

Review

Recent progress of electrospun nanofiber dressing in the promotion of wound healing

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Abstract: The nanofiber materials of three-dimensional spatial structure synthesized by electrospun has the characteristics of high porosity, high specific surface area, and high similarity to the natural extracellular matrix (ECM) of the human body. These are beneficial for absorbing wound exudate, effectively blocking the invasion of external bacteria, promoting cell respiration and proliferation, which provides an ideal microenvironment for wound healing. Moreover, electrospun nanofiber dressings can flexibly load drugs according to the condition of the wound, further promoting wound healing. Recently, electrospun nanofiber materials have shown promising application prospects as medical dressings in clinical. Based on current research, this article reviewed the development history of wound dressings and the principles of electrospun technology. Subsequently, based on the types of base material, polymer-based electrospun nanofiber dressing and electrospun nanofiber dressing containing drug-releasing factors were discussed. Furthermore, the application of electrospun nanofiber dressing on skin tissue is highlighted. This review aims to provide a detailed overview of the current research on electrospun nanomaterials for wound healing, addressing challenges and suggesting future research directions to advance the field of electrospun dressings in wound healing.

Keywords: Electrospun; Wound healing; Nanofiber; Polymer

1. Introduction

Skin, the largest organ of the human body, has the functions of blocking the invasion of foreign pathogens and preventing the loss of body fluids[1]. Skin is not only an important protective barrier for human body, but also an important part of the immune system. Local skin tissue is damage due to instrument trauma, burns and pathological ulcers, resulting in the loss of its original function. Once harmful microorganisms invade the wound surface, they will cause infection, delay wound healing and even affect the normal life activities of human body[2]. According to WHO, an estimated 180 000 deaths every year are caused by burns, which vast majority occur in low- and middle-income countries[3]. Globally, diabetes foot ulcers affect about 20 million people every year. Diabetes foot ulcers are the main cause of disability, death[4, 5]. The process of wound repair is long and complex, which imposes a huge burden on patients and society. Therefore, ideal wound dressings need to be developed to replace damaged skin as a temporary barrier, avoiding or managing wound infection, providing a nurturing atmosphere that promotes wound healing, shortening wound repair time and promoting wound repair[6]. At present, wound dressings can be divided into traditional dressings and new medical dressings.

Traditional dressings such as gauze and cotton pads can only temporarily cover and protect the wound. However, the hemostasis effect of traditional dressings is not satisfactory. Then they tend to adhere to the wound site, which can lead to secondary

damage when the dressing is removed[7]. Traditional dressings cannot control the humidity of the wound microenvironment, which makes it difficult to inhibit the invasion of pathogenic microorganisms in the process of long-term use and increase the risk of wound infection. Currently, traditional dressings can no longer meet people's needs for wound treatment[8].

The new medical dressing significantly overcomes the disadvantage of traditional dressings by ensuring local moisture for the wound, maintaining an oxygen environment in the local microcirculation of the wound, facilitating the dissolution of necrotic tissue, and promoting the proliferation as well as differentiation of cells.[9]. The new medical dressing retains the active substances in the exudate and promote them to release, creating a healing environment that closely resembles the physiological state. Research shows that the new wound dressing effectively promotes wound healing, significantly reduces the adverse effects of inflammatory response, and alleviates patients' suffering[10, 11]. At present, new medical dressings mainly include hydrocolloids[12], alginate[13], hydrogels[14], synthetic fibers[15] and more. Among these, the nanofiber materials synthesized by electrospun technology are characterized by high porosity, large specific surface area and a high degree of similarity to the human body's natural extracellular matrix, which provides an ideal platform for various tissue regeneration applications [16]. Electrospun nanofiber dressing are capable of absorbing wound exudate and effectively blocking the external environment, thereby facilitating wound healing. At the same time, electrospun can not only selectively load appropriate drugs according to different wounds to achieve functional enhancement, but also does not affect the drug activity with the high voltage in the preparation process of electrospun nanofiber dressing[17]. Electrospun nanofiber dressing has broad prospects in the field of promoting wound repair.

Electrospun is a process for producing nanofiber materials. Under a strong electric field, polymer solution or melt droplets transform from spherical to conical shapes, extending from the cone's tip to form fibers with a nano-sized diameter[16]. Electrospun technology has attracted the attention of researchers due to its simple operation, wide variety of raw materials available for spinning, and controllable process[18]. At present, the preparation of new wound dressings using electrospun technology is in a rapid development stage. Due to the influence of factors such as spinning raw materials, spinning process, and spinning environment, the application of the final products are mostly still in the experimental stage and has not yet achieved large-scale industrial production. This article summarized and analyzed the performance characteristics of nanofiber wound dressings prepared by electrospun technology with different polymers and additives, and discussed the application cases and research progress of electrospun nanofiber materials in promoting wound healing. Finally, the challenges in the research of electrospun nanofiber wound dressing were pointed out, which provided references for promoting the functional development and application of electrospun nanofiber materials in wound healing.

2. The stages of wound healing

Skin is the largest organ of the human body, which directly contacts with the external environment and plays a role in protecting, excreting, regulating body temperature and feeling external stimuli[19]. The normal tissue structure of the skin can be damaged by sharp tools, burns and other pathological factors and resulted in wounds[20]. The wound healing process mainly includes four phases, shown on Figure 1: hemostasis phase, inflammatory phase, cell proliferation phase and tissue remodeling phase. It is a complex repair process in which cells at different stages cooperate.

Hemostasis phase[21]: Preventing massive bleeding after further vascular damage. Usually, in the first stage, coagulation and hemostasis occur within a few hours. After vasoconstriction, platelets and inflammatory cells initiate primary hemostasis at the site of injury, while platelets secreting a variety of growth factors. These growth factors

facilitate the recruitment of epithelial cells and other cells, laying the groundwork for the inflammatory phase.

Inflammatory phase[22]: Early changes in wounds. The inflammatory phase follows the initial vasoconstriction at the onset of the hemostasis phase. The inflammatory phase usually lasts from 48 to 72 hours, but it may also take 5 to 7 days to completely end. There are varying degrees of tissue necrosis and vascular rupture with bleeding locally within the wound. Due to vascular dilation and increased permeability, fibrin and growth factors derived from plasma leak out, facilitating the infiltration of inflammatory cells into the blood vessels. Within hours, an inflammatory response ensues, ultimately resulting in tissue fluid accumulation within the wound and swelling at the wound site.

Cell proliferation phase[23]: After 2-3 days, the entire layer of skin and subcutaneous tissue at the wound's edge migrates towards the center, so that the wound rapidly shrinks. During this phase, the release of various growth factors primarily stimulates cell proliferation. At the same time, the influence of the ECM facilitates cell differentiation, subsequently promoting tissue granulation, angiogenesis and wound contraction. The cell proliferation phase will last for several weeks.

Tissue remodeling phase[24]: At this phase, the collagen of the wound gradually reorganizes and remodels to form new skin with enhanced strength and elasticity. Simultaneously, the new blood vessels further develop and mature to maintain the skin's normal physiological function. The duration of the remodeling phase varies based on individual differences and the size of the wound, usually taking several months or even longer.

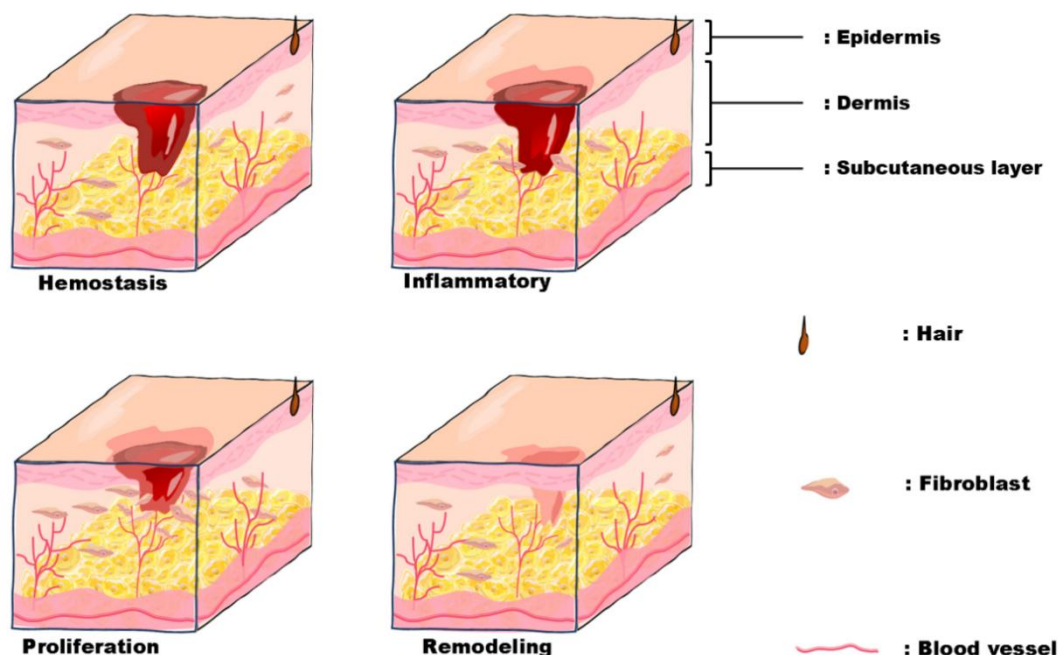


Figure 1. Wound healing process.

Proper management of skin injuries can help to accelerate the process of tissue repair and minimize the occurrence of complications. As a result, wound dressings were invented and have been continuously evolving[25].

3. Development of wound dressings

The main role of wound dressing in wound repair is to cover the damaged skin, maintain the moist environment and appropriate temperature, provide physical and microbial protection, absorb excessive tissue fluid and relieve pain[26]. Traditional

dressings are mainly used to directly cover mechanical injuries or wounds, using honey paste, animal fat and plant fiber, and other materials, which serve as a barrier for the external environment. Because the drugs loading in traditional dressings typically are physical adsorption, the release time and effective time of drugs cannot be precisely controlled, thereby prolonging the wound healing time. In addition, traditional dressings are prone to adhere to the wound, potentially causing secondary damage during removal, and do not allow for good air permeability during wound healing. Therefore, traditional dressings are suitable for temporary treatment of simple uninfected wound surfaces.

Different from traditional dressings, new medical dressings are developed on the basis of the moist healing theory. In 1962, British zoologist George Winter proposed the theory of moist healing, which states that a moderately moist and airtight environment is conducive to the rapid growth of epithelial cells and wound healing[27]. According to the mechanism of wound healing, an ideal wound dressing should be able to absorb excess exudate, prevent microbial infection of the wound, maintain a moist healing environment at the wound site, and meet the criteria of being non-toxic, biocompatible and biodegradable[9]. With ongoing research into the wound healing process and advancements in material technology, new medical dressings now mainly include hydrocolloid dressings, alginate dressings, hydrogel dressings, synthetic nanofibers dressings and more. Hydrocolloid dressings can maintain temperature, create a hypoxic environment and provide a moist healing environment. However, the loss of adhesion in hydrocolloid wound dressings is a prevalent clinical issue[28]. Repeated replacements can harm the surrounding delicate skin, severely compromising treatment efficiency and patient experience[12]. Alginate is a popular biomaterial. Alginate dressings can absorb a large amount of exudate from the wound, hydrate with necrotic tissue, and aid in self-digesting debridement[13]. But, due to its fibrous nature, it should not be used for wounds with a small amount of exudation and eschar, as it may leave excess fibers in the wound and trigger inflammation[29]. The hydrogel dressing's inherent water-containing property can provide a moist environment for the wound and create favorable conditions for tissue regeneration, making it suitable for eschar debridement[14]. However, fluid accumulation may also lead to wound infection and bacterial growth. Synthetic nanofiber dressings have high biocompatibility and exhibit similarity to the ECM, and are frequently utilized in the pharmaceutical and biomedical sectors[30]. In addition, synthetic nanofiber dressings also have biodegradable and bioabsorbable properties, which can promote the reconstruction of new tissues without causing inflammation.

The fibers prepared by dry spinning, wet spinning, and gel spinning methods rarely achieve the submicron level, but electrospun can easily obtain continuous and slender nano-sized fibers due to its unique process technology. Compared with traditional dressings, nanofiber dressings synthesized by electrospun technology possess outstanding characteristics such as high porosity, high specific surface area, high similarity to the natural ECM of the human body, and controlling drugs release [31]. Electrospun nanofiber dressings are more conducive to wound tissue repair. In addition, strong electric fields will not affect the activity of drugs in the process of synthesizing electrospun nanofiber materials. By utilizing suitable materials as carriers and incorporating functional loads such as antimicrobial, growth factors, vitamins, and proteins, the wound repair capabilities of electrospun nanofiber dressings are further enhanced.

4. Principle of electrospun

Electrospun is a production technology that can continuously produce nanofiber materials. As early as the 16th century, Gilbert found that after the solution was electrified, the droplets suspended in the solution transformed from circular to conical under the influence of an external electric field, which was the first time that the concept

of electrospun was proposed[32]. In 1915, Taylor applied mathematical modeling to describe the process of charged polymer solution or polymer melt from circular to conical, which proved that the electric field force causes the charged droplet to stretch and deform. When reaching the critical tension of the droplet, the droplet is conical and shoots a straight jet at the apex of the cone. This conical droplet is called "Taylor cone"[33]. At the beginning of this century, the focus on electrospun has broadened significantly, with more new materials being utilized in the fabrication of ceramic and composite nanofibers. Concurrently, innovative advancements in electrospun technology have led to the widespread application of electrospun nanofiber materials, particularly in the field of wound dressing, where research has seen remarkable progress over the past two decades.

The principle of electrospun as shown in Figure 2, involves applying a high voltage between the needle and the collector plate. As the voltage increases, the hemispherical droplets at the needle mouth experience a growing electric field force, leading to the formation of a "Taylor cone"[34]. This eventually overcomes the surface tension, causing the droplets to fall. As the solvent evaporates, the polymer solidifies, transforming from droplets into nanofiber materials.

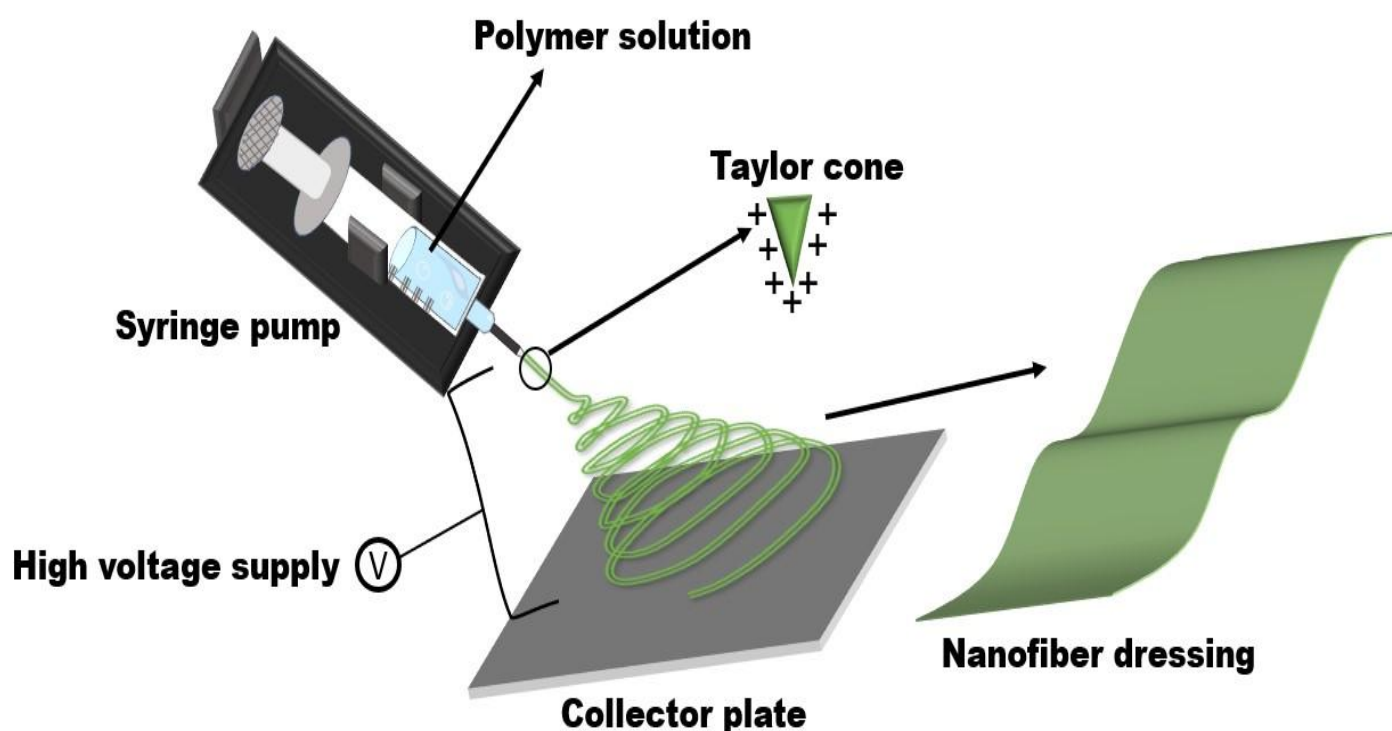


Figure 2. Schematic diagram of electrospun principle.

The following are several common electrospun methods:

Co-electrospun: Co-electrospun involves mixing two or more polymer solutions into a homogeneous solution for electrospun to obtain multicomponent nanofibers, which makes electrospun nanofiber materials have better morphology and wider applications. Feng Yunbo[35] prepared a novel multi-component zwitterionic gradient wound dressing using the co-electrospun method, achieving low biological adhesion, good humidity control, and long-term antibacterial performance during the healing process of chronic wounds[36]

Coaxial electrospun: Coaxial electrospun employs coaxial needles with inner and outer layers, which are respectively injected with a core solution and a shell solution. The two solutions are then extruded through the needles at a constant flow rate,

resulting in the preparation of composite nanofibers with a 'core-shell' structure. Compared to traditional methods, coaxial electrospun offers enhanced stability. Furthermore, it can also utilize polymers as the 'shell' to serve as templates for substances that cannot be spun into fibers alone (such as proteins, drugs, etc.), thereby broadening its range of applicability. Majid Salehi[37] et.al used coaxial electrospun technology to load kaolin into electrospun polyvinyl alcohol/chitosan polymer mixture to develop composite nanofiber dressing for melanoma postoperative treatment. This nanofiber dressing not only possesses the capability for the sustained release of chemotherapy drugs, but also promotes wound healing, offering a novel and effective approach for the post-operative treatment of melanoma[38].

Emulsion electrospun: Under the action of an emulsifier, two immiscible solutions are emulsified into emulsions, and "core-shell" structured fibers are directly obtained through spinning using a single needle. The two most common types of emulsions are oil-in-water (O/W) and water-in-oil (W/O). Compared to coaxial electrospun, this technique significantly simplifies equipment complexity and operability, while also enhancing efficiency. Basar, A. O.[39] et al. mixed a poly(ϵ -caprolactone) (PCL) solution containing ketoprofen as the oil phase with gelatin dissolved in acidified water in a 7:3 (wt/wt). The obtained water-in-oil (O/W) emulsion stabilized by the PCL-gelatin complex (also containing ketoprofen at 5 wt%) was electrospun to prepare a binary wound dressing, demonstrating a sustained drug release capability of up to 4 days[40].

5. Types of electrospun nanofiber dressings

The important application of electrospun nanofiber materials in biomedical field is medical dressing[41]. The high specific surface area and high porosity of electrospun nanofiber dressing contribute to the absorption of wound exudates and drug release, ensure gas exchange and effectively isolate the invasion of external liquids and bacteria, which provide an ideal microenvironment for promoting cell respiration and wound healing. Moreover, the flexible and convenient electrospun technology incorporates antibacterial agents, vitamins, growth factors, among others, according to the actual situation of the wound, to further promote wound healing. In order to meet the actual demand, the release rate of drugs loaded on nanofiber materials is regulated by selecting different types of polymers, controlling the position of drugs within the nanofiber materials, and altering the drug content[42, 43].

5.1. Polymer-based electrospun nanofiber dressing

5.1.1. Natural polymer-based electrospun nanofiber dressing

Natural polymers, such as polysaccharides, chitosan and proteins, have antibacterial and hemostasis function[44]. Natural polymers are synthesized into nanofiber dressings by electrospun technology, which can better promote cell adsorption and propagation and accelerate wound healing[45]. Hajali, Hadi[46] et.al demonstrated that the nanofiber dressings, which combine the natural polymer sodium alginate with lavender essential oil, offer advantages in reducing infection risk and controlling inflammatory response, proving their effectiveness in burn treatment. Natural polymer-based electrospun nanofiber dressing possesses excellent biocompatibility, degradability, low antigenicity, strong antibacterial and hemostasis properties, which can promote wound healing. They are primarily utilized in tissue engineering and postoperative wounds. However, natural polymers have complex components and limitations of poor mechanical properties. At present, the spinnability is mostly improved by adding some substances with high mechanical strength[47].

5.1.2. Synthetic polymer-based electrospun nanofiber dressing

Synthetic polymers such as polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL) and more, have excellent mechanical properties, thermal

stability, and processing flexibility, making them widely used.[48-50]. Blanquer Andreu's [51] team produced nanofiber dressings composed of PCL and PVA layers rich in platelet lysates using a needle-free multi-jet electrospun method, which enabled cell adhesion and growth, and was utilized as a continuous release system for bioactive compounds. However, synthetic polymers lack cellular binding sites and are non-biodegradable, which limits their effectiveness in promoting wound healing[16].

5.1.3. Composite materials

Electrospun wound dressings prepared from a single raw material are insufficient to meet the demands of wound care. To enhance the functionality of these dressings, researchers frequently combine natural polymers with synthetic polymers in the preparation of electrospun dressings, aiming to provide a more conducive microenvironment for accelerated wound healing[52, 53]. Fatemeh Amini [54] et.al prepared poly-hydroxybutyrate/chitosan nanofibers loaded with gentamicin and attached a layer of polyvinylidene fluoride by electrospun, which enabled controlled release of the drug and enhanced mechanical strength, making it suitable for use as a wound dressing for post-operative ulcers.

5.2. Electrospun nanofiber dressing containing drug-releasing factors

Although natural polymers and synthetic polymers possess numerous excellent properties, their capacity to promote wound healing is limited. Nanofiber materials are utilized as the substrate of dressings, loaded with drug factors, enabling them to fulfill their roles during various stages of wound healing and promote wound repair[52]. Electrospun nanofiber dressings containing drug factors mainly add drugs or growth factors with antibacterial and hemostasis properties into the electrospun solution, thereby enhancing the performance of wound excipients and facilitating wound healing[55, 56].

5.2.1. Adding antimicrobial agents

Bacterial infections often lead to an inflammatory response and delay wound healing[57]. Silver ions have strong bactericidal and antibacterial effects[58, 59]. As a type of new medical dressing, silver (Ag) nano dressing can release Ag during the treatment of wound healing, which effectively prevent wound cross infection and promote wound healing[60]. Samanta, A.[61] et.al synthesized high-yield nano silver in an aqueous medium using silver nitrate (AgNO_3) as the precursor, with sodium borohydride (NaBH_4) and polyethylene oxide (PEO) serving as the dispersed phase of the emulsion. The continuous phase of the emulsion was composed of the PCL solution in toluene. They varied the concentrations of AgNO_3 and PCL to investigate their impact on the emulsion's stability. In comparison to the emulsion formed using NaBH_4 , the nano silver produced with PEO as the reducing agent resulted in a highly stable emulsion. The in-situ synthesized silver nanoparticles were utilized as Pickering stabilizers for the poly(ϵ -caprolactone) (PCL) water-in-oil emulsion. The resulting dressing exhibited uniformity in its fiber matrix, which contained silver nanoparticles and demonstrated antibacterial properties. Ag dressing is mainly applied to open wounds, which can absorb exudates, effectively inhibit bacterial reproduction and promote wound healing[62]. Currently, most Ag dressings available in the market have shortcomings in limited antibacterial duration, frequent dressing changes, high cost and controversial toxicity in wound healing[63, 64].

5.2.2. Adding antibiotics

Antibiotics have become the first choice for the preparation of antimicrobial electrospun wound dressing because of their good antimicrobial properties. The antimicrobial dressing is prepared by electrospun the polymer solution containing

antibiotics, which can enlarge the surface area of the dressing that are insoluble in water or not easily absorbed by the human body. This makes the antibiotics to gradually diffuse into the human body with the fibers degrade, facilitating the absorption by human tissues, prolonging the drug release duration and enhancing the efficacy of the drug. Therefore, nanofiber dressings containing antibiotics are widely used in drug wound repair. Liu Shuiping [65] et.al, prepared coaxial nanofiber mats with poly(L-lactyl-co-ε-caprolactone) (PLLACL) as the shell and Tetracycline Hydrochloride (TCH) as the core through coaxial electrospun technology. In the in vitro environment at 37 °C, the release duration of TCH reached up to 180 hours, achieving effective encapsulation of TCH within the (PLLACL) nanofibers, ensuring a prolonged drug release effect. In addition, researchers have also utilized antibiotics such as cefazolin[66] and ofloxacin[67] as antimicrobial agents for electrospun nanofiber dressings, all of which exhibited good antimicrobial effects. Antibiotic dressings possess excellent antimicrobial properties, however, with the increasing resistance of bacteria to antimicrobial agents, especially antibiotics, there is an urgent need to develop new dressing that can effectively inhibit pathogenic microorganisms.

5.2.3. Adding animal and plant extracts

Numerous studies have shown that animal and plant extracts, as natural active substances, possess excellent antimicrobial ability to promote wound healing. Aloe vera gel applied to the burned area can promote skin healing and provide relief[68, 69]. Consequently, the development of electrospun wound dressings incorporating animal and plant extracts has emerged as a research hotspot in recent years[46, 70]. Cláudia Mouro[71] et al. developed a poly(L-lactic acid) (PLLA)/poly(vinyl alcohol) (PVA)/chitosan (CS) wound dressing material through W/O emulsion electrospun shown on Figure 3, produced in a single step using uniform gel-like suspensions of two different and incompatible polymer solutions. The electrospun PLLA/PVA/CS fiber mats were loaded with two different amounts of Hypericum perforatum (HP) (2.5% and 5.0%). The electrospun PLLA/PVA/CS fiber mats containing 2.5% of HP can prevent the growth of the Gram-positive bacterium staphylococcus aureus without causing cytotoxicity to normal human dermal fibroblasts, contributing to the prevention of wound infections and provides appropriate support and a microenvironment for wound healing. Herbs, as traditional medicine, have been utilized for many years in many countries such as China and India. The effective components extracted from them can address the shortcomings of inorganic antimicrobial dressings, particularly with regards to water solubility and cytotoxicity. The application value of herbs in antimicrobial dressings still requires further research.

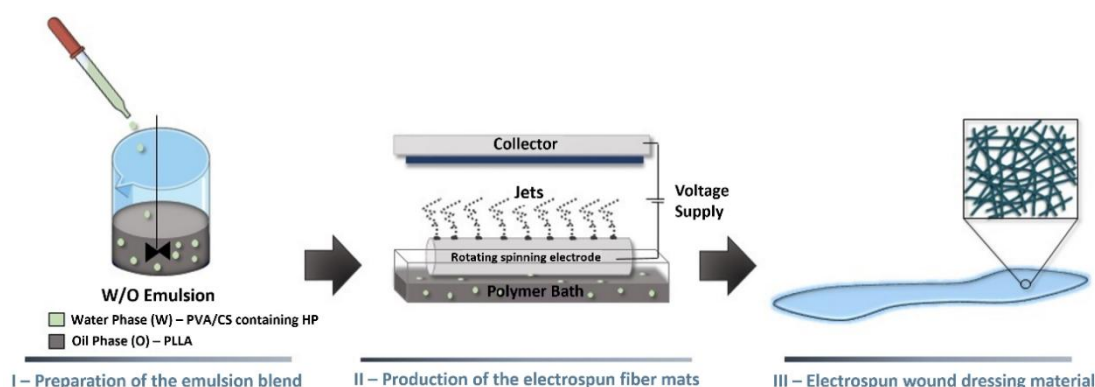


Figure 3. Preparation process of PLLA/ PVA/ CS wound dressing by W/O emulsion electrospun. reproduced from [71] MDPI 2023

5.2.4. Adding growth factors

In the stage of granulation tissue reconstruction and remodeling, drugs that can accelerate cell tissue migration and promote cell regeneration are needed. These drugs, when added to wound dressings, can shorten wound healing time and improve wound healing rate[72]. Many researchers incorporate growth factors as active substances into wound dressings, thereby promoting wound healing and enhancing performance[20]. A. Schneider[73] functionalized the electrospun nanofiber pad by adding epidermal growth factor, which gradually released over time and increased the wound closure rate by more than 3.5 times. Zhang[74] et al. used the emulsion electrospun method to prepare basic fibroblast growth factor sustained-release nano dressings with active wound healing properties from adenosine triphosphate or its salt and metal ion emulsions, which include basic fibroblast growth factor and electrospun nanofiber dressings.

6. Research progress of electrospun nanofiber dressings on skin tissue

Skin is often directly exposed to adverse environmental factors (such as harmful pathogens, physical hazards, and chemicals), making it susceptible to damage[75, 76]. Typically, wounds undergo several consecutive and overlapping stages of cellular and biochemical activities to heal. Based on the healing time, wounds can be divided into acute wounds and chronic wounds[77], including surgical wound, diabetic foot ulcer and more. As a global medical issue, wound repair faces significant clinical challenges[78]. In order to meet the clinical needs, new multifunctional medical dressings are developing rapidly. In recent years, nanofiber materials prepared by electrospun possess porous structure and high porosity, offering hemostasis and absorbent properties[79]. Moreover, these electrospun nanofiber materials can simulate the microstructure of ECM, capable of promoting cell migration and proliferation, thereby holding great promise for application in the field of wound dressing[80].

6.1. Acute wound

Acute wound refers to a wound that suddenly forms and heals quickly, or a wound that can heal within the expected time without complications after proper treatment[81]. During the normal healing process of a wound, if it is affected by certain factors such as ischemia, infection, dryness, etc., the wound healing can be delayed or even stalled, resulting in a chronic wound that is difficult to heal[82].

6.1.1. Surgical wound

Most surgeries leave a wound with its edges sewn together, using suture, staples, clips or glue[83, 84]. Postoperative wound infections are a common occurrence and can lead to pain, delay wound healing, the need for long-term antibiotic use, prolong hospital stays and increase economic burden[85]. Proper selection of postoperative dressings can provide a moist wound environment, reduce the risk of infection and blistering at the surgical site, and promote effective wound healing. At present, a variety of different electrospun nanofiber materials have been used in the treatment of surgical wounds[18, 86]. Lowe, A [87]et.al used electrospun to incorporate acrylonitrile-based ternary copolymers and NO into the main chain polymer by forming azo-dicarboxylic acid groups, thereby producing nanofiber dressings. This study created a single excised wound with an average diameter of 0.50cm² on the back of mice to observe the release of NO dressing. The NO dressings were applied to the wounds, which demonstrated that delivery of NO with a novel bandage accelerates wound healing through NO-induced angiogenesis. Kao[88]et.al prepared lidocaine/ human epidermal growth factor embedded nanofiber membranes using coaxial electrospun technology for the treatment of postoperative pelvic adhesions. Abdominal surgery was performed on rats to simulate gynecological surgery in order to evaluate the biocompatibility and efficacy of antiadhesion membranes embedded with anesthetics/growth factors. Human epidermal growth factor participates in skin wound healing by stimulating, proliferating, and

migrating keratinocytes, endothelial cells, and fibroblasts; It is beneficial for skin regeneration. And lidocaine can effectively relieve pain. Anesthetics and human epidermal growth factor nanofibers have great potential for the treatment of postoperative adhesions. But the main limitation of local anesthetics is systemic blood toxicity. Dressings should be scientifically loaded with anesthetics to ensure their safety for the human body.

6.1.2. Burn wound

Burn wound encompasses skin damage resulting from exposure to heat, extreme cold, electrical currents, chemicals, among others[89]. Due to the increase of oxygen free radicals in burn wounds, the damage to vascular endothelial cells is exacerbated, resulting in ischemia and hypoxia in the wound, which slows down wound healing[90]. Additionally, the destruction of blood vessels and sweat glands in burn wounds complicates maintaining adequate local blood circulation and keeping the wound moist, further hindering healing[91]. Hence, burn dressings must ensure local blood circulation, facilitate wound debridement and resist bacterial invasion to prevent infection[45, 92]. Given the severity of burn injuries and the urgency of treatment, the research and development of burn dressings are increasingly vital. Mateusz et.al[93] made a biodegradable wound dressing from poly(lactic-co-glycolic acid) (PLGA) and propolis solution by electrospun method as shown on Figure 4A . Creating wounds on the skin of domestic pigs through electrode heating to simulate clinical skin burns. On 21-day in vivo experiment, four domestic pigs with third-degree burns are no need to administer active substances in the form of ointment or cream daily. The propolis released from the non-woven cloth promoted burn wound healing. Alexandru [94] et al. prepared fully biodegradable chitosan/N,N,N-trimethyl chitosan (TMC) nanofiber dressings using electrospun and poly(ethylene glycol) as a sacrificial additive, which is shown on Figure 4B. This dressing exhibits strong antibacterial activity, high swelling capacity, fluid exchange, biodegradability and biocompatibility. The application in a rat deep burn model demonstrated wound closure and positive healing effects with complete restoration of the epidermis. Electrospun nanofiber materials can absorb exudates and isolate external bacteria, so they have broad prospects in the treatment of burn wounds.

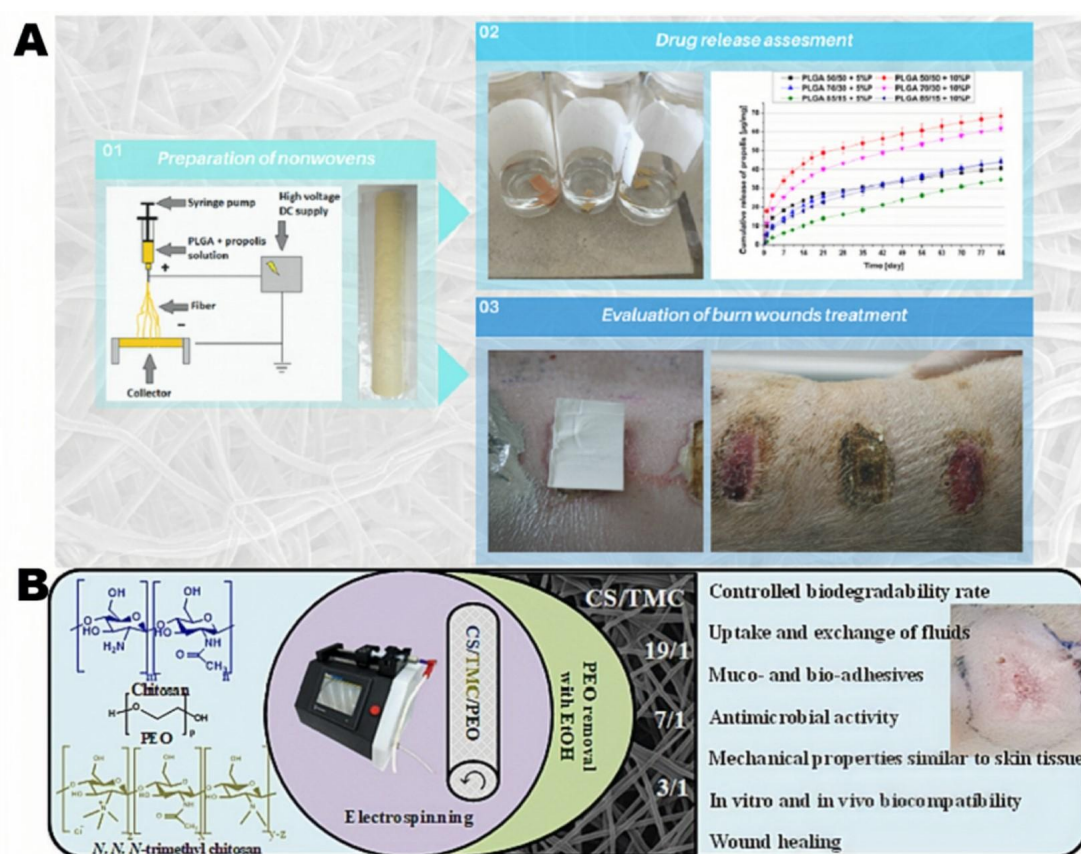


Figure 4. Preparation process of electrospun wound dressing of (A) PLGA and (B)chitosan/ TMC. A: reproduced from [93] MDPI 2020. B: adapted with permission from [94] ELSEVIER 2023.

6.2. Chronic wounds

Chronic wounds are those that cannot fully heal within a short period of time, presenting a significant challenge to clinicians and patients[95]. Generally speaking, wounds that fail to heal completely within 4-8 weeks can be considered chronic. If wound healing stops during the inflammation or proliferation stage, a normal wound can turn into a chronic wound, leading to impaired wound cell function and failure of normal healing[96, 97].

6.2.1. Diabetic foot ulcer

Diabetic foot ulcer(DFU) is a common and serious type of chronic wound in clinical settings[98]. In the clinical pathogenesis of DFU, peripheral neuropathy has a significant impact. Neuropathy of the lower extremities leads to loss of protective sensation and foot muscle atrophy and subcutaneous hemorrhage and skin ulcers[99, 100]. DFU management standard practices include wound off-loading, surgical debridement, blood glucose control and dressings, which aims to promote a moist wound environment, control exudation, assess vascular function and manage infection.[101-103].Choosing appropriate wound dressing can effectively promote wound healing and may reduce the incidence rate and economic burden on patients. Li [104] et.al prepared gelatin(Gel)/poly (lactic acid) (PLLA) nanofibrous loading with or without Salvia miltiorrhiza Bunge-Radix Puerariae herbal compound (SRHC) for wound treatment of diabetic patients through a modified electrospun strategy. The typically streptozotocin-induced diabetic mouse model with the full thickness skin wound was created and employed to evaluate the biological functions of the Gel/PLLA nanofiber dressing. Macrophages usually secrete proinflammatory factors at the wound surface. The Gel/PLLA-0 %SRHC nanofibers could inhibit the IL-6 secretion of LPS-induced M1 macrophage phenotype.

The dressings with Gel/PLLA-5 %SRHC could significantly shorten the healing time, which wound closure rate reached to be 100 % after 18 days of treatment. Yuan[105] et.al prepared polyvinyl alcohol/ astragalus polysaccharide (APS)/ astragaloside IV (AS) nanofiber membrane dressings using electrospun technology. In diabetic rat models displayed on Figure 5B, the nanofiber membrane dressings loaded with APS and AS exhibited significant wound repair capabilities, capable of inhibiting inflammation, enhancing collagen fiber deposition and regenerating epithelial repair, thereby significantly promoting the healing of diabetic wounds. Electrospun nanofiber materials hold great promise for wound dressings for diabetic wounds and tissue engineering.

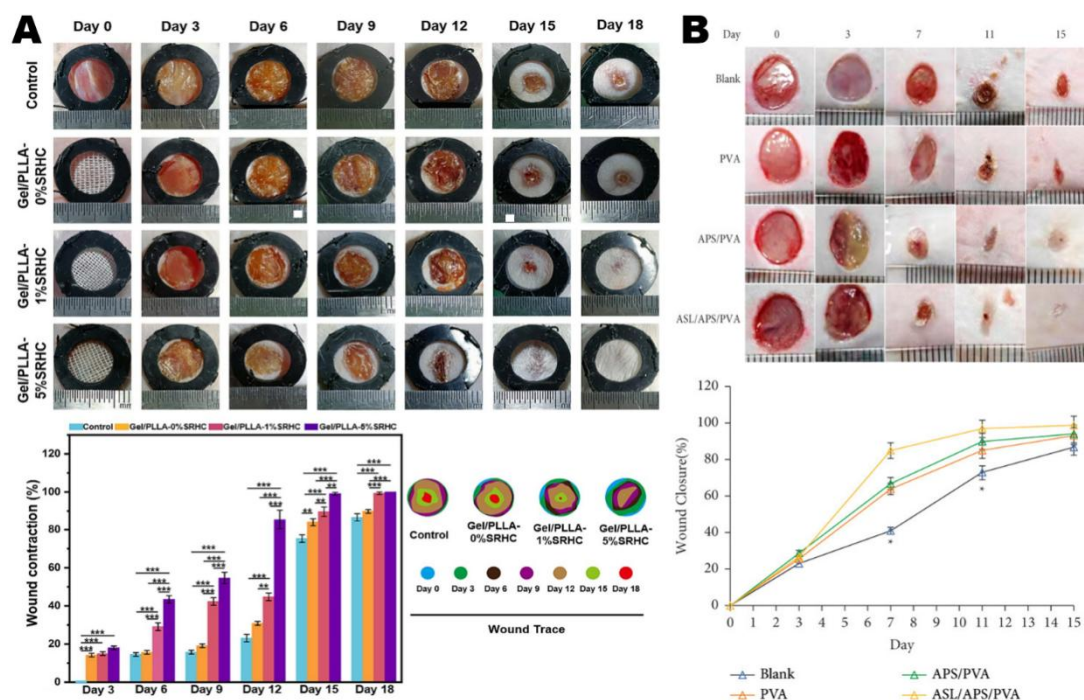


Figure 5. (A) Gel/PLLA-0% SRHC, Gel/PLLA-1% SRHC and Gel/PLLA-5% SRHC fabric dressing patches were used to treat the wounds of diabetic mice (** $p < 0.01$, *** $p < 0.001$). Adapted with permission from [104] ELSEVIER 2023. (B) The application of polyvinyl alcohol/ APS/ AS nanofiber membrane dressings using electrospun technology in the wound healing of diabetic rat. Reproduced from [105] WILEY 2022.

6.2.2. Chronic leg ulcer

Leg ulcer affecting deep tissues is the most common type of chronic wounds, which bring a heavy economic burden to the health care system and lead to long-term suffering of patients. Monika[106] et.al conducted on a novel antibacterial dressing consisting by polyurethane techophilic™, which was created through electrospun and mixed with a tetraphenylporphyrin photosensitizer that is activated by visible light. The prepared new antibacterial dressing was clinically applied to 162 patients with leg ulcers using group comparison test, which treated with and without light or dressing. In 89 patients, wounds exhibited a reduction in size, decreased levels of exfoliated tissue and fibrin cover, and increased levels of healthy granulation tissue formation and epithelialization. Additionally, there was a reduction in wound-related pain. The study of Monika et.al demonstrates the exciting application of electrospun nanofiber dressing in leg ulcer wounds, which is shown on Figure 6A. But tetraphenylporphyrin is a photosensitizer, which is irritating to skin. For such dressings, skin irritation and other adverse effects should be more fully considered.

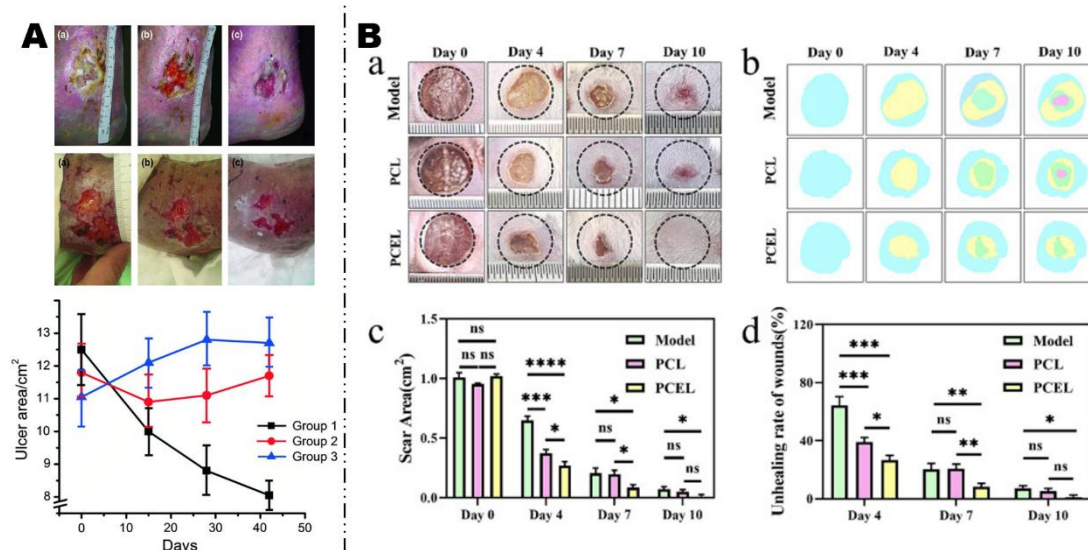


Figure 6. (A) Changes in the area of leg ulcers over time under using antibacterial dressing consisting mixed with a tetraphenylporphyrin photosensitizer by polyurethane techophilic™ and electrospun. Adapted with permission from [106] WILEY 2012. (B) The electrospun polycaprolactone/chitosan/hEGF/lidocaine nanofibers dressing for the treatment of 2 stage pressure ulcers. (a) The images of wounds in the model group, PCL group and PCEL group on different days. (b) Image software simulates the process of wound healing. (c) Scar area. (d) Wound unhealing rate. (*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, ns is no significant difference). Adapted with permission from [107] ELSEVIER 2024.

6.2.3. Pressure sore

Pressure sore is ulcer caused by applying prolonged pressure to the tissue, usually located on bone prominences[108]. They are a common complication among hospitalized patients. Because pressure sore often cannot successfully go through the inflammatory stage of wound healing, current clinical adjunctive treatments mainly involve using dressings to provide moisture and absorb exudate, local application of biological agents, debridement surgery to remove necrotic tissue and frequently rotating patients to alleviate pressure[109]. To minimize damage to the skin, protecting the wound site to reduce the risk of infection and accelerating the wound healing process is crucial. Dong[107] et.al prepared electrospun nanofiber dressings, which were combined with chitosan and polycaprolactone as scaffold materials and loaded with human epidermal growth factor (hEGF) and lidocaine. Using ischemia-reperfusion method to simulate the stage 2 pressure ulcer wound of human body on the surface of mice skin. Then the prepared nanofiber dressing was applied in stage 2 pressure ulcers shown on Figure 6B. In Dong's research, hEGF provided to promote cell proliferation, while chitosan exhibited significant antibacterial properties. Lidocaine, an analgesic, can be released immediately upon contact with the wound to reduce pain. The multifunctional electrospun nanofiber dressings offer an ideal auxiliary method for chronic wound healing and showcase the potential application of electrospun nanofiber dressing in the treatment of chronic wounds such as pressure ulcers.

7. Summary

Electrospun nanofiber materials with the high porosity, high specific surface area and micron-sized pore size, can effectively prevent external bacteria and maintain a moist wound environment, thereby facilitating the absorption of wound exudate and providing a conducive microenvironment for wound healing. Additionally, electrospun nanofiber materials can easily be loaded with drugs, thereby shortening the wound healing process. Currently, significant advancements have been made in the research of electrospun nanofiber dressings, but there are still some limitations. Firstly, the

development of electrospun devices and the setting of spinning parameters significantly impact the diameter and performance of nanofiber materials, making it challenging to obtain high-quality nanofiber materials. Secondly, electrospun nanofiber dressings are predominantly prepared in laboratories, so the efficiency of industrial batch production needs improvement. Therefore, it is necessary to develop more advanced equipment to facilitate sustainable commercial and industrial operations. Furthermore, after loading the functional additives onto the nanofiber materials, it is crucial to minimize the residual organic solvents present in the nanofibers and transition to eco-friendly solvents, or even solvent-free systems. This ensures that the prepared dressings are not only safer but also more environmentally friendly, thereby enabling a smoother transition from theoretical experiments to clinical practice.

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References

- [1] H. Nosrati, R. Aramideh Khouy, A. Nosrati, M. Khodaei, M. Banitalebi-Dehkordi, K. Ashrafi-Dehkordi, S. Sanami, Z. Alizadeh, Nanocomposite scaffolds for accelerating chronic wound healing by enhancing angiogenesis, *Journal of Nanobiotechnology* 19(1) (2021). <https://doi.org/10.1186/s12951-020-00755-7>
- [2] Y. Sun, R. Ogawa, B.-H. Xiao, Y.-X. Feng, Y. Wu, L.-H. Chen, X.-H. Gao, H.-D. Chen, Antimicrobial photodynamic therapy in skin wound healing: A systematic review of animal studies, *International Wound Journal* 17(2) (2020) 285-299. <https://doi.org/10.1111/iwj.13269>
- [3] World Health Organization. Burns [EB/OL] . (2023-10-13) [2024-1-30] . [https : //www. who. int/news-room/fact_sheets/detail/burns](https://www.who.int/news-room/fact_sheets/detail/burns).
- [4] D.G. Armstrong, J.R. Ingelfinger, A.J.M. Boulton, S.A. Bus, Diabetic Foot Ulcers and Their Recurrence, *New England Journal of Medicine* 376(24) (2017) 2367-2375. doi: 10.1056/NEJMra1615439
- [5] R. Hashempour, S. Mirhashemi, F. Mollajafari, S. Damiri, A. Arabahmadi, B. Raei, Economic burden of diabetic foot ulcer: a case of Iran, *Bmc Health Services Research* 24(1) (2024). doi: 10.1186/s12913-024-10873-9
- [6] K. Ousey, H. Hodgson, M.G. Rippon, A.A. Rogers, Hydro-responsive wound dressings for treating hard-to-heal wounds: a narrative review of the clinical evidence, *Journal of Wound Care* 30(12) (2021) 980-992. doi: 10.12968/jowc.2022.31.4.330.
- [7] M. Rippon, P. Davies, R. White, Taking the trauma out of wound care: the importance of undisturbed healing, *Journal of Wound Care* 21(8) (2012) 359-360. doi: 10.12968/jowc.2012.21.8.359
- [8] M. Salunke, V. Viswalingam, V. Shinde, Electrospun nanofibers of carbohydrate polymers for neoteric wound dressing: a review, *International Journal of Polymeric Materials and Polymeric Biomaterials* (2024). <https://doi.org/10.1080/00914037.2024.2316172>
- [9] X. Liu, H. Xu, M. Zhang, D.G. Yu, Electrospun Medicated Nanofibers for Wound Healing: Review, *Membranes*

- 11(10) (2021). doi: 10.3390/membranes11100770
- [10] K. Wikblad, B. Anderson, A comparison of three wound dressings in patients undergoing heart surgery, *Nursing Research* 44(5) (1995) 312-316. doi: 10.1097/00006199-199509000-00009
- [11] H.K.R. Nair, T.D. Yan, Use of bioelectric dressings for patients with hard-to-heal wounds: a case report, *Journal of Wound Care* 32 (2023) S8-S14. doi: 10.12968/jowc.2023.32.Sup10a.S8
- [12] D. Kong, Q. Zhang, J. You, Y. Cheng, C. Hong, Z. Chen, T. Jiang, T. Hao, Adhesion loss mechanism based on carboxymethyl cellulose-filled hydrocolloid dressings in physiological wounds environment, *Carbohydrate Polymers* 235 (2020). <https://doi.org/10.1016/j.carbpol.2020.115953>
- [13] K. Varaprasad, T. Jayaramudu, V. Kanikireddy, C. Toro, E.R. Sadiku, Alginate-based composite materials for wound dressing application: A mini review, *Carbohydrate Polymers* 236 (2020). <https://doi.org/10.1016/j.carbpol.2020.116025>
- [14] S. Misterka, Clinical evaluation of hydrogel-type dressing materials after their 8-year use, *Polimery w medycynie* 21(1-2) (1991) 23-30.
- [15] L.g. Li, J.k. Chai, Z.r. Guo, H.m. Yang, X.m. Jia, M.h. Xu, F. Li, W.h. Cao, G. Feng, Z.y. Sheng, Application of carbon fiber dressing on burn wounds, *Zhonghua wai ke za zhi [Chinese journal of surgery]* 44(15) (2006) 1047-1049.
- [16] X. Zhang, Y. Wang, Z. Gao, X. Mao, J. Cheng, L. Huang, J. Tang, Advances in wound dressing based on electrospinning nanofibers, *Journal of Applied Polymer Science* 141(1) (2024). <https://doi.org/10.1002/app.54746>
- [17] J. Pang, X. Zhou, J. Huang, Preparing drug-loaded medical dressing useful as antibacterial dressing material, comprises preparing electrospinning solution, electrospinning, and testing drug controlled release using drug-loaded medical dressing, *Jinling Inst Technology*.
- [18] R. Mohamadinooripoor, S. Kashanian, E. Arkan, An Overview on Wound Dressings and Sutures Fabricated by Electrospinning, *Biotechnology and Bioprocess Engineering* 28(1) (2023). DOI:10.1007/s12257-021-0364-y
- [19] S. Tavakoli, A.S. Klar, Advanced Hydrogels as Wound Dressings, *Biomolecules* 10(8) (2020). DOI: 10.3390/biom10081169
- [20] E.M. Tottoli, R. Dorati, I. Genta, E. Chiesa, S. Pisani, B. Conti, Skin Wound Healing Process and New Emerging Technologies for Skin Wound Care and Regeneration, *Pharmaceutics* 12(8) (2020). doi: 10.3390/pharmaceutics12080735.
- [21] M.G. Rippon, A.A. Rogers, K. Ousey, L. Atkin, K. Williams, The importance of periwound skin in wound healing: an overview of the evidence, *Journal of Wound Care* 31(8) (2022) 648-658. doi: 10.12968/jowc.2022.31.8.648.
- [22] R. Yu, H. Zhang, B. Guo, Conductive Biomaterials as Bioactive Wound Dressing for Wound Healing and Skin Tissue Engineering, *Nano-Micro Letters* 14(1) (2022).
- [23] R.B. Diller, A.J. Tabor, The Role of the Extracellular Matrix (ECM) in Wound Healing: A Review, *Biomimetics* 7(3) (2022). doi: 10.3390/biomimetics7030087.
- [24] P.H. Wang, B.S. Huang, H.C. Horng, C.C. Yeh, Y.J. Chen, Wound healing, *Journal of the Chinese Medical Association* 81(2) (2018) 94-101. doi: 10.1016/j.jcma.2017.11.002.
- [25] J. Boateng, O. Catanzano, Advanced Therapeutic Dressings for Effective Wound Healing A Review, *Journal of Pharmaceutical Sciences* 104(11) (2015) 3653-3680. DOI: 10.1002/jps.24610
- [26] Z. Obagi, G. Damiani, A. Grada, V. Falanga, Principles of Wound Dressings: A Review, *Surgical Technology International-International Developments in Surgery and Surgical Research* 35 (2019). https://www.researchgate.net/publication/335609538_Principles_of_Wound_Dressings_A_Review
- [27] W. Sun, M. Chen, D. Duan, W. Liu, W. Cui, L. Li, Effectiveness of moist dressings in wound healing after surgical suturing: A Bayesian network meta-analysis of randomised controlled trials, *International Wound Journal* 20(1) (2023)

- 69-78. DOI: 10.1111/iwj.13839
- [28] S. Abraham, G.G.S. Harsha, K. Desai, S. Furtado, B. Srinivasan, Nano Calcium Oxide Incorporated Hydrocolloid Dressings for Wound Care, *Journal of Pharmaceutical Innovation* 17(1) (2022) 215-226. DOI:10.1007/s12247-020-09521-6
- [29] X. Chen, G. Wells, D.M. Woods, Production of yarns and fabrics from alginate fibres for medical applications, 2nd International Conference on Medical Textiles, Bolton Inst, Fac Technol, Bolton, England, 1999, pp. 20-29. <https://doi.org/10.1533/9781845693145.1.20>
- [30] K. Ye, H. Kuang, Z. You, Y. Morsi, X. Mo, Electrospun Nanofibers for Tissue Engineering with Drug Loading and Release, *Pharmaceutics* 11(4) (2019). DOI: 10.3390/pharmaceutics11040182
- [31] S. Zhang, W. Yang, W. Gong, Y. Lu, D.G. Yu, P. Liu, Recent progress of electrospun nanofibers as burning dressings, *Rsc Advances* 14(20) (2024) 14374-14391. 10.1039/D4RA01514B
- [32] X. Chen, J. Wang, J. Zhang, H. Lin, M. Tian, M. Li, Y. Tian, Development and application of electrospun fiber-based multifunctional sensors, *Chemical Engineering Journal* 486 (2024) 150204. <https://doi.org/10.1016/j.cej.2024.150204>
- [33] G. Taylor, 1964, "Disintegration of Water Drops in an Electric Field," *Proc. R.Soc. London, Ser. A*, 2801382, pp. 383-397. <https://doi.org/10.1098/rspa.1964.0151>
- [34] L.E. Uhljar, R. Ambrus, Electrospinning of Potential Medical Devices (Wound Dressings, Tissue Engineering Scaffolds, Face Masks) and Their Regulatory Approach, *Pharmaceutics* 15(2) (2023). doi: 10.3390/pharmaceutics15020417.
- [35] Y. Feng, Q. Wang, M. He, X. Zhang, X. Liu, C. Zhao, Antibiofouling Zwitterionic Gradational Membranes with Moisture Retention Capability and Sustained Antimicrobial Property for Chronic Wound Infection and Skin Regeneration, *Biomacromolecules* 20(8) (2019) 3057-3069. DOI: 10.1021/acs.biomac.9b00629
- [36] W.B. Zhu, X.C. Zhang, Y.P. Wang, Y.M. Wang, Preparation of Microfibers with Multi-Hollow Structure by Co-electrospinning, *International Conference on Advanced Design and Manufacturing Engineering (ADME 2011)*, Guangzhou, PEOPLES R CHINA, 2011, pp. 536-537.
- [37] M. Salehi, S. Farzamfar, A. Ehterami, Z. Paknejad, F. Bastami, S. Shirian, H. Vahedi, G.S. Koehkonan, A. Goodarzi, Kaolin-loaded chitosan/polyvinyl alcohol electrospun scaffold as a wound dressing material: in vitro and in vivo studies, *Journal of Wound Care* 29(5) (2020) 270-280.
- [38] R. Longo, M. Catauro, L. Vertuccio, L. Guadagno, Comparison between Morphological and Mechanical Properties of Membranes Produced via Coaxial and Monoaxial Electrospinning, *International Polymer Characterization Conference (POLY-CHAR)*, Siegen, GERMANY Electr Network, 2022. <https://doi.org/10.1002/masy.202200155>
- [39] A.O. Basar, S. Castro, S. Torres Giner, J.M. Lagaron, H.T. Sasmazel, Novel poly(ϵ -caprolactone)/gelatin wound dressings prepared by emulsion electrospinning with controlled release capacity of Ketoprofen anti-inflammatory drug, *Materials Science & Engineering C-Materials for Biological Applications* 81 (2017) 459-468. <https://doi.org/10.1016/j.msec.2017.08.025>
- [40] B. Zhan, M. Aliabadi, G.Y. Wang, Z.B. Chen, W.T. Zhou, T. Stegmaier, W. Konrad, G. Gresser, C. Kaya, Y. Liu, Z.W. Han, L.Q. Ren, Underwater Oleophobic Electrospun Membrane with Spindle-Knotted Structured Fibers for Oil-in-Water Emulsion Separation, *Langmuir* (2023). DOI: 10.1021/acs.langmuir.2c02943
- [41] C. Huang, X. Xu, J. Fu, D.G. Yu, Y. Liu, Recent Progress in Electrospun Polyacrylonitrile Nanofiber-Based Wound Dressing, *Polymers* 14(16) (2022). <https://doi.org/10.3390/polym14163266>
- [42] M. Joshi, B.S. Butola, K. Saha, Advances in Topical Drug Delivery System: Micro to Nanofibrous Structures, *Journal of Nanoscience and Nanotechnology* 14(1) (2014) 853-867. doi: 10.1166/jnn.2014.9083.

- [43] N. Akombaetwa, A. Bwanga, P.A. Makoni, B.A. Witika, Applications of Electrospun Drug-Eluting Nanofibers in Wound Healing: Current and Future Perspectives, *Polymers* 14(14) (2022). <https://doi.org/10.3390/polym14142931>
- [44] A.D.J. Bombin, N.J. Dunne, H.O. McCarthy, Electrospinning of natural polymers for the production of nanofibres for wound healing applications, *Materials Science and Engineering C-Materials for Biological Applications* 114 (2020). <https://doi.org/10.1016/j.msec.2020.110994>
- [45] R.R. Ujjwal, A. Yadav, S. Tripathi, S.T.V.S. Krishna, Polymer-based Nanotherapeutics for Burn Wounds, *Current Pharmaceutical Biotechnology* 23(12) (2022) 1460-1482. DOI: 10.2174/1389201022666210927103755
- [46] H. Hajiali, M. Summa, D. Russo, A. Armirotti, V. Brunetti, R. Bertorelli, A. Athanassiou, E. Mele, Alginate-lavender nanofibers with antibacterial and anti-inflammatory activity to effectively promote burn healing, *Journal of Materials Chemistry B* 4(9) (2016) 1686-1695. DOI: 10.1039/c5tb02174j
- [47] G.B. Park, BURN WOUND COVERINGS - REVIEW, *Biomaterials Medical Devices and Artificial Organs* 6(1) (1978) 1-35. DOI: 10.3109/10731197809118690
- [48] K. Sutjarittangtham, S. Sanpa, T. Tunkasiri, P. Chantawannakul, U. Intatha, S. Eitssayeam, Bactericidal effects of propolis/polylactic acid (PLA) nanofibres obtained via electrospinning, *Journal of Apicultural Research* 53(1) (2014) 109-115. <https://doi.org/10.3896/IBRA.1.53.1.11>
- [49] S.A. Karthick, T.K. Ragavi, K. Naresh, P.S.R. Sreekanth, A study on collagen-PVA and chitosan-PVA nanofibrous matrix for wound dressing application, 1st International Conference on Advances in Mechanical Engineering and Material Science (ICAMEMS), Electr Network, 2022, pp. 1347-1350. <https://doi.org/10.1016/j.matpr.2021.11.421>
- [50] L. Yin, Q.W. Tang, Q. Ke, X.Y. Zhang, J.Y. Su, H. Zhong, L.M. Fang, Sequential Anti-Infection and Proangiogenesis of DMOG@ZIF-8/Gelatin-PCL Electrospinning Dressing for Chronic Wound Healing, *Acs Applied Materials & Interfaces* 15(42) (2023) 48903-48912. DOI: 10.1021/acsami.3c09584
- [51] A. Blanquer, E.K. Kostakova, E. Filova, M. Lisnenko, A. Broz, J. Mullerova, V. Novotny, K. Havlickova, S. Jakubkova, S. Hauzerova, B. Heczkova, R. Prochazkova, L. Bacakova, V. Jencova, A novel bifunctional multilayered nanofibrous membrane combining polycaprolactone and poly (vinyl alcohol) enriched with platelet lysate for skin wound healing, *Nanoscale* 16(4) (2024) 1924-1941. DOI:10.1039/D3NR04705A
- [52] A. Gul, I. Gallus, A. Tegginamath, J. Maryska, F. Yalcinkaya, Electrospun Antibacterial Nanomaterials for Wound Dressings Applications, *Membranes* 11(12) (2021). DOI: 10.3390/membranes11120908
- [53] M. Liu, X.-P. Duan, Y.-M. Li, D.-P. Yang, Y.-Z. Long, Electrospun nanofibers for wound healing, *Materials Science and Engineering C-Materials for Biological Applications* 76 (2017) 1413-1423. <https://doi.org/10.1016/j.msec.2017.03.034>
- [54] F. Amini, D. Semnani, S. Karbasi, S.N. Banitaba, A novel bilayer drug-loaded wound dressing of PVDF and PHB/Chitosan nanofibers applicable for post-surgical ulcers, *International Journal of Polymeric Materials and Polymeric Biomaterials* 68(13) (2019) 772-777. <https://doi.org/10.1080/00914037.2018.1506982>
- [55] F. Cheng, J. Gao, L. Wang, X. Hu, Composite chitosan/poly(ethylene oxide) electrospun nanofibrous mats as novel wound dressing matrixes for the controlled release of drugs, *Journal of Applied Polymer Science* 132(24) (2015). <https://doi.org/10.1002/app.42060>
- [56] S. Yang, X. Li, P. Liu, M. Zhang, C. Wang, B. Zhang, Multifunctional Chitosan/Polycaprolactone Nanofiber Scaffolds with Varied Dual-Drug Release for Wound-Healing Applications, *Acs Biomaterials Science & Engineering* 6(8) (2020) 4666-4676. <https://doi.org/10.1021/acsbiomaterials.0c00674>
- [57] Q. Yu, Y. Yan, J. Huang, Q. Liang, J. Li, B. Wang, B. Ma, A. Bianco, S. Ge, J. Shao, A multifunctional chitosan-based hydrogel with self-healing, antibacterial, and immunomodulatory effects as wound dressing, *International Journal of Biological Macromolecules* 231 (2023). DOI: 10.1016/j.ijbiomac.2023.123149
- [58] J.Y. Cheon, S.J. Kim, Y.H. Rhee, O.H. Kwon, W.H. Park, Shape-dependent antimicrobial activities of silver

- nanoparticles, *International Journal of Nanomedicine* 14 (2019) 2773-2780. DOI: 10.2147/IJN.S196472
- [59] K. Zheng, M.I. Setyawati, D.T. Leong, J. Xie, Antimicrobial silver nanomaterials, *Coordination Chemistry Reviews* 357 (2018) 1-17. DOI: 10.1016/j.ccr.2017.11.019
- [60] K. Kalantari, E. Mostafavi, A.M. Afifi, Z. Izadiyan, H. Jahangirian, R. Rafiee-Moghaddam, T.J. Webster, Wound dressings functionalized with silver nanoparticles: promises and pitfalls, *Nanoscale* 12(4) (2020) 2268-2291. DOI: 10.1039/c9nr08234d
- [61] A. Samanta, S. Takkar, R. Kulshreshtha, B. Nandan, R.K. Srivastava, Nano-silver stabilized Pickering emulsions and their antimicrobial electrospun fibrous matrices, *Biomedical Physics & Engineering Express* 3(3) (2017) 035011 (8 pp.). DOI 10.1088/2057-1976/aa6c32
- [62] M.A.J. Kouhbanani, S. Mosleh-Shirazi, N. Beheshtkhoo, S.R. Kasaee, S. Nekouian, S. Alshehery, H. Kamyab, S. Chelliapan, M.A. Ali, A.M. Amani, Investigation through the antimicrobial activity of electrospun PCL nanofiber mats with green synthesized Ag-Fe nanoparticles, *Journal of Drug Delivery Science and Technology* 85 (2023). <https://doi.org/10.1016/j.jddst.2023.104541>
- [63] N. Lewis, V. Kolimarala, A. Lander, Conservative management of exomphalos major with silver dressings: are they safe?, *Journal of Pediatric Surgery* 45(12) (2010) 2438-2439. <https://doi.org/10.1016/j.jpedsurg.2010.08.013>
- [64] S.B. Zou, W.Y. Yoon, S.K. Han, S.H. Jeong, Z.J. Cui, W.K. Kim, Cytotoxicity of silver dressings on diabetic fibroblasts, *International Wound Journal* 10(3) (2013) 306-312. DOI: 10.1111/j.1742-481X.2012.00977.x
- [65] S. Liu, X. Li, Y. Su, L. Tan, Y. Zhang, Y. Chen, Study of Electrospun PLLACL Nanofibrous Mats for Drug Delivery System, *International Materials Research Conference, Chongqing, PEOPLES R CHINA, 2008*, pp. 1319-1322. DOI:10.4028/www.scientific.net/MSF.610-613.1319
- [66] G. Rath, T. Hussain, G. Chauhan, T. Garg, A.K. Goyal, Development and characterization of cefazolin loaded zinc oxide nanoparticles composite gelatin nanofiber mats for postoperative surgical wounds, *Materials Science & Engineering C-Materials for Biological Applications* 58 (2016) 242-253. <https://doi.org/10.1016/j.msec.2015.08.050>
- [67] F.N. Morad, A. Rashid, R. Khajavi, M.K. Rahimi, A. Bahador, Producing Ofloxacin Loaded Gum Tragacanth/Bassorin Electrospun Nano Fibers and Evaluation Its Antibacterial Activity, *Ekoloji* 28(107) (2019) 391-400. <https://www.researchgate.net/publication/319122943>
- [68] M.P. Sikka, J.A. Bargir, S. Garg, Modern developments in burn wound dressing, *Research Journal of Textile and Apparel* (2024). DOI:10.1108/rjta-08-2023-0084. DOI:10.1108/rjta-08-2023-0084
- [69] H. Liu, Y. Bai, C. Huang, Y. Wang, Y. Ji, Y. Du, L. Xu, D.-G. Yu, S.W.A. Bligh, Recent Progress of Electrospun Herbal Medicine Nanofibers, *Biomolecules* 13(1) (2023). <https://doi.org/10.3390/biom13010184>
- [70] R. Ramalingam, C. Dhand, V. Mayandi, C.M. Leung, H. Ezhilarasu, S.K. Karuppannan, P. Prasannan, S.T. Ong, N. Sunderasan, I. Kaliappan, M. Kamruddin, V.A. Barathi, N.K. Verma, S. Ramakrishna, R. Lakshminarayanan, K.D. Arunachalam, Core-Shell Structured Antimicrobial Nanofiber Dressings Containing Herbal Extract and Antibiotics Combination for the Prevention of Biofilms and Promotion of Cutaneous Wound Healing, *Acs Applied Materials & Interfaces* 13(21) (2021) 24356-24369. DOI: 10.1021/acsami.0c20642
- [71] C. Mouro, A.P. Gomes, I.C. Gouveia, Emulsion Electrospinning of PLLA/PVA/Chitosan with Hypericum perforatum L. as an Antibacterial Nanofibrous Wound Dressing, *Gels* 9(5) (2023). <https://doi.org/10.3390/gels9050353>
- [72] S. Yamakawa, K. Hayashida, Advances in surgical applications of growth factors for wound healing, *Burns & Trauma* 7 (2019). DOI: 10.1186/s41038-019-0148-1
- [73] A. Schneider, X.Y. Wang, D.L. Kaplan, J.A. Garlick, C. Egles, Biofunctionalized electrospun silk mats as a topical bioactive dressing for accelerated wound healing, *Acta Biomaterialia* 5(7) (2009) 2570-2578. <https://doi.org/10.1016/j.actbio.2008.12.013>

- [74] S. Zhang, Z. Su, S. Che, Basic fibroblast growth factor slow-release nano-dressing with active wound healing function used for preparing material for promoting wound healing, comprises basic fibroblast growth factor and electrospun nanofiber membrane prepared by emulsion of adenosine triphosphate or salt and metal ions, *Inst Process Eng Chinese Acad Sci*.
- [75] L. Qi, C. Zhang, B. Wang, J. Yin, S. Yan, Progress in Hydrogels for Skin Wound Repair, *Macromolecular Bioscience* 22(7) (2022). DOI: 10.1002/mabi.202100475
- [76] A. Jakovija, T. Chtanova, Skin immunity in wound healing and cancer, *Frontiers in Immunology* 14 (2023). <https://doi.org/10.3389/fimmu.2023.1060258>
- [77] P. Martin, R. Nunan, Cellular and molecular mechanisms of repair in acute and chronic wound healing, *British Journal of Dermatology* 173(2) (2015) 370-378.
- [78] Y. An, S. Lin, X. Tan, S. Zhu, F. Nie, Y. Zhen, L. Gu, C. Zhang, B. Wang, W. Wei, D. Li, J. Wu, Exosomes from adipose-derived stem cells and application to skin wound healing, *Cell Proliferation* 54(3) (2021). DOI: 10.1111/cpr.12993
- [79] T.A. Jackson, Y.P. Neo, S.P. Sisinthy, B. Gorain, Delivery of Therapeutics from Layer-by-Layer Electrospun Nanofiber Matrix for Wound Healing: An Update, *Journal of Pharmaceutical Sciences* 110(2) (2021) 635-653. <https://doi.org/10.1016/j.xphs.2020.10.003>
- [80] S. Chen, B. Liu, M.A. Carlson, A.F. Gombart, D.A. Reilly, J. Xie, Recent advances in electrospun nanofibers for wound healing, *Nanomedicine* 12(11) (2017) 1335-1352. <https://doi.org/10.1016/j.eurpolymj.2022.111490>
- [81] M.E. Okur, I.D. Karantas, Z. Senyigit, N.U. Okur, P.I. Siafaka, Recent trends on wound management: New therapeutic choices based on polymeric carriers, *Asian Journal of Pharmaceutical Sciences* 15(6) (2020) 661-684. <https://doi.org/10.1016/j.ajps.2019.11.008>
- [82] K. Raziyeve, Y. Kim, Z. Zharkinbekov, K. Kassymbek, S. Jimi, A. Saparov, Immunology of Acute and Chronic Wound Healing, *Biomolecules* 11(5) (2021). DOI: 10.3390/biom11050700
- [83] J.C. Dumville, T.A. Gray, C.J. Walter, C.A. Sharp, T. Page, Dressings for the prevention of surgical site infection, *Cochrane Database of Systematic Reviews* (9) (2014). DOI: 10.1002/14651858.CD003091.pub4
- [84] J.C. Dumville, T.A. Gray, C.J. Walter, C.A. Sharp, T. Page, R. Macefield, N. Blencowe, T.K.G. Milne, B.C. Reeves, J. Blazeby, Dressings for the prevention of surgical site infection, *Cochrane Database of Systematic Reviews* (12) (2016). DOI: 10.1002/14651858.CD003091.pub4
- [85] B.M. Andersen, Prevention of Postoperative Wound Infections, in: B.M. Andersen (Ed.), *Prevention and Control of Infections in Hospitals: Practice and Theory*, Springer International Publishing, Cham, 2019, pp. 377-437. DOI: 10.1007/s00104-009-1860-3
- [86] R.H. Dong, Y.X. Jia, C.C. Qin, L. Zhan, X. Yan, L. Cui, Y. Zhou, X. Jiang, Y.-Z. Long, In situ deposition of a personalized nanofibrous dressing via a handy electrospinning device for skin wound care, *Nanoscale* 8(6) (2016) 3482-3488. DOI: 10.1039/c5nr08367b
- [87] A. Lowe, J. Bills, R. Verma, L. Lavery, K. Davis, K.J. Balkus, Electrospun nitric oxide releasing bandage with enhanced wound healing, *Acta Biomaterialia* 13 (2015) 121-130. <https://doi.org/10.1016/j.actbio.2014.11.032>
- [88] C.W. Kao, Y.Y. Tseng, K.S. Liu, Y.W. Liu, J.C. Chen, H.L. He, Y.C. Kau, S.J. Liu, Anesthetics and human epidermal growth factor incorporated into anti-adhesive nanofibers provide sustained pain relief and promote healing of surgical wounds, *International Journal of Nanomedicine* Volume 14 (2019) 4007-4016. DOI: 10.2147/IJN.S202402
- [89] C. Shi, C. Wang, H. Liu, Q. Li, R. Li, Y. Zhang, Y. Liu, Y. Shao, J. Wang, Selection of Appropriate Wound Dressing for Various Wounds, *Frontiers in Bioengineering and Biotechnology* 8 (2020). DOI: 10.3389/fbioe.2020.00182
- [90] Q. Liu, L. Yang, Q. Peng, Study on scar repair and wound nursing of chitosan-based composite electrospun

- nanofibers in first aid of burn, *Materials Express* 11(8) (2021) 1420-1437. DOI:10.1166/mex.2021.2041
- [91] A. Noor, A. Afzal, R. Masood, Z. Khaliq, S. Ahmad, F. Ahmad, M.-B. Qadir, M. Irfan, Dressings for burn wound: a review, *Journal of Materials Science* 57(12) (2022) 6536-6572. DOI:10.1007/s10853-022-07056-4
- [92] K.J. Quinn, J.M. Courtney, J.H. Evans, J.D.S. Gaylor, W.H. Reid, PRINCIPLES OF BURN DRESSINGS, *Biomaterials* 6(6) (1985) 369-377. DOI: 10.1016/0142-9612(85)90095-x
- [93] M. Stojko, J. Wlodarczyk, M. Sobota, P. Karpeta Jarzabek, M. Pastusiak, H. Janeczek, P. Dobrzynski, G. Starczynowska, A. Orchel, J. Stojko, O. Batoryna, P. Olczyk, K. Komosinska-Vassev, K. Olczyk, J. Kasperczyk, Biodegradable Electrospun Nonwovens Releasing Propolis as a Promising Dressing Material for Burn Wound Treatment, *Pharmaceutics* 12(9) (2020). <https://doi.org/10.3390/pharmaceutics12090883>
- [94] A. Anisie, B.I. Andreica, L. Mititelu Tartau, C.G. Coman, R. Bilyy, G. Bila, I. Rosca, A.-I. Sandu, E. Amler, L. Marin, Biodegradable trimethyl chitosan nanofiber mats by electrospinning as bioabsorbable dressings for wound closure and healing, *International Journal of Biological Macromolecules* 249 (2023). <https://doi.org/10.1016/j.ijbiomac.2023.126056>
- [95] S. Barrientos, H. Brem, O. Stojadinovic, M. Tomic-Canic, Clinical application of growth factors and cytokines in wound healing, *Wound Repair and Regeneration* 22(5) (2014) 569-578. DOI: 10.1111/wrr.12205
- [96] P. Monika, M.N. Chandrababha, A. Rangarajan, P.V. Waiker, K.N. Chidambara Murthy, Challenges in Healing Wound: Role of Complementary and Alternative Medicine, *Frontiers in Nutrition* 8 (2022). <https://doi.org/10.3389/fnut.2021.791899>
- [97] P. Krzyszczyk, R. Schloss, A. Palmer, F. Berthiaume, The Role of Macrophages in Acute and Chronic Wound Healing and Interventions to Promote Pro-wound Healing Phenotypes, *Frontiers in Physiology* 9 (2018). DOI: 10.3389/fphys.2018.00419
- [98] M. Saco, N. Howe, R. Nathoo, B. Cherpelis, Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success, *Dermatology online journal* 22(8) (2016). DOI:10.1016/j.jaad.2016.02.1129
- [99] R. Torkington-Stokes, D. Metcalf, P. Bowler, Management of diabetic foot ulcers: evaluation of case studies, *British journal of nursing* (Mark Allen Publishing) 25(15 Suppl) (2016) S27-33. doi: 10.12968/bjon.2016.25.15.S27.
- [100] T. Fu, P. Stupnitskaia, S. Matoori, Next Generation Diagnostic Wound Dressings for Diabetic Wounds, *Acs Measurement Science* 2(5) (2022) 377-384. DOI: 10.1021/acsmeasuresciau.2c00023
- [101] E.A. Yahia, A.E. El Sharkawey, M.M. Bayoumi, Quantitative Evaluation of Diabetic Foot Wound Healing Using Hydrogel Composite Nanosilver (AgNPs) - Based Dressing Vs. Traditional Dressing: A Prospective Randomized Control Study, *Pakistan Journal of Medical & Health Sciences* 15(6) (2021) 2043-2047. DOI:10.53350/pjmhs211562043
- [102] E. Everett, N. Mathioudakis, Update on management of diabetic foot ulcers, *Annals of the New York Academy of Sciences* 1411(1) (2018) 153-165. DOI: 10.1111/nyas.13569
- [103] F. Huang, X. Lu, Y. Yang, Y. Yang, Y. Li, L. Kuai, B. Li, H. Dong, J. Shi, Microenvironment-Based Diabetic Foot Ulcer Nanomedicine, *Advanced Science* 10(2) (2023). <https://doi.org/10.1002/advs.202203308>
- [104] Y. Li, W. Zhao, S. Chen, H. Zhai, S. Wu, Bioactive electrospun nanoyarn-constructed textile dressing patches delivering Chinese herbal compound for accelerated diabetic wound healing, *Materials & Design* 237 (2024). <https://doi.org/10.1016/j.matdes.2023.112623>
- [105] Y. Yue, X. Liu, L. Pang, Y. Liu, Y. Lin, T. Xiang, J. Li, S. Liao, Y. Jiang, Astragalus Polysaccharides/PVA Nanofiber Membranes Containing Astragaloside IV-Loaded Liposomes and Their Potential Use for Wound Healing, *Evidence-Based Complementary and Alternative Medicine* 2022 (2022). <https://doi.org/10.1155/2022/9716271>

- [106] M. Arenbergerova, P. Arenberger, M. Bednar, P. Kubat, J. Mosinger, Light-activated nanofibre textiles exert antibacterial effects in the setting of chronic wound healing, *Experimental Dermatology* 21(8) (2012) 619-624. <https://doi.org/10.1111/j.1600-0625.2012.01536.x>
- [107] D. Dong, X. Lv, Q. Jiang, J. Zhang, Z. Gu, W. Yu, Z. Han, N. Wang, W. Hou, Z. Cheng, Multifunctional electrospun polycaprolactone/chitosan/hEGF/lidocaine nanofibers for the treatment of 2 stage pressure ulcers, *International Journal of Biological Macromolecules* 256 (2024). <https://doi.org/10.1016/j.ijbiomac.2023.128533>
- [108] J.S. Mervis, T.J. Phillips, Pressure ulcers: Pathophysiology, epidemiology, risk factors, and presentation, *Journal of the American Academy of Dermatology* 81(4) (2019) 881-890. DOI: 10.1016/j.jaad.2018.12.069
- [109] S. Bale, S. Hagelstein, V. Banks, K.G. Harding, Costs of dressings in the community, *Journal of wound care* 7(7) (1998) 327-30. DOI: 10.12968/jowc.1998.7.7.327