proliferation, and differentiation [70]. Cross-linked gel/zein scaffolds have shown promising results in bone regeneration in vivo, with improved bone volume and reduced bone resorption, although the presence of zein did not enhance the regeneration process. Furthermore, a tri-component scaffold composed of polyd,l-lactide, gelatin, and RKKP glass-ceramics was developed. RKKP's inclusion promoted cell viability and osteogenic differentiation, driven by La3+ and Ta5+ ions within the scaffold [71]. This indicates a potential for directing mesenchymal stem cell differentiation towards bone or cartilage tissue regeneration.

Structures of many natural materials, like chitosan and its bioactive polymers, closely resemble glycosaminoglycan (GAG), a vital component of bone extracellular matrix (ECM) facilitating cell-cell adhesion with collagen fibers. These biomaterials possess favorable characteristics such as biodegradability, biocompatibility, and mechanical properties, making them attractive for biomedical applications. Electrospun chitosan (Chi) nanofibers were fabricated from aqueous chitosan solutions using acetic acid, blended with polyethylene oxide (PEO) to enhance spinnability. MTT-assay and ALP expression analysis demonstrated cell proliferation and osteoblast differentiation on electrospun Chi scaffolds [72]. Metformin-loaded polycaprolactone/chitosan nanofibrous membranes were electrospun for bone repair, showing improved osteoinductive properties after glutaraldehyde crosslinking. In vitro experiments with rat bone mesenchymal stem cells showed enhanced cell attachment, proliferation, and osteogenic differentiation [73]. Helium cold atmospheric plasma (CAP) cured electrospun PCL/carboxymethyl chitosan (PCL/CMChi) nanofibers, combined with bone morphogenic protein-2 (BMP-2), promoted osteodifferentiation of human bone marrow-derived mesenchymal stem cells (hMSCs) in vitro [74].

Electrospinning techniques were employed to fabricate electrospun collagen matrices and electrospun collagen-Chi matrices for guided bone regeneration. In vivo studies on rat calvarial bone defects coated with these membranes demonstrated excellent attachment and proliferation of periodontal ligament cells. Electrospun collagen-Chi matrices exhibited superior physiochemical characteristics and enhanced bone ALP levels and osteocalcin compared to other groups, suggesting their potential in new bone formation [75].

Recently, thermoplastic polyurethane (TPU) nanofibers were functionalized with cellulose nanofibril (CNF) particles and polydopamine (PDA) to produce TPU/CNF-PDA nanocomposite nanofibers. These nanofibers exhibited improved swelling, hydrophilicity, and mechanical properties compared to TPU and TPU/CNF nanofibers. Mouse embryonic osteoblast cells (MC3T3-E1) seeded on TPU/CNF-PDA nanocomposite nanofibers showed enhanced adhesion and viability [76].

1.3.3. Nerve Regeneration

Peripheral nerve injuries (PNI), often resulting from traffic accidents, natural disasters, and inadequate treatments, present persistent challenges in clinical settings [77]. Electrospinning nanofiber materials, such as an aligned fibrin/functionalized self-assembling peptide (AFG/fSAP) interpenetrating hydrogel, have shown promise in nerve regeneration. These hydrogels combine topographical and biochemical cues to effectively enhance peripheral nerve regeneration, upregulate gene expression related to regeneration, and activate key signaling pathways like PI3K/Akt and MAPK [77].

Additionally, the development of silk fibroin (SF)-based nerve conduits, enhanced with carbon nanofibers (CNFs) and biomolecule-loaded polycaprolactone (PCL) nanocomposite coatings, has been explored [78]. These conduits, featuring varied concentrations of CNFs (5, 7.5, 10% w/w) in a 10% (w/v) PCL solution, are braided to optimize scaffold structure and functionality. The increase in CNF concentration has been found to improve conductivity, strength, and mechanical properties of the conduits, while in vitro studies confirm their cytocompatibility and effectiveness in promoting cell adhesion, growth, and proliferation, thereby aiding the regeneration of peripheral nerve tissues [78]. Zhan et al.

developed a nanofiber conduit using a blood vessel filled with a self-assembling amphiphilic hydrogel scaffold (SAPNS), which was used to repair a 10 mm gap in a sciatic nerve transection. An empty vessel served as the control. The results demonstrated that the SAPNS-treated conduit significantly enhanced motoneuron protection, axonal regeneration, and remyelination across the gap [79]. In another study, Entekhabi et al. created a porous scaffold from hyaluronic acid and polycaprolactone (PCL/HA), which was optimized for nerve regeneration by improving mechanical and chemical properties. This scaffold increased cell adhesion and proliferation, showing promising potential for applications in neural tissue engineering [80].

1.4. Blood and skin

Blood vessel networks are crucial for delivering nutrients and oxygen, removing waste, and facilitating stem cell trafficking, which are essential for organ growth and wound healing. Vascular reconstruction, especially in coronary and peripheral bypass surgeries, is complex, driving the need for innovative solutions such as tissue-engineered vascular grafts (TEVGs) [81-83]. These grafts integrate patient-derived cells with synthetic scaffolds to repair damaged vessels.

Recent advances have been made in this field, including Jiang et al.'s development of electrospun PCL/gelatin composite scaffolds that enhance cell adhesion and proliferation due to improved wettability and mechanical properties [84]. Pektok et al. achieved better endothelialization and healing with PCL-based grafts compared to traditional e-PTFE, using nanofibers to accelerate matrix formation [85]. Ju et al. engineered bilayered vascular scaffolds with varying fiber diameters to support endothelial cell adhesion and smooth muscle cell infiltration, thereby enhancing vessel formation [86].

The blood coagulation properties of chitosan have been utilized in vertically graded CS/PCL nanofibrous scaffolds, boosting endothelial cell proliferation and showing promise for small-diameter grafts [87]. Tecophilic/gelatin blends have been electrospun into scaffolds that mimic native ECM, offering durability and antithrombotic properties [88]. Yuan et al. demonstrated that HA/PLLA nanofibers could regenerate vSMCs and endothelium, benefiting vascular scaffolding with their anisotropic wetting and mechanical characteristics [89]. Yu et al. blended natural silk fibroin with synthetic TPU to create hydrophilic vascular grafts that enhance cell-matrix interactions [90]. Aydogdu et al. identified an optimal concentration of PCL/Ethyl Cellulose/Collagen for producing thin-fibered biomimetic blood vessels [91]. Finally, Kong et al. developed gelatin/PCL nanofibers with chondroitin sulfate, which enhance anticoagulant properties and cellular responses, making them suitable for blood vessel repair [92].

Skin, the body's largest organ, acts as a barrier between the internal and external environments and comprises three layers: the epidermis, dermis, and hypodermis. In cases of deep injuries or burns, healing may be inadequate, necessitating skin grafts for areas larger than 4 cm in diameter [93]. The extracellular matrix (ECM) in the dermis, mainly composed of collagen, elastin, and reticular fibers, provides crucial spatial and mechanical signals to cells, underscoring the need for skin substitutes that replicate the ECM to aid regeneration [94].

Advancements in electrospinning have facilitated the creation of effective skin substitutes. Pezeshki–Modaress et al. developed gelatin/GAG nanofibrous mats, finding optimal electrospinning conditions to produce fibers with desirable diameters and distributions [95]. Lin et al. enhanced the strength and functional lifespan of chitosan nanofibers through pectin cross-linking, which also improved fibroblast growth and wound healing capabilities [96]. Asran et al. explored the effects of blending polyvinyl alcohol (PVA) with polyhydroxybutyrate (PHB) on cell adhesion and proliferation, noting specific compositions favorable for different cell types [97].

Shalumon et al. fabricated aligned PLA-CS nanofibers, which directed cell orientation and supported skin tissue engineering by mimicking the ECM's structure [98]. Park et al. used a novel electrospinning technique with salt leaching to create highly porous silk fibroin scaffolds that enhanced cell infiltration and layering [99]. Levengood et al. found that electrospun chitosan–poly(caprolactone) (CPCL) scaffolds expedited wound healing in a mouse skin model, supporting keratinocyte and fibroblast migration for faster closure [100].

Abdul Khodir et al. incorporated gentamicin into collagen/PCL nanofibers, creating a scaffold that effectively released the antibiotic over 72 hours to treat infected wounds without toxicity [101]. Movahedi et al. demonstrated that core-shell PU/St and PU/St (HA) nanofibers were non-toxic and promoted significant cell adhesion and viability, marking them as promising for wound healing and skin tissue engineering [102]. Lastly, Varshney et al. developed soy protein isolate/silk fibroin (SPI/SF) nanofibrous scaffolds, which, despite losing some transparency after ethanol vapor treatment, proved non-toxic and effective in regenerating full-thickness wounds in rats [103].

2. Conclusion

In summation, recent research over the past decade has underscored the significant potential of nanofibers in addressing critical challenges within the biomedical sector, particularly in areas such as antimicrobial treatments, tissue engineering scaffolds, and advanced wound care. These fibers, which effectively mimic the natural extracellular matrix, have demonstrated essential qualities that make them integral to the advancement of medical applications. Developments in fabrication methods like electrospinning and 3D printing have led to the creation of scaffolds that exhibit uniform porosity and enhanced mechanical strength, which are vital for a broad spectrum of tissue engineering applications.

However, despite their advantageous attributes—including high surface-to-volume ratios, ease of functionalization, economic efficiency, and excellent biocompatibility—nanofibers are not without limitations. Issues such as insufficient pore size for effective cellular integration and suboptimal mechanical properties for hard tissue regeneration present ongoing challenges that limit their practical deployment in clinical settings. Looking forward, the outlook for nanofiber technology in biomedical applications remains promising, with research currently focused on refining fabrication techniques to facilitate the transition from laboratory-scale production to commercial and industrial scales. Furthermore, the exploration of sustainable polymers derived from abundant natural resources represents a significant opportunity to develop biodegradable and biocompatible materials. To overcome existing barriers and unlock new possibilities for these versatile materials, a concerted effort from multiple scientific disciplines is essential. As research continues to progress, it is expected that novel insights into polymer properties and their blends will significantly enhance the effectiveness and sustainability of nanofibers, thereby augmenting their practical utility in the healthcare and medical fields.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

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