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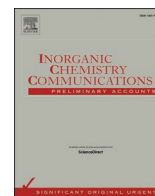
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Research Article

Surface modification of electrospun nanofibers via nonthermal plasma for wound healing: A comprehensive review

Reyhaneh Fatahian^a, Rasool Erfani^{b,c,*}^a Department of Textile Engineering, Yazd Branch, Islamic Azad University, Yazd, Iran^b Department of Engineering, Manchester Metropolitan University, Manchester M1 5GD, UK^c Department of Civil, Environmental and Geomatic Engineering, University College London, London WC1E 6BT, UK

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ABSTRACT

Electrospun nanofibers are widely studied in biomedical applications, particularly in wound healing, due to their high surface area, porosity, and structural similarity to the extracellular matrix. However, their clinical performance is often limited by poor mechanical strength and suboptimal surface properties, which hinder cell attachment and therapeutic effectiveness. Surface modification is therefore critical. Among available techniques, cold atmospheric plasma (CAP) has emerged as a highly effective, non-contact, and environmentally friendly method to functionalise nanofiber surfaces without altering their bulk properties. This review provides a comprehensive overview of electrospinning technology and explores how CAP treatment enhances the physicochemical and biological performance of electrospun nanofibers. Key improvements include increased surface wettability, enhanced cell adhesion, improved antimicrobial activity, and controlled drug release, making CAP-treated nanofibers particularly well-suited for advanced wound care applications. By synthesizing current evidence, identifying effective plasma treatment parameters, and evaluating clinical outcomes, this paper highlights the synergistic potential of combining electrospinning and CAP technologies. The review concludes by outlining future directions and challenges in translating plasma-modified nanofiber dressings into clinical practice.

1. Introduction

Nanofibers have garnered considerable interest as advanced nanomaterials because of their distinct physicochemical properties, lack of surfactants, and substantial commercial potential [1,2]. Their ability to form highly porous, interconnected networks [3], fiber diameters below 1000 nm, a high surface area-to-volume ratio, nanoporous structure, and excellent drug-loading capacity make them perfect for diverse applications [4]. These applications leverage the structural resemblance of nanofibers to the extracellular matrix, making them particularly effective in tissue engineering [5,6], encompassing biosensing, bioimaging [7,8], wound care [9], and drug delivery systems [10].

However, nanofibers face significant challenges in biomedical applications despite their many advantages. These include limited mechanical strength, which can hinder their structural integrity in load-bearing tissues; inconsistent reproducibility across fabrication batches, leading to variability in scaffold quality; and insufficient control over surface properties, which affects cell adhesion, proliferation, and overall biocompatibility. These limitations necessitate the use of advanced

surface modification strategies, such as plasma treatment, to enhance their biocompatibility and functional performance [11,12].

Table 1 outlines various nanofiber fabrication techniques, highlighting their benefits and drawbacks. Compared to other nanofiber fabrication techniques listed in Table 1, electrospinning offers a unique combination of scalability, material versatility, and precise control over fiber morphology, making it particularly well-suited for biomedical applications. Methods such as drawing, while simple in setup, are intermittent, poorly scalable, and offer limited control over fiber size [13]. Template-based synthesis provides some control over fiber dimensions but is constrained by limited scalability and the complexity of template removal [14]. Phase splitting enables the formation of 3D porous structures with tunable mechanical properties, yet it is restricted to specific polymers, involves complex processing, and produces poorly aligned fibers [15]. Self-assembly allows for injectable nanostructures with good 3D shape control; however, it is limited by short fiber lengths, narrow diameter ranges, low production yields, and restricted polymer compatibility, rendering it unsuitable for large-scale biomedical applications [16]. In contrast, electrospinning stands out for its ability to

* Corresponding author at: Department of Engineering, Manchester Metropolitan University, Manchester M1 5GD, UK.

E-mail address: r.erfani@mmu.ac.uk (R. Erfani).

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Table 1
Nanofiber fabrication techniques.

Fabrication Methods	Advantages	Disadvantages
Drawing	• Straightforward devices	• Intermittent process • Limited scalability • Lack of control over fiber size • Limited scalability
Template-based synthesis	• Ongoing process • Fiber size can be adjusted by using different templates	• Limited scalability
Phase splitting	• Basic apparatus • Easy to process • Mechanical properties of fiber matrices can be adjusted by altering the polymer composition • 3D pore structure • Pore size and shape are highly customizable	• Only compatible with specific polymers • Complicated processes • Poor control over fiber alignment (size and orientation) • Low output yield
Self-assembly	• Only nanofibers with diameters of a few nanometers and lengths of a few microns can be produced • Cells can be easily integrated during fiber formation • Three-dimensional pore structure • Injectable for in vivo use • Excellent control over 3D shape	• Complicated process • No control over fiber size • Restricted fiber diameter and short fiber length • Low production yield • Limited polymer compatibility
Electrospinning	• Basic equipment • Capable of producing fiber diameters ranging from a few nanometers to several microns • Simple and cost-efficient method • Long, continuous fibers • Ability to use a wide variety of materials • Controllable process parameters for different fiber diameters and orientations • Well-established and well-characterized technique • Customizable • Adjustable mechanical properties	• Jet instability • Use of toxic solvents • Challenges in packaging, shipping, and handling • Limited cell infiltration into the scaffold core • Primarily 2D scaffolds • Difficulty in controlling pore size and shape

produce long, uniform fibers using simple, cost-effective equipment in a continuous process. It offers precise control over fiber diameter, orientation, and surface texture, enabling the fabrication of scaffolds that closely mimic the extracellular matrix an essential attribute for tissue engineering and wound healing [17,18]. Additionally, electrospinning is compatible with a wide variety of natural and synthetic polymers, allowing for the integration of bioactive agents and drugs to enhance therapeutic outcomes [19].

The electrospinning setup comprises three main components: a high-voltage power supply, a spinneret, and a grounded collector. This arrangement produces nano- or microfibrillar structures that feature high porosity, a large surface area-to-volume ratio, and excellent tensile strength [20]. The performance of electrospun scaffolds in tissue engineering is primarily determined by the choice of materials, which influence key properties such as mechanical strength, biocompatibility, and degradation rates. While various materials, including polymers [21], ceramics [22,23], and inorganic compounds [24], can be used for electrospun fibers, polymers are the preferred material. Their flexibility in design and superior bulk properties allow for the development of scaffolds tailored for specific biomedical uses. The widespread use of both synthetic and natural polymers has been pivotal in advancing tissue engineering and regenerative medicine [25,26]. The adaptability of electrospinning also enables the incorporation of bioactive molecules

and drugs into the fibers, enhancing scaffold functionality. This is particularly advantageous in drug delivery, where precise control over release profiles is critical. Additionally, electrospun nanofibers can be customized with specific surface chemistries to support cell attachment, proliferation, and differentiation, improving scaffold performance and aiding integration into living tissues [27,28].

Plasma science is gaining significant attention for its versatility and potential across diverse applications. Plasmas are broadly categorized into two main types based on the thermal equilibrium of their particles: thermal (hot or equilibrium) plasma and non-thermal (cold or non-equilibrium) plasma. In thermal plasma, the electron and ion temperatures are in equilibrium, meaning the energy distribution among the particles is uniform. This results in extremely high gas temperatures, which makes thermal plasma unsuitable for applications involving heat-sensitive materials. For example, tissue engineering scaffolds, which are delicate and can be easily damaged by excessive heat, would not survive exposure to such high temperatures. It is mainly used for applications that can withstand high temperatures, such as surface modification of metals and silicon wafers, nanoparticle production, and hazardous waste destruction. Non-thermal plasma or cold plasma, is characterized by a temperature imbalance between electrons and ions [29–33]. Generated by strong electric or magnetic fields, it accelerates electrons, causing ionization without significantly heating the ions. As a result, electron temperatures are much higher than ion temperatures, keeping the overall gas temperature low, typically at or slightly above room temperature [34]. This makes non-thermal plasma ideal for applications involving thermosensitive materials, as the low gas temperatures prevent damage to these materials. One of its key uses is in the modification of polymeric nanofibrous scaffolds, commonly used in biomedical applications [35–38].

Plasma technology is extensively applied across diverse domains, such as the microfabrication of electronic devices, biomedicine, dentistry, agriculture, ozone production, chemical synthesis, surface modification, coating processes, and disease treatment [39]. Plasma treatment is particularly significant in improving the adhesion of coatings, inks, and adhesives to various surfaces, including polymers, metals, and ceramics. It can also be used to clean surfaces by removing contaminants and activating them for subsequent processes like bonding or painting. Additionally, plasma treatment is applied in sterilization, modifying biomaterial surfaces to promote cell adhesion, and enabling controlled drug release [40,41]. In the textile industry, plasma treatment improves dye absorption, coating adhesion, and surface functionality [42]. It is also vital in the production of optical components, such as lenses, mirrors, and waveguides, where it is used for surface cleaning and modification. Lastly, in semiconductor manufacturing, plasma treatment is essential for cleaning and activating surfaces to ensure proper adhesion of thin films and coatings [43]. Plasma surface treatment is vital in several biomedical applications, including tissue engineering and wound healing. A major advantage of this technique is its enhanced sterilization capability, which surpasses traditional methods due to its superior cleaning properties. Moreover, plasma surface modification has demonstrated improvements in the drug release behavior of non-degradable polymers. By influencing the water absorption rate of polymer scaffolds, plasma treatment can regulate the rate at which drugs are released [44]. Studies have also demonstrated the effectiveness of plasma treatment in accelerating ulcer healing, with treated wounds showing faster healing times and a more rapid reduction in ulcer size. Cold plasma treatment promotes healing by mechanisms such as acidification, angiogenesis, improved dermal blood circulation, and stimulation of cell activity [45].

Electrospun polymer nanofibers offer significant advantages for a wide range of biomedical applications due to their structural similarity to the extracellular matrix, high surface area-to-volume ratio, and tunable mechanical properties. These characteristics make them particularly well-suited for tissue engineering, drug delivery, and, notably, wound healing. However, to fully realize their potential, it is

essential to enhance their surface properties to improve biocompatibility and therapeutic performance. Plasma treatment has emerged as a powerful and versatile surface modification technique that can substantially enhance the physicochemical characteristics of nanofibers without altering their bulk structure. By precisely adjusting parameters such as gas composition, discharge power, and exposure duration, plasma offers a flexible and controllable approach for tailoring nanofiber surfaces to meet specific biomedical requirements. This review aims to provide a comprehensive overview of the electrospinning process, surface modification strategies, and the critical role of plasma treatment in surface functionalization. It also evaluates the performance of plasma-treated nanofibers and highlights the most effective plasma techniques for improving surface properties in wound healing applications.

Despite the extensive body of research on electrospinning and plasma treatment as separate fields, there is still a lack of integrated understanding of how specific plasma parameters influence the surface functionality and therapeutic efficacy of electrospun nanofibers particularly in the context of wound healing. Existing literature often presents generalized or fragmented perspectives, focusing narrowly on aspects such as sterilization or drug release, without offering a holistic framework for the systematic optimization of plasma treatment for biomedical use. This review addresses that critical gap by thoroughly examining the interplay between the intrinsic properties of electrospun nanofibers and the effects of plasma-induced surface modifications, with a particular emphasis on cold plasma technologies for wound healing. By synthesizing recent advancements, comparing treatment methodologies, and identifying best practices, this manuscript serves as a comprehensive and up-to-date resource. It bridges fundamental principles with emerging biomedical applications, providing valuable insights for researchers seeking to optimize nanofiber-based therapeutic strategies in modern healthcare.

2. Electrospinning

Electrospinning is a widely recognized method for producing nanofibers ranging from the submicron to nanoscale, providing various morphologies, including non-woven, core-sheath, porous, and aligned structures. These versatile morphologies make electrospun nanofibers ideal for a broad range of applications [42]. Due to their one-dimensional structure, nanofibers have become highly sought after in biomedical engineering, offering benefits such as a high surface area-to-volume ratio, nanoporosity, excellent absorption capacity, biocompatibility, biodegradability, and favorable properties for breathability and mass transport [2,46–48]. Furthermore, the flexibility of the

electrospinning technique enables continuous nanofiber production for various applications, including electronics, energy storage, textiles, protective clothing, sensors, and filtration systems [3,49,50]. The process involves balancing the surface tension of the polymer solution at the spinneret tip with an externally applied electric field. When a high voltage is applied between the polymer solution and a grounded collector, the electrostatic forces from the accumulated charges on the solution's surface overcome its surface tension, causing the polymer to jet toward the collector. As the charged jet stretches and accelerates in the electric field, fibers form and deposit onto the collector [5]. A schematic diagram of this process is shown in Fig. 1.

Nanofibers can be made from a variety of materials, such as polymers [21], ceramics [51], and inorganic compounds [52], with polymers being the material of choice due to their flexibility in design and superior bulk properties. Consequently, electrospun scaffolds are primarily composed of synthetic and natural polymers [25]. Natural polymers like chitosan, collagen, gelatin, and silk are particularly valued for medical applications because of their biodegradability and exceptional bioactive properties. These materials are often derived from the native extracellular matrix (ECM) or other biological sources [53].

The application of natural polymers is often restricted by issues such as limited availability, variability between batches, weak mechanical properties, and fast degradation in aqueous conditions. To address these limitations, synthetic polymers have emerged as viable alternatives in recent decades, offering enhanced performance, cost-effectiveness, ease of production, and more consistent properties [54,55]. Synthetic biodegradable polymers, including polycaprolactone (PCL), poly (l-lactic acid), poly (glycolic acid), and poly (lactic-co-glycolic acid), offer several advantages over natural polymers, such as improved processability during electrospinning and more precise control over nanofiber morphology [56]. Numerous studies have investigated the electrospinning of both natural and synthetic polymers. For example, Noorani et al. [57] created nanofibrous scaffolds using a chitosan/gelatin blend, with fibers having a diameter of 180 nm. Their findings showed that while gelatin incorporation improved the scaffold's hydrophilicity and degradation rate, it also compromised the mechanical strength. The 50/50 chitosan/gelatin blend exhibited the highest tensile strength (6.93 ± 0.63 MPa), whereas the scaffold containing 30 % chitosan had a lower tensile strength of 3.51 ± 0.45 MPa ($p < 0.05$). The Young's modulus values were 1.05 MPa for the 70/30 blend and 2.24 MPa for the 50/50 blend. In another investigation, Noh et al. [58] developed bacterial cellulose-collagen composite scaffolds in ratios of 1:1, 3:1, and 5:1 to examine their influence on human mesenchymal stem cells (hMSCs). The composites exhibited better physical stability and enhanced water absorption compared to pure collagen, with higher bacterial cellulose

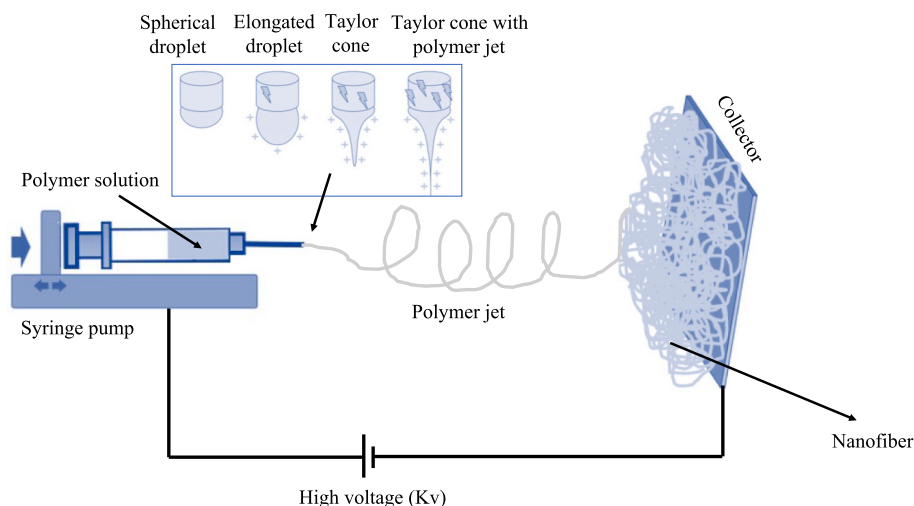


Fig. 1. The conceptual illustration of the electrospinning process.

content improving these properties. Gene and protein analyses of UCB-MSCs cultured for three weeks showed that the 5:1 bacterial cellulose-collagen ratio provided the most optimal substrate, and *in vivo* experiments confirmed successful cell engraftment within the scaffolds. Gu et al. [59] investigated the mechanical and biological characteristics of aligned conductive nanofibrous scaffolds composed of chitin and polyaniline (Chi/PANi) to assess their effect on human dermal fibroblast cell (HDFC) behavior. They used electrospinning with a drum collector to produce both random and aligned nanofibers. The aligned fibers were 49 % thinner and showed a 91 % increase in electrical conductivity compared to the random fibers. After one week of culture, cell viability on aligned fibers was about 2.1 times higher than on random fibers, highlighting the advantages of fiber alignment for guiding cellular growth. Additionally, Fu et al. [60] enhanced the surface properties of PLLA nanofibers by promoting extracellular matrix (ECM) deposition. MC3T3-E1 cells cultured on the electrospun nanofibers supported ECM formation, and after two weeks, the cells were removed through decellularization. The ECM-coated scaffolds demonstrated significantly better cell adhesion and osteogenic differentiation compared to untreated PLLA nanofibers. Tian et al. [61] fabricated aligned nanofibers of poly(lactic acid) and poly(pyrrole) for nerve regeneration, incorporating poly(pyrrole) to introduce electrical conductivity. The composite was coated with polyornithine to enhance surface hydrophilicity. Neuronal differentiation of PC12 cells showed positive results even without electrical stimulation. The aligned fibers facilitated increased cell proliferation, while the poly(lactic acid)-poly(pyrrole) blend reduced fiber diameters, though it did not improve the biocompatibility of the scaffold.

3. Techniques for surface modification of electrospun nanofibers

Nanofiber surface modification is typically achieved through physical or chemical methods. Physical techniques, such as plasma treatment, physical vapor deposition (PVD), and ion beam implantation, modify the surface using weak adsorption forces, often resulting in unstable changes that are not suitable for long-term or biological applications. In contrast, chemical methods like surface grafting, cross-linking, and chelation form more stable modifications by creating covalent bonds or adding functional groups. However, these processes often require harsh conditions, such as organic solvents, high temperatures, or extended reaction times, which can produce toxic byproducts, degrade the nanofiber material, and reduce biocompatibility, limiting their applicability in biomedical settings. Both physical and chemical methods offer effective ways to modify nanofiber properties, but they come with drawbacks: physical methods tend to provide less stable surface modifications, while chemical methods may compromise material integrity and introduce toxicity. Therefore, there is a need for more refined, biocompatible surface modification techniques that can overcome these limitations for enhanced biomedical applications [62,63].

4. Plasma treatment

Plasma, the most energetic and abundant state of matter, accounts for approximately 99.9 % of the visible matter. It consists of charged particles, electrons, photons, and free radicals. Unlike solids, liquids, and gases, plasma is a complex mixture of ions, electrons, and neutral particles in both ground and excited states. Although plasma is electrically conductive due to the presence of free charge carriers, it remains electrically neutral on a macroscopic scale. Plasma is not naturally found in Earth's atmosphere and is usually generated from a neutral gas [64]. Plasma technology is highly versatile for material treatment, as it can involve single components or combinations of components. The ability to generate and control plasma is essential for its wide range of applications in fields such as materials science, nanotechnology, and

biomedical engineering [65]. Plasma treatment is an effective and widely used method for chemical and physical modifications, sterilization, decontamination, thin-film formation (plasma polymerization), and precise surface property adjustments. It is applicable to a wide variety of materials, particularly polymers and polymer fibers [66,67]. Effective plasma modification requires precise control over the plasma generation process and treatment parameters, such as power, pressure, gas flow rate, and exposure time. These factors influence key plasma characteristics, such as density, temperature, and composition, which determine the degree of surface modification on the material [65]. Plasma processing of polymers is a simple, cost-effective, and safe technique that alters surface properties without affecting the bulk properties of the material.

It is commonly used in tissue engineering to improve scaffold surfaces, enhancing wettability and introducing new functionalities. Plasma surface modification can adjust mechanical properties, roughness, hydrophilicity, and surface chemistry, making it highly suitable for biomedical applications [68–72]. Cold atmospheric plasma (CAP) is a promising approach for wound healing. Preclinical and early clinical studies in animals and humans have shown that CAP reduces bacterial load and promotes healing without harming healthy tissue. It modulates inflammation, stimulates growth factors linked to angiogenesis, and introduces tissue-reactive species (e.g., NO, OH, O) that aid repair. Additionally, helium-based CAP lowers pH levels, contributing to wound acidification and enhanced healing [73]. These therapeutic benefits of CAP have also been consistently observed across multiple clinical trials involving patients with chronic wounds (see Table 2).

By using inert gases like Ar, He, and N₂, plasma treatment generates functional groups or radicals that enhance adhesion, facilitate polymer grafting, immobilize biomolecules, or increase surface hydrophilicity. This clean, fast, and reliable process affects only the surface, preserving the material's core properties while improving adhesion for biomaterials [78,79].

Table 3 presents some of the advantages and disadvantages of the plasma modification technique.

4.1. Classification of plasma treatment

Classifying plasma types is difficult due to the complexity of selecting the right criteria. Plasma variations stem from differences in their physical and chemical properties, as well as the materials they interact with. Surface plasma treatment can be categorized according to plasma type, operating conditions, and intended applications [80]. The key classifications will be discussed in the following sections.

4.1.1. Based on plasma temperature

Plasmas are categorized into thermal (hot) and nonthermal (cold) types. Thermal plasmas, which are fully ionized and have a uniform temperature, have been utilized for decades in industrial processes like metal extraction, refining, ceramic powder production, spray coatings, and hazardous waste treatment. In medicine, thermal plasmas are frequently used for endoscopic tissue coagulation, hemostasis during surgery, and tissue ablation (e.g., tumor removal or treating actinic keratosis). However, because of their high temperatures, thermal plasmas are unsuitable for sensitive applications involving living cells or temperature-sensitive medical equipment. Nonthermal plasma (NTP), also known as cold atmospheric plasma, differs from thermal plasma in the behavior of electrons, ions, and overall neutrality. Unlike thermal plasma, which is generated under high pressure and power with electrons and heavier particles at the same temperature, NTP is produced at low pressure and power, where electrons have significantly higher temperatures than the heavier particles, which stay near or at room temperature [81–86].

NTP treatment is an effective technique for modifying the hydrophilicity and hydrophobicity of materials without altering their bulk properties. This eco-friendly, simple, and efficient method can change

Table 2
Clinical Outcomes of Cold Plasma Therapy in Chronic Ulcer Treatment.

Plasma System	Number of wound cases	Wound Type	Cases with Wound Size ≤ 0.5 (%)	Bacterial load	Refs.
Cold Atmospheric Plasma	44	Diabetic Foot Ulcers	SC: 36.4 % vs SC + CAP: 77.3 %	Significant immediate bacterial load reduction after CAP sessions; no long-term difference between groups	[73]
Cold Atmospheric Plasma (CAP) – PlasmaDerm® VU-2010 Figure 2 :	14	Chronic Venous Leg Ulcers	Not reported exactly; 1 complete closure; >50 % reduction in 4/7 CAP patients	Significant reduction in bacterial load ($p = 0.04$)	[74]
Low-Temperature Atmospheric Pressure Plasma (LTAPP)	50	Pressure Ulcers	–	Significant reduction in bacterial load after 1 treatment; improved PUSH scores and exudate amount after 1 week	[75]
Cold Atmospheric Plasma (Helium gas plasma, 4.5 kV, 22 kHz)	20	Diabetic Foot Ulcers	Significant reduction in wound size ($p = 0.007$), exudate reduction ($p = 0.039$), and improved wound grading ($p = 0.019$)	antibacterial effects observed	[76]
Cold Plasma Therapy (CPT)	48	Chronic Wounds (mixed)	≥ 90 % closure: 16 % (CPT), 0 % (SWT); ≥ 60 %: 28 % (CPT), 0 % (SWT); ≥ 40 %: 40 % (CPT), 18 % (SWT); ≥ 25 %: 56 % (CPT), 27 % (SWT)	Lower antibiotic use in CPT group (4 % vs 23 %, $p = 0.049$); faster wound healing ($2.14\times$ faster, $p = 0.039$)	[77]

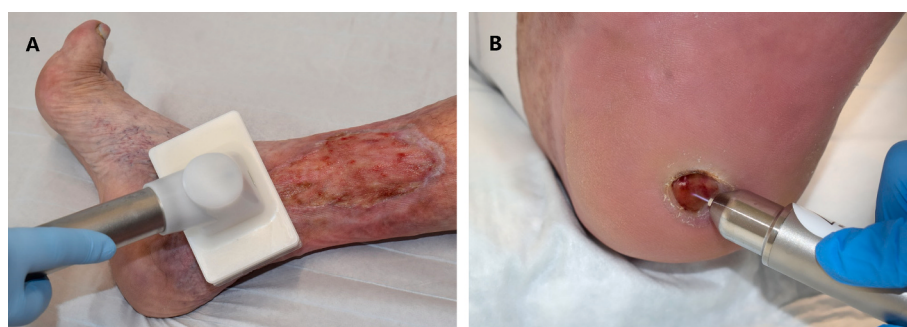


Fig. 2. (A) The PlasmaDerm® DBD plasma device (CINOGY GmbH, Duderstadt, Germany) has been utilized in the treatment of venous ulcers on the lower leg. (B) The kINPen® MED plasma jet device (neoplas med GmbH, Greifswald, Germany) has been applied to treat diabetic pressure ulcers on the foot.

surface functional groups such as hydroxyl, carbonyl, carboxyl, and nitrile. Because it operates at low temperatures, NTP is particularly suitable for treating various biological materials, including solids, liquids, and aerosols [87]. NTP devices, such as jet plasma, dielectric barrier discharge (DBD) plasma, and spark plasma, function under ambient room conditions, making them ideal for life sciences and a broad range of biomedical applications [88,89]. These include sterilization, skin disinfection, dental and oral disease treatment, blood coagulation, wound healing, cancer therapy, and immunotherapy, all of which have benefited from NTP advancements [90]. In environmental applications, devices like gliding arc discharge and corona discharge are commonly used for removing gaseous pollutants. Recently, DBD and jet plasmas have garnered more attention due to their non-thermal characteristics, opening up new possibilities in biological and medical fields, especially for applications involving living tissues, cells, and biomaterials [91].

4.1.2. Based on pressure

Plasmas can be classified by pressure as either low-pressure or atmospheric-pressure. Low-pressure plasmas, typically operating between 0.1 and 10 Pa, are effective for surface modification as they penetrate deeper into materials without damaging the surface [92,93]. The increased mean free path of plasma particles allows them to travel greater distances, promoting more efficient surface interaction and leading to enhanced modification [94]. Low-pressure plasmas are preferred in biomaterials research for their stability and controllable reactions. However, atmospheric-pressure plasmas (APP) have gained popularity for industrial use due to their easier integration into production lines and lower costs, as they eliminate the need for vacuum equipment [67].

Atmospheric-pressure plasmas are perfect for large-scale surface

modification because they operate at or near room temperature and do not require vacuum systems. This makes them cost-effective for treating extensive surfaces and suitable for modifying heat-sensitive materials safely [65]. To address homogeneity issues in atmospheric-pressure plasmas, operation in a pulsed regime can be employed, while high temperatures resulting from high current densities can be controlled using dielectric barrier discharges (DBDs) [67].

4.1.3. Based on plasma source

Plasma sources such as capacitively coupled plasma (CCP), inductively coupled plasma (ICP), and microwave plasma provide unique benefits depending on factors like power input, plasma density, and ease of control, making them ideal for various industrial and research applications. CCP is especially favored for surface modification because it can generate low-pressure, easily controllable plasma. It operates by applying high-frequency alternating current between two electrodes, ionizing the gas around them to create plasma with low ion density and moderate electron temperature, enabling precise control over surface interactions. The key advantages of CCP include its flexibility in adjusting power and gas flow, allowing for targeted surface treatments such as improving wettability, adhesion, and biocompatibility. It is commonly used for modifying polymer surface energy, enhancing metal corrosion resistance, and in processes like thin film deposition, etching, and sterilization. CCP's versatility makes it valuable across various industries, including electronics, automotive, biomedical, and packaging. Its ability to function at low pressures and create uniform plasma makes it especially suited for high-throughput applications. Additionally, CCP can be combined with other plasma sources, such as ICP or microwave plasmas, to further optimize performance for specific tasks [95,96]. Microwaves serve as an alternative energy source for chemical reactions and processes, offering energy through dielectric heating. This allows

Table 3

Advantages and disadvantages of plasma modification technique.

Surface Modification Technique	Advantages	Disadvantages
Plasma treatment	• Allows the attachment of various chemical functionalities • Environmentally friendly processes (use minimal chemicals and generate little waste) • Suitable for treating a wide range of materials (without altering the bulk properties) • Utilizes relatively simple and easily scalable equipment • Reduced processing time and fewer steps involved • Highly cost-effective • Enhances biocompatibility (promoting cell growth and adhesion) • Capable of modifying the surface properties of polymers by replacing chemical groups • Improved wettability • Increased flame resistance • Enhanced adhesive bonding • Better reflection of electromagnetic radiation • Increased surface hardness • Control over surface roughness • Economically advantageous over time	• Surface Damage and Degradation • Non-Uniform Treatment • Surface-only Effects • Parameter Sensitivity • Potential Toxicity • Manufacturing Scale-Up • Complexity of Equipment • Gas Emissions (use of certain gases in plasma treatment) • Energy Consumption (Some plasma treatment processes)

the reaction mixture to be uniformly mixed without direct contact with the walls. Microwave plasma sources are gaining popularity for producing low-pressure, high-density plasmas because of their energy efficiency and versatility. By exciting gas molecules with microwave electromagnetic fields, these sources create highly ionized plasmas with uniform electron energy, making them ideal for applications like materials processing, surface treatment, sterilization, and environmental remediation. In materials processing, these plasmas enable precise etching, deposition, and thin-film coating, critical for semiconductor and advanced materials manufacturing. For surface treatment, they provide effective cleaning and modification without the need for high temperatures or harmful chemicals. In sterilization, microwave plasmas are used to decontaminate surfaces and equipment in healthcare and food processing, ensuring hygiene. Microwave plasma sources offer advantages over traditional plasma sources, including higher process efficiency, better control, and the ability to process sensitive materials with minimal thermal damage. As a result, they are increasingly applied in both industrial and scientific fields, such as electronics, materials science, and medical sterilization [97–100].

4.1.4. Based on gas type

Plasma can be classified based on the type of gas used, which falls into two main categories: inert gases and reactive gases. Oxygen gas is commonly employed for polymer surface activation because, under low power conditions (<200 W), it generates reactive oxygen atoms that selectively modify the surface without altering the bulk material. For example, Nair et al. demonstrated that oxygen plasma treatment of polycarbonate and PEEK microneedle arrays increased surface energy and enhanced protein adsorption, potentially improving drug delivery capabilities for polymer microneedles [101]. Recently, Omrani and her team utilized oxygen plasma treatment to modify the surface of polyether ether ketone (PEEK) with gelatin for applications in bone injury

treatment [102]. Similarly, Ghorbani et al. immobilized gelatin onto oxygen plasma-treated PCL, forming tunable pore structures that are well-suited for wound healing and skin tissue engineering [103]. Oxygen is also widely used in plasma etching to oxidize surfaces and produce volatile byproducts. In a study by Amornsudthiwat and Damrongsakkul, oxygen plasma treatment was applied to silk fibroin, altering its surface stiffness and enhancing the adhesion of L929 cells and human mesenchymal stem cells [104]. On the other hand, argon plasma is commonly used to activate polymer surfaces by reducing hydrophobicity through ion bombardment. For oxygen-containing polymers, argon plasma can generate new functional groups, such as peroxides and hydroperoxides, which promote subsequent grafting. For instance, collagen was successfully grafted onto argon-treated PCL membranes via peptide coupling, resulting in improved cell proliferation compared to untreated membranes [105].

4.2. Plasma treatment of the electrospun nanofibers

A range of strategies, including physical, chemical, and biological methods, have been employed to design surface-functionalized nanofibers. Techniques for modifying the surface of nanofibers include plasma treatment, wet chemical methods, surface graft polymerization, and co-electrospinning of surface-active agents with polymers. Among these, plasma treatment is a commonly used approach for both physical and chemical modifications of polymer surfaces and nanofibers [11]. Fig. 3 illustrates the various methods used to modify the surface of nanofibers individually. Surface-functionalized nanofibers are characterized using techniques such as SEM and TEM for imaging, FTIR for chemical analysis, DSC for thermal properties, and AFM for surface topography. XRD reveals crystallinity, while XPS and EDAX provide chemical and elemental analysis. BET analysis measures surface area and porosity, and mercury porosimetry assesses pore size distribution. These methods offer a comprehensive evaluation of nanofiber properties [106,107].

Plasma treatment is an eco-friendly, clean, and sustainable method for modifying the surface of nanofibers without affecting their bulk properties. It enhances the adhesion and wettability of materials such as nanofibers by altering their surface chemistry and structure. It introduces functional groups and increases surface roughness, enhancing interaction with liquids. This process is crucial for boosting the biocompatibility of nanofibers in biomedical applications, such as tissue engineering and drug delivery, by promoting cell attachment, growth, and reducing bacterial adhesion. It also minimizes inflammation and improves tissue integration, making plasma-treated nanofibers more effective in clinical use [108–111]. Plasma treatment incorporates polar functionalities, such as oxygen- or amine-rich groups, which improve the hydrophilicity and surface topography of nanofibrous mats. These changes enhance cellular proliferation, adhesion, and viability, while also facilitating protein interactions and promoting better integration with surrounding tissues [112–114].

Furthermore, the impact of plasma treatments on the mechanical properties of nanofibrous materials used in biomedical applications is a crucial consideration. These treatments not only modify surface chemistry but also affect key mechanical characteristics such as tensile strength, elasticity, and stiffness, which are essential for the material's performance in tissue engineering and wound healing. The type of plasma treatment whether atmospheric, low-pressure radio frequency, or microwave can have a significant impact on the mechanical properties of nanofibrous mats. Each plasma method differs in terms of energy, reactive species, and treatment duration, leading to unique changes in the morphology and structural integrity of the fibers [12,115]. When applied with the correct parameters, plasma treatment can induce cross-linking that enhances both the thermal and mechanical properties of electrospun membranes, while also improving their storage stability. It also addresses low surface functionality by facilitating the grafting, polymerization, or immobilization of molecules onto the nanofiber

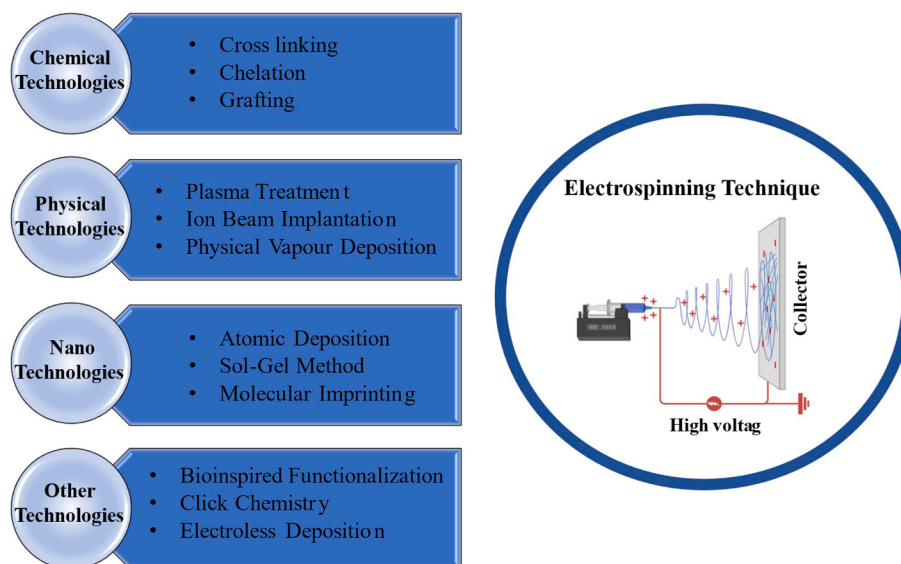


Fig. 3. Surface modification techniques for nanofibers.

surface. Moreover, plasma treatment can raise the porosity of nanofibers, thus expanding the surface area and enhancing their interaction potential with the surrounding environment. Plasma treatment modifies nanofiber surfaces by increasing hydrophilicity, roughness, and porosity, enhancing drug diffusion and enabling tunable release profiles based on drug-polymer interactions. Additionally, plasma treatment results in a higher drug release rate as treatment time increases, improving the antibacterial activity of the nanofibers and creating a sustained inhibition zone over an extended period [116–118].

While surface plasma treatment offers numerous benefits and applications, there are several negative points and limitations to consider, particularly when applied to sensitive materials like electrospun nanofibers for medical applications: High-energy plasma can cause degradation or alteration of the nanofiber structure, affecting their mechanical properties and performance. The increase in surface roughness of nanofibers after plasma treatment can be attributed to the bombardment by energetic particles, including electrons, ions, radicals, neutrals, and excited atoms/molecules. These high-energy species interact with the nanofiber surface, causing physical etching and modifying the surface topography, which results in increased roughness. This alteration in surface morphology can enhance properties like wettability, cell adhesion, and interaction with biomolecules, making it particularly beneficial for biomedical applications. Some plasma gases or treatment byproducts may be toxic or harmful to biological systems. Careful selection of plasma gases and thorough characterization of treated nanofibers are necessary to ensure biocompatibility and safety for medical applications. Achieving consistent and uniform treatment across large batches of electrospun nanofibers may require optimization of process parameters and equipment. Despite its positive and negative aspects, plasma treatment provides a versatile, efficient, and environmentally friendly method for improving the surface properties of a wide variety of materials, making it highly valuable in numerous industrial and biomedical applications [119,120] [36]. Table 4 summarizes various studies conducted on the use of plasma for surface treatment of nanofibers across different applications.

4.3. Plasma modification of nanofibers for wound healing

Wound healing is a multifaceted and carefully controlled process that unfolds in four overlapping stages, as shown in Fig. 4: (1) coagulation/hemostasis, (2) inflammation, (3) proliferation, and (4) remodeling. Various factors, including advanced age, diabetes, and obesity,

can interfere with the normal healing process, frequently leading to persistent inflammation and delayed or impaired tissue repair [140].

Key factors such as wound closure, interaction with exudates, mechanical properties, and biocompatibility are essential performance indicators for medical dressings. While traditional treatments have faced challenges in addressing the complexities of wound healing, nanomaterials present an opportunity for precise manipulation at the atomic level, allowing dressings to cater to the specific requirements of both acute and chronic wound care. Electrospinning, renowned for its high versatility, is utilized to produce ultrafine fibers that offer numerous advantages. These include enhanced adaptability to the wound environment, controlled release of biopharmaceuticals, promotion of gas exchange between the wound and its surroundings, absorption of exudates, and potential surface functionalization to improve biocompatibility and wound management. These properties enable electrospun nanofibers to positively impact skin cells at the wound site, promoting extracellular matrix (ECM) deposition, as well as cell proliferation, migration, and differentiation. Furthermore, electrospun nanofibers are becoming increasingly popular in wound healing due to their antibacterial properties, ability to promote rapid hemostasis, and exceptional biocompatibility, which supports cell growth [141–145].

Plasma-treated nanofibers have emerged as multifunctional platforms for wound healing, functioning both as scaffolds for cell attachment and as vehicles for the controlled delivery of therapeutic agents. Plasma treatment enhances the surface properties of nanofibrous materials, such as wettability, permeability, and antimicrobial activity—thereby improving their interaction with cells and overall regenerative potential [146,147]. Compared to untreated fibers, plasma-functionalized nanofibers exhibit superior cell behavior, including enhanced attachment and proliferation, significantly advancing tissue regeneration. Moreover, plasma treatment facilitates the covalent immobilization of bioactive molecules, such as proteins, directly onto wound dressing surfaces, further supporting the healing process [148–150]. This technique also enables the integration of therapeutic cells and genetic materials, including stem cells, siRNA, mRNA, microRNA, and antimicrobial peptides, into wound care systems. These advancements hold particular promise for treating chronic and complex wounds, including cancer-related lesions [151,152].

Recent preclinical studies further demonstrate the practical applicability of plasma-functionalized nanofibers in wound management. For instance, a cold atmospheric plasma-integrated gelatin scaffold (CAP-GS) enabled sustained, localized CAP delivery without repeated

Table 4

Plasma modification in different nanofiber materials.

Nanofiber material	Plasma system	Process gases	Properties/Results	Application	Refs.
Gelatin	Atmospheric Air Plasma	Argon /argon-oxygen	Increased Surface roughness/ improvement hydrophilicity/ the number of fibroblast cells was increased	Skin Tissue engineering	[121]
Polylactic acid	Radio-frequency (RF)	–	Enhanced antimicrobial activity/ sufficient wettability/ suitable surface and mechanical properties.	Tissue engineering	[69]
Polyamide-6/ polypropylene nonwoven	Diffuse Coplanar Dielectric Barrier Discharge	–	Enhancing the adhesive strength to carrier substrates/DBD treatment of PA6 fibers results in the oxidation of the polymer surface	Coated nonwovens	[66]
Polycaprolactone /Polyaniline	Cold Atmospheric Argon	Argon	Hydrophilic surface/ viability/conductive electrospun nanofibrous	Tissue engineering	[122]
chitosan (CS)/polyethylene oxide (PEO)/ natural coral	Dielectric Barrier Discharge	Argon/Oxygen/ Nitrogen	Enhance wettability/ enhanced the adhesion and proliferation/ enhanced the performance of osteoblasts	Bone tissue engineering	[123]
Polycaprolactone/ hydroxyapatite nanoparticles	Diffuse Coplanar Dielectric Barrier Discharge (DCSBD)	Argon	Improving the material wettability /positive influence on cell activity/enhanced the cell proliferation	Tissue engineering	[124]
polycaprolactone	Dielectric Barrier Discharge	Argon and nitrogen	Improve the wettability/sufficient cell adhesion and proliferation	Biomedical and tissue engineering	[125]
Polyvinylpyrrolidone/ TiO ₂	Diffuse Coplanar Dielectric Barrier Discharge (DCSBD)	Dry ambient air, nitrogen, and pure hydrogen.	Flexible composite core/shell fibers/surface area improvement	Industrial application like photo and heterogeneous catalysis.	[126]
poly(L-lactide-co-ε-caprolactone) (PCL) and poly (L-lactide-coglycolide) (PLGA)	Radio Frequency (RF)	Nitrogen-argon	Increased the surface roughness, wettability, and hydrophilicity of the scaffolds, thereby promoting cell attachment and proliferation.	Biomedical like nerve guide conduits and nerve protectant wraps.	[127]
poly(N-vinylpyrrolidone/ copper (II)	Microwave Argon plasma	Argon	Excellent visible light photocatalytic activity/ highest rate of photodegradation efficacy	Photodegradation of harmful, persistent organic pollutants in the environment.	[128]
poly(3-caprolactone) (PCL)/ calcium carbonate	Dielectric Barrier Discharge	Argon/ Oxygen	Increase surface hydrophilicity/ Increase permeability	Drug delivery platform for tissue engineering	[129]
Polycaprolactone	Radio Frequency (RF)	Hydrogen/Argon	Enhances the wettability of the polymeric mats without altering their morphology, resulting in increased adhesion force.	Tissue engineering	[130]
Polystyrene (PS)/ chitosan (CS)/ bovine serum albumin (BSA)	Low-temperature plasma	Oxygen/Argon	Improved surface charge and wettability following plasma treatment, with low cell cytotoxicity.	Tissue engineering and biomedicine fields	[113]
polylactic acid	Atmospheric pressure barrier discharge at low temperatures	Argon and oxygen	Polymer bond degradation and oxidation processes, leading to improved hydrophilicity and increased surface energy.	Tissue engineering	[131]
Polysuccinimide/ allylamine	Low pressure non-equilibrium air plasma treatment	–	Plasma-treated meshes maintained their integrity, making them a feasible and effective tool for simultaneous crosslinking and sterilization.	Drug delivery	[132]
Polyvinyl alcohol (PVA)/ Bombyx mori silk fibroin (BMSF)/ amoxicillin trihydrate	Dielectric Barrier Discharge	Oxygen	Improves wettability / increasing surface energy /better mechanical behavior/ prolonged antibacterial activities	Wound dressing	[133]
poly lactic acid (PLA)	Atmospheric-pressure argon plasma jet	Argon	Improving the electrospinnability /Production of smooth, uniform, bead-free PLA nanofibers /significant changes to the main physical properties	Tissue engineering	[134]
Polyvinyl alcohol (PVA)/Aloe Vera (AV)	Atmospheric Dielectric Barrier Discharge(A-DBD)	Oxygen	Improved surface wettability/improvement of mechanical parameters/improves surface roughness	Biomedical	[135]

exposure, significantly accelerating wound closure through immune modulation and reduced inflammation [153]. Similarly, study identifies Olfactomedin-like 3 (Olfml3) as a potent ECM-related protein that enhances scaffold performance without prior cell seeding. Gas plasma treatment was used to improve the hydrophilicity of PCL surfaces and introduce functional groups for efficient protein attachment. Plasma-treated and untreated patches were coated with increasing concentrations of recombinant Olfml3-FLAG protein (0–1 µg/mL), and protein binding was quantified using an HRP-conjugated anti-Olfml3 antibody. In vivo, Olfml3 accelerated wound healing, enhanced vascularization, and promoted cell infiltration, supporting its potential for cost-effective, cell-free tissue regeneration [154]. In another study, ibuprofen-loaded polylactic acid (PLA) nanofibrous scaffolds treated with plasma exhibited improved biocompatibility and wound healing performance. When

seeded with human skin cells, these scaffolds not only reduced wound contraction but also significantly enhanced neovascularization [155]. Also, another research demonstrated that plasma-treated electrospun polycaprolactone (PCL)/gelatin nanofiber scaffolds significantly improved wound healing in full-thickness rat skin models by enhancing fibroblast proliferation, collagen synthesis, and neovascularization [156]. Together, these examples underscore the clinical relevance and translational promise of plasma-functionalized nanofibrous materials in regenerative medicine.

In addition to their therapeutic advantages, plasma-treated nanofibers exhibit strong potential for clinical scalability and cost-effectiveness. Plasma surface modification is a dry, solvent-free, and relatively low-cost process that requires minimal reagents and produces little waste, making it environmentally friendly. It can be uniformly

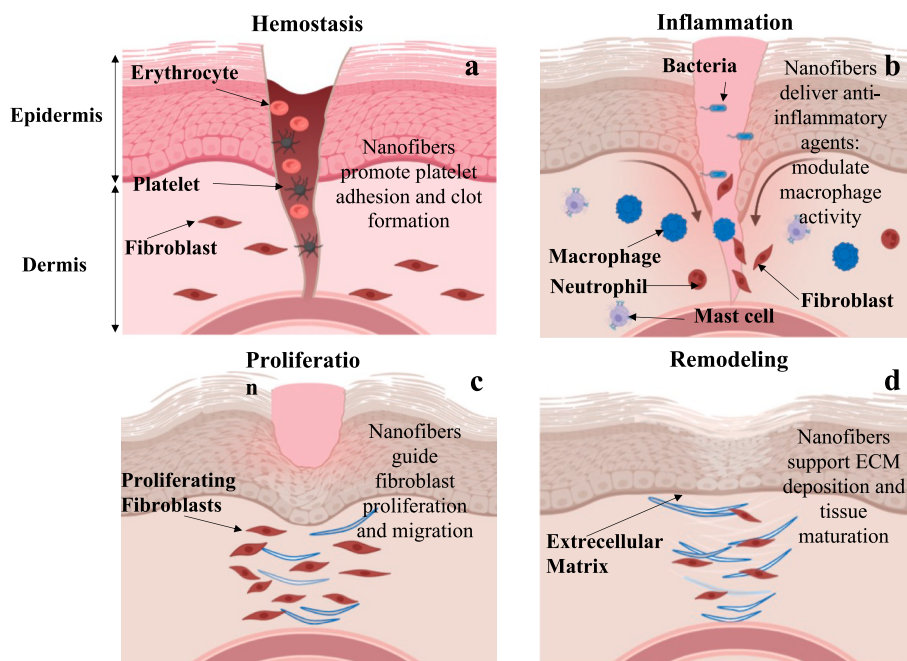


Fig. 4. Stages of wound healing: (a) Hemostasis stage, (b) Inflammation stage, (c) Proliferation stage, (d) Remodeling stage.

applied to large surface areas and easily integrated into existing electrospinning production lines, supporting mass production and chain processing, particularly with atmospheric cold plasma systems. The short processing times and compatibility with scalable fabrication further enhance their industrial appeal [116]. Moreover, plasma treatments enhance material performance without relying on expensive biochemical coatings or complex cell-based therapies, positioning plasma-functionalized nanofiber dressings as practical, cost-efficient solutions for widespread clinical use, even in resource-limited health-care settings [154]. Table 5 summarises various studies conducted on the use of plasma modification of electrospinning nanofiber for wound healing application.

5. Conclusions

Electrospun nanofibers represent a promising innovation in the biomedical field due to their unique features, including high surface area, porosity, and the ability to integrate bioactive molecules. These characteristics make electrospun nanofibers ideal for applications in tissue engineering, drug delivery, and wound healing. The electrospinning process is versatile, scalable, and cost-effective, allowing the production of nanofibers with customized properties to address specific biomedical requirements. Despite these advantages, optimizing their performance for clinical use often requires surface modification to enhance biocompatibility, cell adhesion, and interactions with the surrounding biological environment. Among these approaches, plasma treatment stands out as an environmentally friendly and effective

Table 5
Plasma modification of electrospinning nanofiber for wound healing application.

Nanofiber material	Method	Plasma type	Inert and reactive gases	Observation	Refs.
Polycaprolactone nanofibrous/ Polypropylene spunbond fabric (support)	Plasma treatment after electrospinning	Low-pressure plasma -Atmospheric pressure plasma slit jet	Oxygen -argon or argon/ nitrogen	Improved the adhesion/sufficient wettability	[136]
<i>Bombyxmori</i> silk/Amoxicillin hydrochloride trihydrate (AMOX)/ polyvinyl alcohol (PVA)	Plasma treatment after electrospinning	Dielectric Barrier Discharge	Oxygen	Enhancement in tensile strength, Young's modulus, wettability and surface energy/ good antibacterial activity/ enhanced cell adhesion/ enhanced drug release ability and biocompatibility	[42]
poly (vinyl alcohol) (PVA)/ chitosan (CS)/ poly (ethylene glycol) (PEG)/ Mangifera extract (ME)	Pre-electrospinning plasma treatment	Atmospheric pressure plasma jet	Argon	Enhanced the electrospinnability of various polymers/ production of nanofibers of improved quality/ anti-infective properties/ promote faster wound healing	[137]
Chitosan/ Cotton gauze substrate	Plasma treated cotton substrate	Dielectric Barrier Discharge	Helium/ Oxygen	Increased the adhesion between nanofiber layers and gauze substrate/ reduced degradation of the nanofiber/improve antibacterial properties/ enhance absorption of wound exudates and blood	[138]
Polyvinyl Alcohol/Polylactic Acid	Plasma treatment after electrospinning	Atmospheric pressure plasma	–	Enhanced the interfacial bond strength / reduced fibrous diameter/ increased roughness/ shortened the coagulation time/ improving the hemostatic performance/ good biocompatibility	[139]
Polyvinyl Alcohol /Chitosan	Plasma treatment after electrospinning	Dielectric Barrier Discharge	Oxygen/ Argon	Improve the wettability/ formation of nano-structured roughness/ improved mechanical strength and biocompatibility/ haemolytically safe	[12]

method for functionalizing nanofiber surfaces. This technique improves wettability, promotes cell attachment, and enhances antimicrobial properties, all without altering the nanofibers' bulk characteristics. Additionally, plasma treatment can improve the mechanical strength of nanofibers, broadening their potential for various medical applications, from wound healing to tissue regeneration. The integration of plasma treatment with electrospun nanofibers presents exciting opportunities for advancing biomedical technologies, particularly in creating smart wound dressings, tissue scaffolds, and controlled drug delivery systems. Future research should aim to refine plasma treatment techniques by addressing current challenges, such as optimizing treatment parameters, improving reproducibility, and minimizing potential cytotoxic effects. Moreover, combining plasma treatments with other surface modification methods could yield synergistic benefits, paving the way for more effective and versatile nanofiber-based solutions for clinical applications.

In summary, the combination of electrospinning and plasma treatment offers tremendous potential to transform the field of biomaterials. This approach promises innovative solutions to various healthcare challenges, with the ultimate goal of enhancing patient care and outcomes. This comprehensive review underscores the critical advancements in surface modification techniques and their pivotal role in the future of wound healing technologies. By bridging current knowledge gaps and proposing future research directions, this paper aims to inspire continued innovation and interdisciplinary collaboration in the field of biomedical engineering.

CRediT authorship contribution statement

Reyhaneh Fatahian: Writing – original draft, Visualization, Formal analysis, Conceptualization, Investigation, Data curation. **Rasool Erfani:** Writing – review & editing, Resources, Formal analysis, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Dr. Reyhaneh Fatahian is a multidisciplinary researcher with a Ph.D. in Textile Chemistry and Fiber Science, specializing in nanofiber technologies, electrospinning, and biomedical applications. Her work focuses on the development of advanced wound dressings and tissue engineering scaffolds, integrating machine learning techniques to optimize nanomaterial design. Dr. Fatahian research emphasizes translating nanotechnology innovations into practical healthcare solutions.



Dr. Rasool Erfani is a Senior Lecturer in Mechanical Engineering at Manchester Metropolitan University and an Honorary Associate Professor at UCL. His research spans fluid dynamics, computational modelling, and plasma engineering technologies. He is actively engaged in healthcare innovation and applied research, with a focus on translating engineering solutions into real-world clinical and industrial impact.