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ADVANCES IN ELECTROSPUN NANOFIBERS FOR SCAR REMOVAL AND TISSUE REGENERATION

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ABSTRACT: Nanotechnology has emerged as a promising approach for wound healing and scar removal, offering unique solutions to promote tissue regeneration and reduce scarring. Electrospun nanofibers have gained significant attention owing to their ability to mimic the extracellular matrix and provide an ideal environment for cell adhesion, proliferation, and differentiation. This comprehensive review explores recent advances in electrospinning-related nanotechnology for scar management, focusing on fabrication techniques, therapeutic applications, and safety considerations. Various electrospinning methods, including needle-based, needleless, melt, emulsion, and solution electrospinning, have been discussed, highlighting their advantages and limitations. The incorporation of therapeutic agents such as drugs, growth factors, and stem cells into electrospun nanofibers has been shown to promote wound healing and reduce scar formation. However, the biocompatibility and safety of these nanomaterials remain concerns, necessitating rigorous research to ensure their long-term safety and efficacy. The potential toxicity, biodistribution, immune response, and regulatory aspects of nanotechnology-based scar treatment have been critically examined. Despite these challenges, the future prospects of electrospun nanotechnology in scar management are promising, with the potential to revolutionize wound care and improve patient outcomes. Further research and development in this field are essential for transforming these innovative approaches into clinical practice.

Keywords: Electrospun nanofibers, Wound healing, Scar management, Nanotechnology, Tissue regeneration

YARA İZİ GİDERME VE DOKU REJENERASYONU İÇİN ELEKTROSPUN NANOFİBERLERDEKİ GELİŞMELER

ÖZ: Nanoteknoloji, doku rejenerasyonunu teşvik etmek ve yara izlerini azaltmak için benzersiz çözümler sunarak yara iyileşmesi ve yara izlerinin giderilmesi için umut verici bir yaklaşım olarak ortaya çıkmıştır. Elektrospunnanofiberler, hücre dışı matrisi taklit etme ve hücre yapışması, çoğalması ve farklılaşması için ideal bir ortam sağlama yetenekleri nedeniyle büyük ilgi görmüştür. Bu kapsamlı inceleme, yara izi yönetimi için elektroeğirme ile ilgili nanoteknolojideki son gelişmeleri araştırmakta, üretim tekniklerine, terapötik uygulamalara ve güvenlik hususlarına odaklanmaktadır. İğne tabanlı, iğnesiz, eriyik, emülsiyon ve çözelti elektrospinningdahil olmak üzere çeşitli elektrospinning yöntemleri, avantajları ve sınırlamaları vurgulanarak tartışılmıştır. İlaçlar, büyüme faktörleri ve kök hücreler gibi terapötik ajanların elektroeğirilmişnanolifleredahil edilmesinin yara iyileşmesini desteklediği ve yara izi oluşumunu azalttığı gösterilmiştir. Bununla birlikte, bu nanomalzemelerinbiyouyumluluğu ve güvenliği, uzun vadeli güvenlik ve etkinliklerini sağlamak için titiz araştırmalar gerektiren endişeler olmaya devam etmektedir. Nanoteknoloji temelli yara izi tedavisinin potansiyel toksisitesi, biyo-dağılımı, bağışıklık tepkisi ve düzenleyici yönleri eleştirel bir şekilde incelenmiştir. Bu zorluklara rağmen, yara yönetiminde elektrospunnanoteknolojinin gelecekteki beklentileri, yara bakımında devrim yaratma ve hasta sonuçlarını iyileştirme potansiyeli ile umut vericidir. Bu alanda daha fazla araştırma ve geliştirme yapılması, yara izi tedavisi için elzemdir.

Anahtar Kelimeler: Elektrospun nanofiberler, Yara iyileşmesi, Yara izi yönetimi, Nanoteknoloji, Doku rejenerasyonu

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1. INTRODUCTION

Nanotechnology has been increasingly used in medicine for scar removal [1]. Scar removal is a complex process that involves the regeneration of damaged skin tissues. Nanotechnology offers unique solutions to this problem [2]. One promising application of nanotechnology for scar removal is the use of nanofibers [3]. Nanofibers are tiny fibers with diameters in the nanometer range that can be produced from various materials such as polymers, ceramics, and metals [4]. These fibers can be used to create scaffolds that support the growth of new skin tissues [5]. Nanofibers can also be loaded with drugs or growth factors to promote tissue regeneration and reduce scarring[6]. Another application of nanotechnology in scar removal is the use of nanocarriers for drug delivery [7]. Nanocarriers are tiny particles that can be loaded with drugs and targeted to specific areas of the body [8]. In scar removal, nanocarriers can deliver drugs or growth factors directly to the scar site, promoting tissue regeneration and reducing scarring [2]. Nanotechnology has also been used to develop new materials for skin regeneration[9]. Our previous paper (it is better to say “In a previous study…”) thoroughly discussed nano transdermal delivery systems that aimed to enhance skin mechanisms. This study explored the use of nano-transdermal delivery systems for drug administration. (meaning is still not clear) of herbal extracts, focusing on their potential in dermatological treatments and skin care [10].

Although many of these applications are still in the experimental stage, they offer exciting possibilities for the future of scar removal and skin repair [11]. As research and developmentcontinue, nanotechnology will provide more effective and efficient solutions for scar removal and skin regeneration.

2. UNDERSTANDING THE SCAR FORMATION AND WOUND HEALING: A MOLECULAR PERSPECTIVE

Scar formation is a complex process that involves a series of molecular and cellular events during wound healing. The initial phase of wound healing is the inflammatory phase, during which damaged tissues release pro-inflammatory cytokines and growth factors. This results in the recruitment of immune cells such as neutrophils and macrophages to the wound site [12]. During the subsequent proliferative phase, fibroblasts migrate to the wound site and synthesize extracellular matrix (ECM) proteins such as collagen and fibronectin. This is accompanied by tissue granulation, which provides a scaffold for the growth of new tissues [13]. Finally, during the remodelling phase, the ECM is reorganized and degraded to form a scar [14]. The balance between ECM synthesis and degradation during this phase is critical for determining the quality of new scar tissue [15]. Several molecular pathways that play important roles in scar formation and wound healing have been identified. For example, transforming growth factor-beta (TGF-β) signalling is critical for regulating ECM synthesis during the proliferative phase [16].

Understanding the molecular mechanisms underlying scar formation and wound healing is essential for developing new therapies for scar removal and tissue regeneration. By targeting specific molecular pathways, it may be possible to promote tissue regeneration, while reducing scar formation.

The human skin is the body's largest organ and serves as a protective barrier against the external environment that prevents dehydration and injuries. When skin is injured, a sequence of events begins immediately. Cutaneous wound repair consists of several phases, including overlapping that involves the inflammatory response, formation of tissue granulation that involves angiogenesis and re-epithelialization, and matrix remodelling [17,18]. Fig. 1 illustrates the three fundamental phases of wound healing.

Integumental injuries refer to outer wounds, while inner or closed wounds involve injuries or ruptures of the inner organs and tissues with intact skin. Skin wounds can be closed either by regeneration or repair. Regeneration involves the specific replacement of tissue, such as the superficial epidermis, mucosa, or fetal skin, whereas repair is an unspecific form of healing that involves fibrosis and scar formation. Scar formation is the predominant form of healing in adult skin wounds [19,20]. The interplay between cells, growth factors, and cytokines leads to skin closure following injury. Although disruptions in this delicate balance can occur, recent findings suggest that the absence of a particular cell type or mediator can be compensated for by other factors involved in wound healing, allowing the repair process to proceed [21].

2.1. Wound Healing Phases

The process of wound healing involves four interdependent and interrelated phases: hemostasis, inflammation, proliferation, and tissue remodelling or resolution. These phases are highly integrated and overlap each other [22]. For successful wound healing to occur, these phases and their physiological functions must occur in a specific order, with precise timing, and for a specific duration with optimal intensity [23]. Table 1 shows the wound-healing phases and their timeframes.

During the hemostasis phase, blood vessels constrict to reduce blood loss and platelets aggregate to form a clot. In the inflammation phase, immune cells such as neutrophils and macrophages are recruited to the wound site to clear debris and pathogens. Growth factors and cytokines are released during this phase to stimulate cell proliferation and angiogenesis. The proliferation phase is characterized by the migration and proliferation of fibroblasts and keratinocytes, leading to tissue granulation and re-epithelialization of the wound. During the tissue remodelling or resolution phase, the extracellular matrix is reorganized and then degraded, resulting in scar formation or tissue regeneration, depending on the extent of injury and the location of the wound. Fibroblasts, which originate from mesenchymal cells, are vital for wound healing because they produce new extracellular matrix components. Matrix production

restores tissue homeostasis [26]. The tissue remodelling phase is the final stage of wound healing and can last up to one year after injury. During this phase, collagenase enzymes secreted by fibroblasts, macrophages, and neutrophils break down collagen molecules, leading to their degradation [27]. As collagen breaks down during the tissue remodelling phase, it is gradually replaced by Type I collagen. This replacement increases the tensile strength of the new tissue over time [14]. Here, the collagen fibers in the wound tissue are thinner than those in normal dermal collagen. Over time, these thinner fibers thicken and organize themselves along the stress lines of the injury. However, the resulting scar tissue will never be as muscular as the normal tissue that preceded it [24,28,29]. Several studies have indicated that variations in inflammation during the wound healing process are strongly linked to the extent of scar tissue formation [30]. Fetal wound healing is an example of the correlation between inflammation and scar tissue formation. Fetal wounds lack typical inflammatory markers and are *"scarless"* up to a certain age [14]. In adult wound healing, polymorphonuclear leukocytes are the first immune cells to be recruited to the wound site, followed by macrophages and lymphocytes. In contrast, fetal wounds lack polymorphonuclear leukocytes, and as the healing process progresses, fetal macrophages enter the wound site in smaller numbers than in adults [2]. The lack of an inflammatory response in fetal wounds may be due to a deficiency in appropriate signalling and the immature state of fetal inflammatory cell populations. In non-healing wounds, failure to transition from the inflammatory phase to the proliferative phase can result in abnormal wound repair.

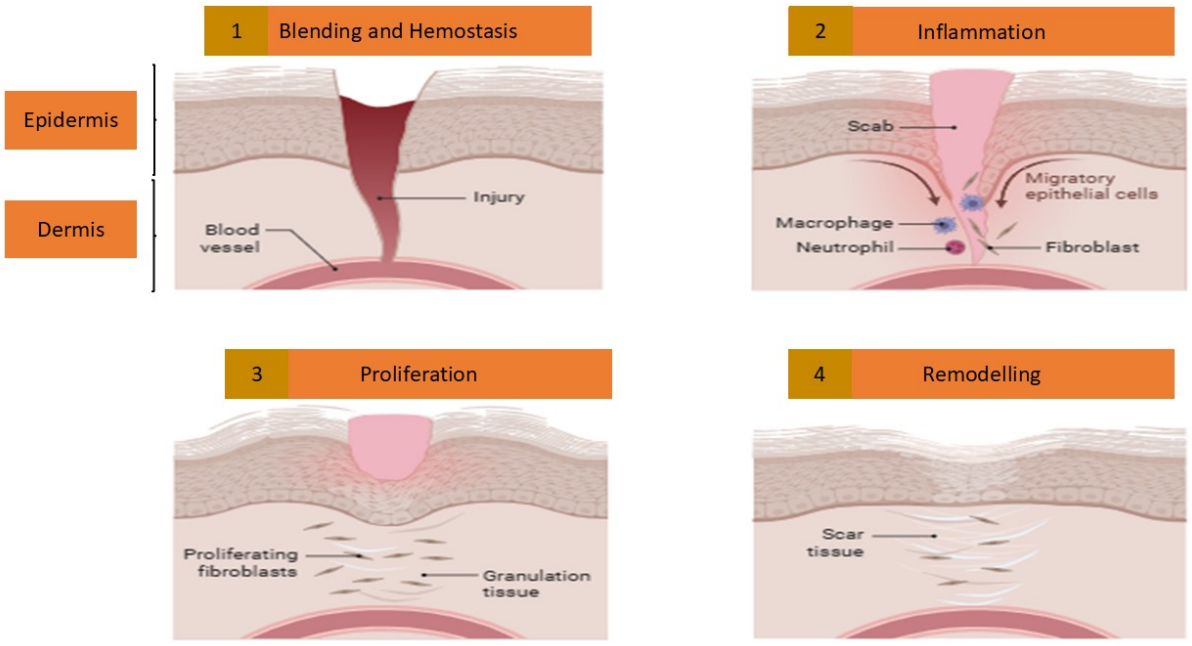

Figure1. The fundamental phases of wound healing

Table 1. Wound healing phases [24,25]

Phase	Timeframe	Description
Hemostasis	0-1 day	This phase occurs immediately after injury and lasts up to a day. It is characterized by vasoconstriction, platelet aggregation, and clot formation to stop bleeding and establish a stable wound environment.
Inflammatory	0-4 days	It begins immediately after injury and lasts up to 4 days. Inflammation is characterized by vasoconstriction, clot formation, and infiltration of immune cells to remove debris and prevent infection.
Proliferative	4-21 days	Duration from day 4 to day 21 after injury. This phase is marked by angiogenesis, fibroblast proliferation, collagen synthesis, and wound contraction.
Remodelling	21 days - 2 years	It can last up to 2 years after injury. During this phase, the wound undergoes remodelling and maturation, with collagen fibres realigning and scar tissue forming. The scar tissue gradually becomes stronger but will never regain the strength of uninjured tissue.

2.2. Factors Affecting the Wound Healing

Several factors, including age, underlying medical conditions, medications, nutrition, and lifestyle-related factors can affect wound healing. For example, older adults may experience delayed wound healing owing to reduced cell proliferation and decreased growth factor production. Diabetes, hypertension, and other chronic diseases can also impair wound healing by negatively affecting both blood flow and immune functions [31]. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) can impair wound healing by reducing the inflammatory response and inhibiting the production of growth factors [32]. Nutritional deficiencies, such as vitamin C deficiency, can impair wound healing by affecting collagen synthesis and angiogenesis [20]. Lifestyle-related factors, such as smoking and alcohol consumption, can also impair wound healing by reducing both blood flow and oxygen delivery to the wound site [31]. In short, impaired wound healing can have significant consequences such as chronic wounds, infection, and scarring. Chronic wounds, such as pressure ulcers and diabetic foot ulcers, can result from impaired wound healing due to underlying medical conditions and/or other factors [33]. Infections can also occur when the inflammatory response is inadequate, or when the wound is contaminated with bacteria. Scarring can result from excessive collagen deposition during tissue remodelling, leading to hypertrophic or keloid scars [25].

The wound healing process involves a series of complex events that involve the coordinated action of cells, growth factors, cytokines, and extracellular matrix components. Numerous factors negatively influence wound healing, leading to impaired or improper tissue repair.

3. SCAR FORMATION

Scarring is a significant burden on healthcare systems worldwide and has prompted extensive research to prevent and reduce its occurrence [34,35]. A fully mature scar is composed of Type I collagen [36]. In scar tissue, Type I collagen is arranged in bundles parallel to the skin surface, unlike the non-parallel arrangement in normal skin [37]. The epidermal basement membrane in scar tissue is flatter than in normal skin because it lacks rete pegs that usually penetrate the dermis [9]. Scar tissue also lacks other typical dermal structures, such as hair follicles or sweat glands [38,39]. As scar tissue matures, the concentration of fibroblasts within the tissue decreases. Scar tissue also has less elastin in its extracellular matrix, which contributes to the loss of tensile strength and increases the likelihood of re-injury compared to healthy tissue [40]. The degree of fibrosis after injury varies depending on the organ or affected tissue. If the molecular regulation of the tissue remodelling phase of wound healing is inefficient or disrupted, problematic scars, such as hypertrophic scars or keloids, can develop. Hypertrophic scars, such as burns, usually arise after surgery or trauma [41]. Scars are formed during wound healing in four phases: hemostasis, inflammation, proliferation, and tissue remodelling. The tissue remodelling phase is the final stage of wound healing, during which collagen is broken down and replaced by Type I collagen. The parallel arrangement of these collagen fibers reduces the tensile strength, and the absence of typical dermal structures, such as hair follicles and sweat glands, characterizes the scar tissue.

3. 1. Scar Types

3. 1. 1. Acne Scars

Acne scarring is a common concern in patients seeking facial rejuvenation. This complexity necessitates a comprehensive evaluation of each patient's unique scar profile to develop a tailored treatment plan [42]. Various treatment modalities, including chemical peels, microneedling, laser resurfacing, and dermal fillers, have shown promising results in addressing different types of acne scars [43]. The selection of an appropriate treatment or combination of treatments depends on factors such as scar type, severity, skin type, and patient preferences. While acne and its resulting scars typically occur in one's teenage years or early adulthood, patients may request treatment for acne scarring at any age [42]. The three primary categories of acne scars are ice pick, rolling, and boxcar, with the optimal treatment modality potentially varying for each subtype [44]. However, most patients have a combination of these subtypes, making determination of the optimal treatment approach more challenging. One of the primary obstacles in developing a standardized approach for treating acne scars is the lack of high-quality studies because existing studies are often small, biased, lack uniform baseline variables and outcomes, or have a limited follow-up period [45]. Fig. 2 illustrates the scar types.

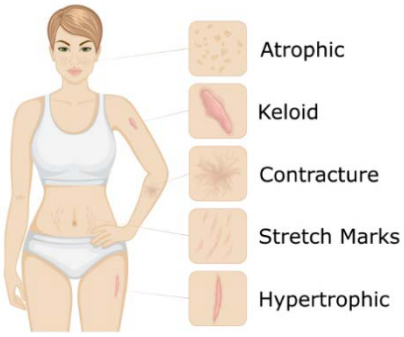

Figure 2. Type of scars

Ice Pick Scars

Ice-pick scars are narrow and deep scars that resemble the puncture made using an Ice Pick. Owing to their depth, these scars can be more challenging to treat than rolling or boxcar scars. However, some treatment options have provided excellent results. Punch excision is an effective treatment option for ice-pick scars. Although this procedure involves creating a new scar, scars from punch excision can often heal and become barely noticeable [46]. Scars should be at least 4-5 mm apart for simultaneous treatment.

If scars are too close to each other, the skin surface experiences excessive tension that can hinder optimal healing. In cases where scars are located within 4-5 mm away from one another, it is best to wait for four weeks between treatments to achieve the best long-term results [44].

Rolling Scars

Rolling scars are broad depressions in the skin with sloping edges that create a rolling or wave-like appearance. They are typically caused by damage beneath the skin surface, which can cause the subcutaneous tissue to adhere to deeper structures. Consequently, the skin surface appeared uneven and dimpled. Rolling scars can be treated using several modalities, including micro-needling and laser resurfacing. These treatments can help break up the underlying fibrous tissue, stimulate collagen production, and promote smoother skin texture. However, the ideal treatment approach may vary based on an individual's skin type and scar's severity [47].

Boxcar Scars

Boxcar scars are angular or rectangular-shaped depressions in the skin with well-defined edges. They are typically wider than Ice Pick scars and have a flat base. These scars are caused by the destruction of collagen, which results in skin depression. The ideal treatment approach for boxcar scars may vary depending on the severity of scarring; however, commonly used treatments include punch excision, dermal fillers, and laser resurfacing. Punch excision involves surgical removal of the scar, suturing the surrounding skin together with the help of dermal fillers to lift the scar and create a smoother skin surface. Laser resurfacing can promote collagen production and improve the overall appearance of skin [48,49].

Erythematous Scars

Erythematous scars are pink or red in color and are caused by excess blood flow to the scar tissue. They are typically raised, thick, and itchy and can be caused by various factors, including acne, surgery, or injury. Treatment options for such scars include the application of topical creams, silicone sheets or gels, and laser therapy. Topical creams and silicone sheets or gels can both help reduce redness and inflammation while promoting healing. Laser therapy can help reduce scar size and stimulate collagen production, resulting in smoother and less noticeable scars. The ideal treatment approach may vary depending on the severity and cause of the scar [50].

3. 1. 2. Surgical Scars

Treating surgical scars requires the consideration of various factors, such as the timing of interventions and the specific type of scar. Scars can be erythematous, raised, or depressed and may require different treatments. Patients may inquire about the benefits of silicone gel sheeting in the immediate aftermath of surgery, but evidence for its effectiveness is weak and susceptible to bias. Physicians must thoroughly understand scar management techniques, including topical treatment, injections, surgery, and laser therapy, to provide optimal patient care. Early intervention and wound care can also improve scar outcomes [51].

Hypertrophic Scars

Hypertrophic scars are raised, red, and thick scars that form because of the overproduction of collagen during healing. They are common after surgery, burns, or trauma and can cause physical and emotional discomfort for patients. The treatment options for hypertrophic scars include topical creams, corticosteroid injections, silicone sheets or gels, laser therapy, and surgery. Surgery may be considered if other treatments are ineffective, but it carries the risk of recurrence or further scarring. A combination of these treatments may be used to achieve the best results in each patient [52].

Atrophic Scars

Atrophic surgical scars are characterized by depression or indentation in the skin and present different challenges than hypertrophic scars. They can be difficult to treat and may require a tailored approach. One treatment option for atrophic surgical scars is fractional laser therapy (FLT). This therapy involves using either non-ablative or fully ablative lasers to target the scar tissue, stimulate collagen production, and improve the scar's color, texture, thickness, and patient satisfaction. Other treatments for atrophic surgical scars include the application of dermal fillers, micro-needling, or surgical scar revision. The choice of treatment depends on the severity and location of the scar as well as the patient's skin type and medical history. Physicians must have a thorough understanding of the scar management techniques to provide the optimal care for their patients with atrophic surgical scars [53–55].

4. TRADITIONAL SCAR TREATMENTS

There are various options for scar treatment depending on the type and severity of the scar. Topical treatments such as creams, gels, and silicone sheets can help improve the appearance of scars by reducing redness, flattening the scar, and improving its texture [50]. Injections of corticosteroids can treat both hypertrophic and keloid scars by reducing inflammation and flattening the scar [56]. Surgical excision is also a standard treatment for hypertrophic and keloid scars, whereas laser therapy can improve the appearance of scars and stimulate collagen production [36]. Cryotherapy involves freezing scar tissue to reduce inflammation and flattening the scar [37]. Pressure therapy involves applying pressure to the scar using a special bandage or dressing to reduce inflammation and flatten it. Radiation therapy can also be used to treat keloid scars by reducing scar size and preventing its recurrence [44].

In short, while treating acne scars, Ice Pick scars may be treated with punch excision, while rolling and boxcar scars can be treated with various methods such as dermal fillers, chemical peels, or micro-needling. Atrophic surgical scars can be treated using

fractional laser therapy, dermal fillers, micro-needling, or surgical scar revision. Table 2 summarizes the general treatment methods for scars.

5. ADVANCED APPLICATIONS OF ELECTROSPUN NANOFIBERS IN SCAR MANAGEMENT

5.1. Electrospinning

Electrospinning is a process driven by a high voltage that utilizes electrohydrodynamic principles to generate fibers from polymeric solutions [66].The application of high voltage to a liquid droplet results in both electrification and jet production, which elongates and stretches to form fibers [67].The resultant fibers exhibited diameters ranging from nanometers to several micrometers [68].The primary advantage of electrospinning is its versatility, which enables the fabrication of fibers with diverse configurations and structures [69].

A typical electrospinning apparatus comprises of three primary components [70].

i. High-voltage power supply: This generates the electric field required for fiber formation.

ii. Spinneret (metallic needle) – Directs the polymer droplet for jet formation.

iii. Grounded collector: Spin fibers are collected in the form of a nonwoven mat.

iv. The collector can assume various forms, including flat plates, spinning drums, or rotating discs.

The fundamental mechanism of electrospinning can be elucidated by considering a charged droplet of conductive liquid. When placed in a vacuum, the droplet experiences two opposing forces:[71]

i. Electrostatic repulsion: Tends to disrupt droplet integrity.

ii. Surface tension: The spherical shape of the droplet is maintained.

As the voltage is applied to the droplet at the spinneret tip, the droplet elongates into a conical shape known as the "Taylor cone." The droplet then generates a stream directed towards the collector when the electrostatic force exceeds its surface tension. This liquid can be a polymer melt, a solution, or an emulsion. Solid fibers are formed as the polymer cools down or as the solvent evaporates during the jet's trajectory from the Taylor cone to the collector, resulting in the deposition of fibers on the collector [72].Electrospinning can be categorized based on its setup, as shown in Fig. 3.

Table 2. General treatment methods for scars.

Treatment Option	Description	Reference
Topical treatments	Creams, gels, and silicone sheets can help improve the appearance of scars by reducing redness, flattening the scar, and improving texture.	[57]
Injections	Corticosteroid injections can help reduce inflammation and flatten hypertrophic and keloid scars.	[58]
Surgery	Surgical excision to remove hypertrophic and keloid scars, followed by suturing the wound closed.	[59]
Laser therapy	Laser therapy reduces redness, flattens the scar, improves texture, and stimulates collagen production to improve the skin's overall appearance.	[60]
Cryotherapy	Freezing the scar tissue to reduce inflammation and flatten the scar.	[61]
Pressure therapy	They are applying pressure to the scar using a special bandage or dressing to reduce inflammation and flatten the scar.	[62]
Radiation therapy	Theywere used to treat keloid scars by reducing the size of the scar and preventing its recurrence.	[63]
Punch excision	Surgical treatment for Ice Pick scars involves excising the scar and allowing it to heal.	[64]
Fractional laser therapy	Laser therapy to improve colour, texture, thicknessof atrophic surgical scars.	[65]

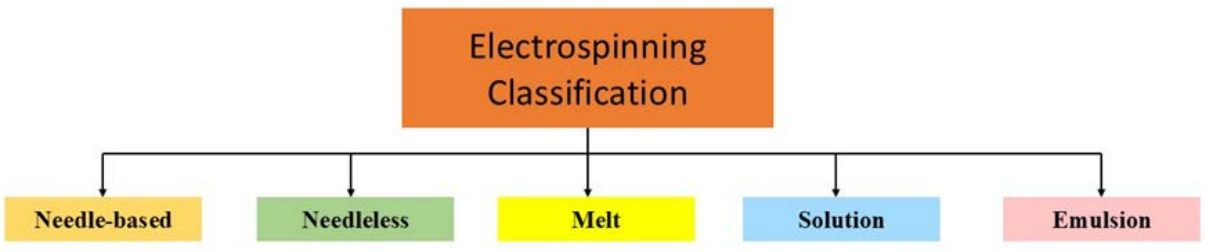

Figure 3. Electrospinning categorisation based on the setup used

This versatile technique can be used to produce fibers with tailored properties for diverse applications, rendering it a critical method in the fields of nanotechnology and materials science.

5.2. Needle-based Electrospinning

During needle electrospinning, a spinneret analogous to a needle is used, and a characteristic cone shape forms at the needle tip when subjected to an electric field [26].

5.2.1 Single NozzleElectrospinning

The fundamental electrospinning configuration employed a single needle as the spinneret, as shown in Fig. 4. This arrangement facilitated the production of individual nanofibers with controlled diameters and orientations. However, single-needle electrospinning has limitations in terms of the production rate and scalability for industrial applications [28]. To address these constraints, researchers have developed various modifications to the basic configuration, including multi-needle systems and needleless electrospinning techniques.During this procedure, an equivalent voltage is applied to both solutions, and the resultant fiber typically separates owing to repulsive forces between the two liquids [29].

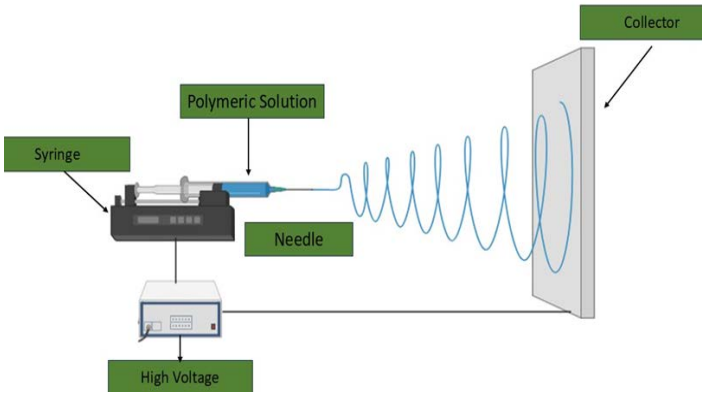

Figure 4. Schematic design of the needle-basedelectrospinning setup

5.2.2 Coaxial Electrospinning

Coaxial electrospinning uses a coaxial needle composed of two concentric hollow needles to generate a coaxially electrified jet. The conventional method of constructing a coaxial needle involves inserting a smaller inner needle into a large outer needle in a coaxial configuration. Here, two syringe pumps were employed to fill both the outer and inner needles with separate solutions, enabling independent flow rate control [30]. When subjected to an external electric field at the coaxial needle exit, the shell solution encapsulates the core solution, forming a compound Taylor cone and subsequently ejecting a coaxial jet, as shown in Fig. 5. The successful fabrication of core-shell nanofibers is contingent upon several factors, including both the inner and outer solution characteristics and electrospinning parameters. Specifically, the inner and outer solutions must possess appropriate viscosities to maintain consistent jet flow.Additionally, precise control of the flow rates of the two solutions is crucial to ensure the complete encapsulation of the inner solution by the outer solution.The modulation of these flow rates also allows the modification of both the nanofiber diameter and shell thickness [31].

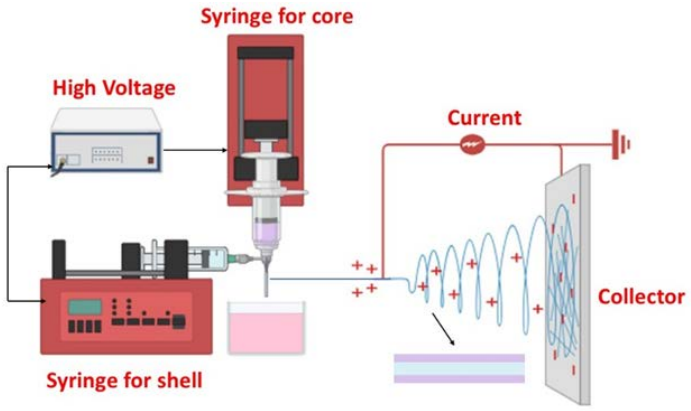

Figure 5. Schematic design of the coaxial electrospinningsetup

Coaxial electrospinning provides enhanced control over nanofiber compositions for diverse applications and facilitates the production of nanofibers from unspinnable liquids by utilizing them as the inner fluid regulated by an outer fluid.Hollow nanofibers with a customizable wall thickness can be fabricated by selective elimination of the core from spun core-shell nanofibers [73].The core-shell structure of coaxially electrospun fibers presents opportunities for the development of multifunctional materials through the incorporation of various functional components into the concentric structures of both the compounds [74].

Wei et al. engineered a core–shell nanofibrous membrane comprising a polycaprolactone (PCL) core and a chitosan/ collagen shell, utilizing an acetic acid/hexafluoroisopropanol (HFIP) mixture for the core solution and methylene dichloride for the shell solution. The PCL core imparts mechanical strength, whereas the chitosan/collagen shell enhances the biocompatibility. Silver nanoparticles embedded in the shell facilitate burst release for antibacterial efficacy, whereas vitamin A palmitate within the core is released gradually over a three-day period during cell proliferation.The evaluation of cell viability and antibacterial properties suggests the potential applicability of the membrane as a clinical wound dressing [75].

5.2.3 Tri-axial Electrospinning

A trilayer spinneret in a triaxial electrospinning apparatus that incorporates three nested metal capillaries is illustrated in Fig. 6.This technique is frequently employed to generate a three-layered structure, typically comprising a drug-infused core, hydrophobic middle section, and hydrophilic exterior layer.A significant challenge in producing high-quality multi-compartment fibers is preventing the mixing of spinning

solutions.To accomplish this, the as-used solutions must be either immiscible or evaporate at identical rates.If one solution evaporates faster than the others, all compartments may separate, thereby compromising the structure of the targeted fiber.Here, spinneret design is crucial for maintaining fiber integrity, as it must be tailored to specific application requirements [34].

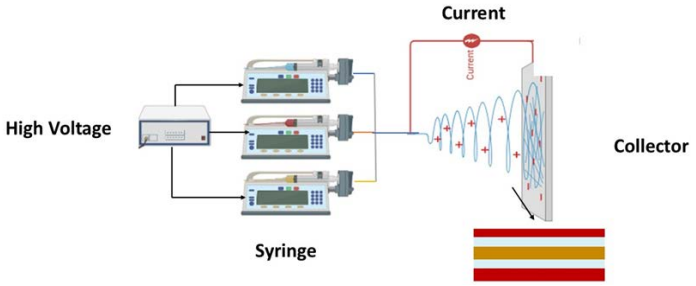

Figure 6. Schematic design of the tri-axial electrospinning setup

A well-engineered spinneret can regulate fluid behavior under an electric field and serve as a template to form the desired nanofiber structures. The initial demonstration of triaxial electrospinning utilized a combination of ethanol, lignin, and glycerin arranged from the outermost to the innermost layer. Ethanol was employed to prevent Taylor cone solidification, and glycerin was used as the template fluid. This pioneering approach established the foundation for the development of intricate fiber architectures for various applications [76].

5.2.4. Multichannel Electrospinning

The fundamental configuration for multichannel electrospinning involves the placement of three metal capillaries at the vertices of an equilateral triangle within a syringe, as illustrated in the schematic representation in Fig. 7. This arrangement facilitates the fabrication of complex fiber structures. One of the initial demonstrations of this technique was the introduction of a multifluid compound jet electrospinning method, which enabled expeditious and efficient production of biomimetic hierarchical multichannel microtubes[77].

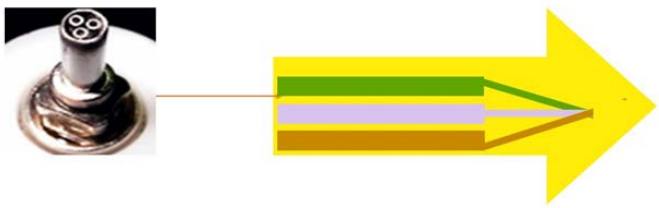

Figure 7. The multichnannelspinneret

In this approach, multiaxial electrospinning was used to develop a biomimetic system by employing multiple inner paraffin oil channels within a titanium isopropoxide solution. The organic components were subsequently removed to form multilayer channels that emulated natural structures.This methodology demonstrates the potential of multichannel electrospinning for fabricating intricate fiber architectures for advanced applications [78].

5.3 Needle-Free Electrospinning

To overcome the limitations of conventional needle-based electrospinning in terms of productivity and scalability, needle-free electrospinning methodologies have been developed and refined [38]. This technique was pioneered by Jirsak et al. at the Technical University of Liberec in the early 2000s [39]. Their primary objective was to overcome the low production rates of needle-based systems, which constrain large-scale manufacturing of nanofibers. This system involves the generation of multiple cones without the need for either a needle or small open structure. The process of jet formation in this methodology is based on self-organizing, occurs on an unconfined liquid surface, and is not driven by capillary action.Instead, it relies on an external agitation force to concentrate the electric field on the free liquid surface and then intensifies it up to the required level to initiate the Taylor cone [40]. A schematic of the needle-free electrospinning setup is shown in Figure 8. In this configuration, the polymer solution is dispensed onto a rotating or vibrating pedestal, and the control pump regulates the solution flow.A high voltage was applied to the pedestal, generating multiple jets of fibers from the polymer solution, which were subsequently collected on the collector surface.This design eliminates the need for a traditional spinneret, thus enabling a higher productivity and large-scale nanofiber production [41].

This innovative approach facilitates a higher throughput and scalability than traditional needle-based electrospinning techniques. The absence of a needle eliminates issues, such as clogging, and enables the use of more viscous polymeric solutions. Furthermore, needle-free electrospinning offers greater flexibility in terms of fiber production because multiple jets can be generated simultaneously from a single liquid surface [42, 43].

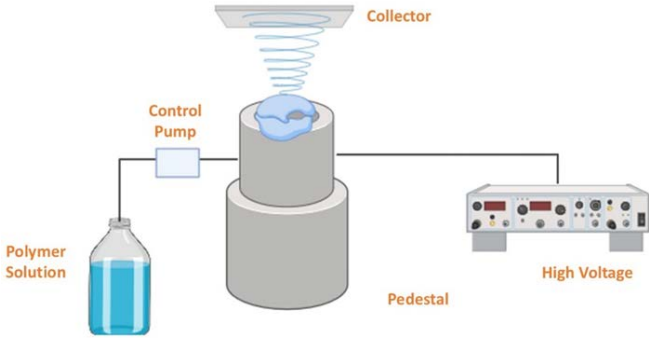

Figure 9. The needle-free electrospinning setup

The primary objective of needle-free electrospinning is to facilitate large-scale production of nanofibers by eliminating the requirement for individual nozzles or needles. In contrast to the utilization of a spinneret for fiber ejection from a single point, a rotating or vibrating surface (such as a wire, disc, or roller) that concurrently generates multiple jets of polymer solution is

employed. This approach substantially enhances throughput and enables the continuous production of nanofiber mats [79].

5. 4 Melt Electrospinning

Melt electrospinning eliminates the requirement for solvent removal and recycling, thereby addressing environmental and toxicity concerns associated with solvent utilization. In this process, the polymer was melted and introduced into a capillary tube. The entire operation must be conducted under vacuum, thereby necessitating the enclosure of a capillary tube, trajectory of the charged melt fluid jet, and metal collector [45].

One advantage of melt electrospinning is the production of highly uniform fibers with minimal variation in diameter. However, this methodology has certain limitations, including the requirement of specialized equipment and the relevant challenges presented by both the polymer melt's high viscosity and its low electrical conductivity [80]. Despite its advantages, melt electrospinning has not achieved widespread adoption or frequent utilization compared with polymeric solution-based electrospinning. This limited implementation is primarily attributed to the high viscosity, elevated process temperatures, and challenge of producing fibers in the nanometer range [81].

5. 5 Emulsion Electrospinning

Emulsion electrospinning involves two distinct methods. The first approach involves propelling an emulsion through a single nozzle during the electrospinning process, facilitating the rearrangement of the emulsion structure and resulting in a core-shell fiber analogous to that produced by coaxial electrospinning [82]. The second methodology utilizes multiple nozzles to electrospin an emulsion by generating multiple jets, thereby increasing the production rate while still forming core-shell fibers through structural reorganization [83].

This technique enhances the loading capacity of drug-polymer systems with limited compatibility, such as water-soluble drugs or proteins incorporated into hydrophobic polymers for extended release. In contrast to conventional blending techniques, emulsion electrospinning eliminates the need for a solvent capable of simultaneously dissolving both the drug and the polymer. Surfactants and other emulsifying agents are frequently used to encapsulate and stabilize the drug phase [84].

5. 6 Solution Electrospinning

Solution electrospinning is the most frequently employed method in which the polymer to be electrospun is dissolved in an appropriate solvent at an appropriate concentration. The production of nanofibers is predominantly accomplished through solution electrospinning, a technique preferred because of its straightforward methodology and versatility. Here, the selection of both the solvent and the solution concentration is critical, as they directly affect the viscosity, surface tension, and solution conductivity, which in turn influence the fiber formation and morphology [85].

The prepared polymer solution was loaded into a syringe or capillary tube connected to a high-voltage power supply. An electric field was generated between the needle tip and the grounded collector as the solution was ejected through a fine needle or nozzle. This electric field induces charges in the polymer solution, causing it to form a Taylor cone at the needle tip. When the electrostatic force exceeds the surface tension of the solution, a fine jet is ejected from the cone towards the collector. Along the trajectory, the solvent evaporates, and the jet undergoes stretching and whipping motions, resulting in the formation of ultrafine fibers that are deposited on a collector in the form of a non-woven mat [86].

6. Electrospun Nanofiber Treatments for Scar Removal

The versatility of electrospinning allows for the formation of fibrous structures from a wide range of synthetic and natural polymers, potentially facilitating scar-free wound healing. However, not all polymers can be easily electrospun because this is influenced by factors such as viscosity, concentration, and entanglement. Copolymers can be used to enhance the overall mechanical properties of polymers without suitable electrospinning characteristics. Alginate, a naturally occurring polymer, has a well-established history of improving wound healing. Its exceptional ability to swell and sustain a moist microenvironment contributes to the healing process [87]. Nevertheless, alginate lacks the optimal characteristics for electrospinning, primarily owing to its insufficient chain entanglement [88].

In a previous study,it is demonstrated that the electrospun collagen/hyaluronic acid nanofibers enhanced skin regeneration by promoting superior cell adhesion and proliferation, while providing both moisturization and structural support to the skin [89]. The incorporation of growth factors and bioactive molecules into such nanofibers can further enhance their regenerative potential. Additionally, the use of crosslinking agents may improve both the mechanical properties and stability of nanofibers in physiological media. Future studies should focus on optimizing the composition and fabrication parameters of these nanofibers to maximize their efficiency in skin tissue engineering. Polyvinyl alcohol (PVA) is a well-known polymer for electrospinning and is commonly used as a copolymer. PVA is widely utilized in industrial applications and is preferred in the medical field because of its outstanding physical characteristics, ease of processing, and compatibility with biological systems. Tarun et al. created an electrospun matrix consisting of PVA and sodium alginate [90]. The matrix demonstrated superior water vapor transmission properties, contributing to the maintenance of a moist environment conducive to wound healing. Furthermore, in vivo experiments utilizing rats with full-thickness wounds revealed new epithelial growth without any indications of local adverse effects. Indeed, maintaining wound moisture facilitates

the migration of epithelial cells across the surface, thereby promoting effective healing [91].

Chitosan, another naturally occurring polymer, exhibits notable antibacterial and antifungal properties, making it particularly advantageous for application in wound dressings. Ignatova et al. proposed that combining PVA with Q-chitosan (a modified form of chitosan) through a photo-crosslinking electrospinning method would yield a material that is efficacious against both Gram-positive and Gram-negative bacteria [92]. The results of this study demonstrate that the matrix effectively inhibited bacterial growth by exhibiting efficacy against *E. coli* and *S. aureus*. However, it is essential to acknowledge that polymers, such as chitosan, possess certain inherent limitations. For instance, chitosan is characterized by its low solubility and typically requires acidic media such as acetic acid or trifluoroacetic acid to dissolve [93,94].

Silk fibroin, a protein synthesized by certain insects such as silkworms, is another naturally occurring polymer recognized for its efficacious wound healing properties. This material is an exemplary candidate for wound repair applications owing to its high biocompatibility, anti-inflammatory characteristics, and substantial anti-scarring potential. Consequently, there has been a considerable focus on electrospinning silk to create bioactive wound dressings. Ju et al. fabricated electrospun silk fibroin nanofibers to treat burn wounds. Their research, conducted on male Sprague-Dawley rats with induced second-degree burn wounds on their dorsal regions, revealed that the silk fibroin-treated skin exhibited significantly lower expression levels of the pro-inflammatory cytokine IL-1α compared to the gauze-treated controls. Additionally, the expression profile of TGF-β1 in silk fibroin-treated wounds peaked on day 21 post-wounding before decreasing, whereas the gauze-treated wounds reached their maximum on day 7. In this study, silk fibroin nanofibers promoted rapid collagen formation, which was organized within the wound in a pattern resembling normal skin rather than scar tissue [95].

Electrospinning is compatible with a wide range of synthetic and natural polymers, enabling the selection of suitable materials to create biocompatible wound dressings. An advantage of this technique is that any potentially toxic organic solvent used during electrospinning evaporates, thereby ensuring that it does not contribute to cytotoxicity in the final products. Various polymers are commonly used in the preparation of electrospun wound dressings, including polyurethane (PU), polyvinylpyrrolidone (PVP), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly(vinyl alcohol) (PVA), and poly(ethylene glycol) (PEG) as synthetic polymers. Additionally, natural polymers, such as collagen, hyaluronic acid, gelatin, chitosan, and alginate, are also commonly used. This diverse selection of polymers allows the tailoring of wound dressings with specific properties and functionalities. Electrospun membranes can also serve as carriers for therapeutic components, further enhancing their effectiveness for wound healing. Therapeutic components may include biological, organic, or metallic substances, each serving different purposes such as inactivating pathogenic microorganisms or promoting cell proliferation. Examples of loaded components in electrospun nanofibers for skin tissue engineering and wound healing include antibiotics, biocides, metallic nanoparticles, natural extracts, growth factors, vitamins, and even cells.

Tören E. et al. [89], needleless electrospun collagen/hyaluronic acid (HA) nanofibers were evaluated for skin moisturization applications. The nanofibers had an average diameter of 300 nm and high water absorption capacity of approximately 500%. Cell culture tests revealed that fibroblast cell adhesion to the nanofiber surface exceeded 95% and cell proliferation increased by 120% after 7 days. These results highlight the potential of collagen/HA nanofibers for biomedical applications including skin moisturization and wound healing.

Zhou et al. [96] developed a wound dressing using electrospun marine collagen. The ability of the dressing to support keratinocyte adhesion and wound healing was also evaluated. Tilapia collagen was dissolved in HFP at 8 wt. % and electrospun at 16–18 kV. The collagen nanofiber membrane had an average fiber diameter of 310 nm and a pore size of 2. 75 μm. It enabled keratinocyte adhesion within 24 h and showed a 114% increase in proliferation after five days in vitro. The nanostructure of collagen fibers affects keratinocyte behavior. Hydrophilic collagen with a contact angle of 26° improved water absorption and promoted cell growth.

Pal et al. [97] conducted an investigation into the application of polycaprolactone (PCL)-chitosan nanofibers coated with collagen type I to facilitate rapid re-epithelialization. The bilayer wound dressing was fabricated by electrospinning a solution of PCL and chitosan in a chloroform:methanol (3:1) mixture and 90% acetic acid to form the initial layer. Subsequently, the membranes were immersed in fish-derived collagen solution, freeze-dried, and crosslinked using EDC/NHS. A secondary layer of fibers was electrospun onto the collagen-coated membranes. In a rat model with third-degree burns, this dressing achieved a closure rate of 96. 99 ± 0. 5% after 20 days, significantly exceeding the performance of the control Tegaderm dressing, which exhibited a closure rate of 57. 6 ± 1. 2%, and resulted in reduced scarring.

Keller and colleagues [98] developed a nanofibrous wound dressing by combining human dermal collagen with recombinant human tropoelastin in a 9:1 ratio, utilizing HFIP as the solvent at a voltage of 24-27 kV. This dressing accelerated wound healing in diabetic mouse models compared with the Oasis dressing. After 28 days, it more closely resembled natural skin and encouraged follicular neogenesis, a result that was not observed in the control group. These findings highlight the potential of ECM-mimicking dressings to enhance wound-healing outcomes.

Table 3. Summary of Nanomaterial-Based Methods for Scar Treatment and Wound Healing

Method	Polymer	Result	References
Gas injection	Chitosan	Fast coagulation, accelerated healing, increasing thickness	[99]
Multilayer electrospinning	Gelatin and PCL	Downregulation in the expression of collagen type I and TGF-β	[100]
Aqueous phase fiber reassembly technology	PCL-PEG-PCL	Porous structure, high water absorption, accelerated wound healing	[101]
Nanopattern UV-assisted capillary molding technique	Neonatal rat dermis	More migration in a vertical pattern	[102]
Designing collector	Collagen and PCL	Decreasing the inflammation and increasing migration rate and re-epithelization	[103]
Electrospinning	Gelatin and PCL	Gelatin: smaller wound area; PCL: No significant change	[104]
Rotary jet	Fibronectin	Regeneration of epiderm, derm, and adipose layer	[105]
Electrospinning	Silk fibroin	Decreasing the expression of TGF-β1 and pro-inflammatory cytokine (IL-1 Alfa) - accelerated healing	[95]
Electrospinning	Marine collagen	Accelerated wound healing	[96]
Electrospinning	Bovine collagen	Accelerated wound healing	[106]
Electrospinning	Collagen and hyaluronic acid	Changes in MMPs and TIMPs- minimized scar formation	[106]
Electrospinning	Collagen and chitosan	Increasing the healing rate	[107]
Electrospinning	PCL-PEG-PCL	Increasing keratinocyte proliferation rate	[108]
Electrospinning	PCL-PEG-PCL	Increasing keratinocyte and fibroblast proliferation and migration	[109]
Electrospinning	PLGA	Accelerated wound closure and new epithelization	[110]
Surface modification	PCL-PEG-PCL	Increasing the proliferation and angiogenesis rate	[111]
Surface modification	PCL-PEG-PCL	Downregulating TGF-β1- accelerated wound healing with minimized scar	[112]
Blending in the core	PLGA	Accelerated wound healing	[112]
Blending in the core	PLGA	Increasing the vascularization- accelerated wound healing	[110]
Blending	PCL-PEG-PCL	High water absorption-antibacterial- accelerated wound healing	[109]
pH-sensitive	PLLA	Downregulating TGF-β1 and collagen expression-Scar-free healing	[113]
Blending	PLA	Anti-inflammation and increasing the epithelization-accelerated wound healing	[114]
Secondary carrier	PLA	Capture ROS- Accelerated wound healing	[115]
Multi-jet electrospinning	CA-PEU	Early epithelization- Accelerated wound healing	[116]
Blending	PVA-PLGA	MMP-2 and TIMP downregulation- accelerated wound healing	[117]
Blending	Hyperbranched polyglycerol	Accelerated wound healing	[118]
Blending	PCL	Accelerated wound healing	[119]

In conclusion, electrospinning has proven to be highly versatile for creating advanced wound dressings that can significantly improve healing outcomes. By utilizing a wide range of synthetic and natural polymers, including collagen, PCL, and chitosan, researchers have developed dressings that not only promote keratinocyte adhesion and proliferation, but also support tissue regeneration through controlled release of bioactive agents. Studies have demonstrated that Electrospun nanofiber membranes, such as those incorporating collagen, tropoelastin, and other therapeutic agents, offer superior wound closure rates, enhanced biocompatibility, and reduced scarring. The ability to tailor these materials for specific therapeutic purposes underscores their potential for clinical applications, paving the way for more effective and personalized wound care solutions in the future.

Tören E. et all, developed AHA–BHA Infused nanofiber skin mask, elucidated the potential of nanofiber masks in mitigating inflammation, and promoting skin regeneration, which are crucial factors for both the prevention and treatment of scars [120]. This result is consistent with that of previous research on nanofiber

masks, further supporting the use of nanofiber-based materials in dermatological applications for both improved healing outcomes and scar prevention.

6. 1 Nanoparticle-Based Topical Treatments for Scar Removal

Nanoparticle-based topical treatments have emerged as a promising approach for scar removal owing to their unique properties, such as a high surface area-to-volume ratio, the ability to encapsulate drugs, and growth factors [121]. These nanoparticles can target specific cells involved in wound healing and modulate their behavior to promote scar reduction and tissue regeneration [6]. Some nanoparticles that have shown promise for scar removal include liposomes, solid lipid nanoparticles, and polymeric nanoparticles. These nanoparticles can be loaded with various therapeutic agents, such as anti-inflammatory drugs, growth factors, and antioxidants, to further enhance their efficacy [40]. One of the mechanisms by which nanoparticle-based topical treatments work is through the modulation of the inflammatory response during the wound healing process [20]. By reducing inflammation, these nanoparticles can prevent excessive scar formation and promote tissue regeneration [29]. Additionally, these nanoparticles can enhance both collagen synthesis and remodelling, thus further improving the appearance of scars. Several studies have demonstrated the efficacy of nanoparticle-based topical treatment for scar removal. One study demonstrated that polymeric nanoparticles loaded with an anti-inflammatory drug reduced scar formation and improved tissue regeneration in a mouse model [122]. Nanoparticle-based topical treatments are an exciting area of research for scar removal and tissue regeneration. These treatments have the potential to improve the efficacy of traditional scar treatments by targeting specific cellular and molecular mechanisms involved in scar formation [123]. Different types of nanoparticles, including liposomes, gold nanoparticles, and quantum dots, have been shown to effectively deliver therapeutic agents to the scar site and to promote wound healing through various mechanisms, such as reducing inflammation, enhancing collagen production, and promoting angiogenesis [124]. However, further research is needed to fully understand the safety, efficacy, and long-term effects of these treatments. Nanoparticle-based topical treatments offer promising avenues for scar removal and tissue regeneration. Table 4 presents a general overview of the nanoparticles used in scar treatment applications.

Tören E. Et all, studied nano transdermal delivery systems of herbal extracts for dermatological therapeutics and skin carethe application of nano technology to enhance the transdermal delivery of herbal extracts for dermatological treatments and skin carewasinvestigated. Thisstudyelucidatedtheimprovedefficacy of nanotechnology in facilitatingthe skin penetration of activecompoundsandthetherapeuticbenefits of herbalextracts, along with their reducedadverse effects. These finding sareparticularlyrelevanttoscartreatment, giventhecapacity of nano material stop enetrate deeply in to the skin, expedite wound healing through the iruniquephysicochemicalproperties, andprovide a promisingmethodfortheintegration of natural and biocompatiblesubstanceswithadvanceddeliverymechanisms[10]. Nanomaterials for wound healing have become increasingly popular owing to their unique physicochemical and biological properties [125]. Such nanoparticles have shown potential for promoting hemostasis, anti-infection, immunoregulation, and proliferation, and can be used in wound dressings for the sustained delivery of therapeutic agents. Additionally, nanoparticles can detect and treat bacterial infections by absorbing light and transforming it into heat, resulting in bacterial death [126]. However, there are challenges in transforming nanoparticle-based wound dressings from laboratory experiments to clinical applications, including reproducibility, toxicity, and histocompatibility [127]. Animal trials are often used to examine the behavior of nanoparticle-based wound dressings, but there is still a need for alternative preclinical studies owing to the differences between human and animal models. Intelligent wound dressings that use nanoparticles or chitosan-based formulations to detect and treat bacterial infections show promise for future wound healing processes [128].

Table 4. The most commonly used nanoparticles are used in scar treatment applications [125].

Nanoparticle	Mechanism of Action	Efficacy
Silver nanoparticles	Antimicrobial properties, promotion of collagen synthesis	Reduces scar size and inflammation
Gold nanoparticles	Anti-inflammatory properties, stimulation of cell growth and differentiation	Reduces scar size and thickness
Zinc oxide nanoparticles	Antioxidant properties, promotion of cell migration and proliferation	Reduces scar formation and improves wound healing
Liposome-encapsulated siRNA nanoparticles	Inhibition of fibroblast activity and collagen production	Reduces hypertrophic scarring and improves wound healing

6. 2. ScarTreatment Through Cell Delivery Using Electrospun Polymers

The use of electrospun polymers as scaffolds for cell delivery is a promising approach to scar treatment. These nanofibrous structures mimic the extracellular matrix, and provide an ideal environment for cell adhesion, proliferation, and differentiation. By incorporating stem cells or growth factors into electrospun polymer scaffolds, researchers aim to enhance tissue regeneration and minimize scar formation in various wound-healing applications [129].

In a previous investigation entitled "Pullulan/Collagen Scaffolds Promote Chronic Wound Healing via Mesenchymal Stem Cells," it was observed that the composite scaffolds comprising Pullulan and Collagen enhanced cell viability, reduced cell mortality, and facilitated tissue regeneration. These properties are particularly significant in the treatment of scars as they possess the potential to promote healthy cutaneous regeneration and mitigate the formation of fibrotic tissue [130].

Multiple studies have investigated the use of cellular therapy to promote wound healing and minimize scar formation. However, the conventional methodology for this research typically involves direct cell injection, which is highly inefficient and results in substantial cell death due to the shear forces experienced within the injection needle [106, 107].

In a comparable investigation, Li et al. demonstrated that mesenchymal stem cells (MSCs) incorporated into three-dimensional graphene foam reduced scar tissue formation. Here, the foam induced an increase in both vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF), promoting enhanced blood vessel formation. Furthermore, it elevates the levels of transforming growth factor beta 3 (TGF-β3), which inhibits scarring. The researchers evaluated MSC-loaded foams in vivo by utilizing a full-thickness wound model in wild-type rats. Compared to untreated or without foam load control groups, the MSC-containing foam significantly accelerated wound closure from day 3 post-injury. This trend persisted until the conclusion of the study at 14 d post-wounding [132].

The accelerated wound closure observed with the MSC-containing foam suggested a synergistic effect between the scaffold and stem cells. This combination likely creates an optimal microenvironment for tissue regeneration, promoting rapid healing, and reducing the risk of complications. Additionally, the sustained improvement in wound closure throughout the study period indicates both the potential for long-term benefits and reduced recovery times in patients with severe wounds or chronic ulcers.

7. BIOCOMPATIBILITY AND SAFETY CONSIDERATIONS OF NANOTECHNOLOGY-BASED SCAR REMOVAL

Nanotechnology has significantly shifted wound healing and scar removal [121] because nanotechnology-based approaches have revolutionized the treatment of wounds and scars by providing faster healing and better cosmetic outcomes. However, the biocompatibility and safety of these nanotechnology-based approaches remains a concern. One of the primary concerns is the potential toxicity of nanoparticles (NPs) used in wound healing and scar removal. Some studies have shown that NPs can damage cells and tissues, leading to inflammation and oxidative stress. However, the toxicity of NPs depends on their size, shape, and surface properties [133]. The biodistribution of NPs in the body is another concern, because NPs can accumulate in organs and tissues, leading to long-term adverse effects. Accumulation of NPs in the liver, lungs, and spleen has been reported in some studies. However, more research is needed to fully understand the biodistribution and potential toxicity of NPs [134]. The immune response to NPs is another concern because the immune system can recognize NPs as foreign particles and generate an immune response against them, leading to inflammation and tissue damage, depending on their size, shape, and surface properties [135].

The potential of NPs to induce genotoxicity and mutagenesis is also concerning. Some studies have shown that NPs can damage DNA and cause mutations depending on their size, shape, and surface properties [89, 112]. The biodegradability of NPs is also an important safety consideration. NPs that are not biodegradable can accumulate in the body, leading to long-term adverse effects [137]. Therefore, it is essential to develop biodegradable NPs that can be safely eliminated from the human body. Additionally, the interaction of NPs with other drugs or chemicals is another concern [138] because NPs can interact with other drugs or chemicals, leading to unexpected toxicity or adverse effects. Therefore, it is essential to consider the potential interactions of NPs with other drugs or chemicals when developing nanotechnology-based approaches for wound healing and scar removal. The potential for NPs to enter the bloodstream is also a concern, because NPs can enter the bloodstream and travel to other body parts, leading to systemic toxicity. Therefore, it is essential to develop NPs that can be localized at the site of a wound or scar. The potential for NPs to cause allergic reactions is another concern [139], because NPs can induce allergic reactions in some individuals, leading to inflammation and tissue damage. Therefore, it is essential to consider the potential of NPs to cause allergic reactions when developing nanotechnology-based approaches for wound healing and scar removal [56,130]. The long-term effects of NPs on the environment are another concern, because NPs can enter the environment through wastewater, leading to potential ecological damage. Therefore, the development of biodegradable NPs that do not adversely affect the environment is essential. The regulatory approval of nanotechnology-based approaches for wound healing and scar removal is also a concern, and both the safety and efficacy of these approaches must be demonstrated through rigorous pre-/clinical trials before regulatory approval is obtained.

The biocompatibility and safety of nanotechnology-based approaches for wound healing and scar removal remain concerns, since the potential toxicity, biodistribution, immune response,

genotoxicity, mutagenesis, biodegradability, interactions with other drugs or chemicals, potential for systemic toxicity and allergic reactions, long-term environmental effects, regulatory effects, and regulatory approval are all crucial factors to be considered while developing and evaluating new medical treatments or substances. Understanding these aspects will help to ensure the safety and efficacy of new therapies, minimize adverse side effects, and protect human health and the environment. Therefore, rigorous research and development is essential to ensure the safety and efficacy of these approaches.

8. CONCLUSIONS

This review explores recent advances in electrospun nanotechnology for scar management by focusing on fabrication techniques, therapeutic applications, and safety considerations. Various electrospinning methods, including needle-based, needleless, melt-, emulsion-, and solution-based electrospinning, have been discussed in detail by highlighting their advantages and limitations. Incorporating therapeutic agents into electrospun nanofibers has shown promise for promoting wound healing and reducing scar formation. However, the biocompatibility and safety of these nanomaterials remain concerns, and rigorous research is required to ensure their long-term safety and efficacy. The potential toxicity, biodistribution, immune response, and regulatory aspects of nanotechnology-based scar treatments were examined in a critical manner. Despite these challenges, the future prospects of electrospun nanotechnology in scar management are promising, with the potential to revolutionize wound care and improve patient outcomes.

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Declaration of Competing Interest

An earlier version of this study was published as a preprint on www. zenodo. org server. The DOI number is as follows 10. 5281/zenodo. 14933343.

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