Journal of Drug Delivery Science and Technology 121 (2026) 108314

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review Article

Healing the wound with nanomedicine: The therapeutic potential of liposomes and nanofibers

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ARTICLE INFO

Keywords:
Wound repair
Nanocarriers
Wound dressing
Vesicles
Polymers

ABSTRACT

Wound management remains a significant clinical challenge, particularly in the treatment of chronic and infected lesions where currently available dressings and medications often fail to provide rapid and complete healing. Nanomedicine has the potential to improve wound management efficacy by enabling controlled drug release and providing peculiar biomechanical cues, supporting the different stages of natural healing. This review focuses on the potential of two prominent nanotechnological platforms—liposomes and nanofibers—in accelerating the complex process of wound regeneration. Liposomes, an established and versatile technology, excel for their ability in controlling the release of hydrophilic and lipophilic molecules, promoting membranes and biofilm permeation, and protecting unstable compounds from degradation within the hostile wound environment. On the other hand, electrospun nanofibers have peculiar 3D architectures that support cell proliferation and manage wound exudate levels, while also being able to load and release drugs and biomacromolecules in a controlled fashion. In this work, the recent research on the development of liposomes and nanofibers for wound healing is critically discussed, highlighting the most relevant preclinical results and seminal papers on novel technologies. Regulatory challenges and barriers to translation of such nanosystems are also addressed, providing a balanced outlook on their clinical implementation.

1. Introduction

1.1. Definition and types of wounds

It has been estimated that around 8 million people globally are impacted by wounds and they continue to be a significant clinical challenge, often leading to complications that contribute to morbidity and mortality. Wounds refer to any damage or disruption in the continuity of skin, mucous membranes, or organ tissues [1,2]. Following an injury, swift wound closure and efficient regeneration of the damaged skin are essential for restoring its protective function. Successful repair depends on the interaction and coordination of various cell types, with this process being thoroughly controlled and regulated at several levels [3].

Acute wounds, commonly resulting from injuries, surgical procedures, or burns, typically heal within 14 days, with clinical signs such as erythema, swelling, warmth, and others indicating the healing process [4,5]. The healing time can differ depending on factors such as the injury's type, severity, and size, as well as the patient's age and any existing health conditions [4]. Nevertheless, wounds that do not heal within 12 weeks are classified as chronic wounds and they are commonly seen in the elderly and diabetic populations [6,7]. Chronic wounds are considered a major and increasing economic strain on healthcare systems [8]. Several factors must be considered for optimal wound healing including adequate tissue perfusion, a functioning immune system and proper wound hydration. Moreover, removal of necrotic or nonviable tissue as well as effective management of any existing infection represent a significant part in wound management [9].

This article is part of a special issue entitled: Skin and mucosal drug delivery published in Journal of Drug Delivery Science and Technology.

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https://doi.org/10.1016/j.jddst.2026.108314
Received 31 January 2026; Received in revised form 23 March 2026; Accepted 7 April 2026
Available online 8 April 2026

1.2. Stages of wound healing

Wound healing represents a complex process involving the coordination of various regulated factors that work together to restore the skin's barrier function after injury [10]. It is characterized by a series of synchronized activities and four sequential but overlapping stages: hemostasis, inflammation, proliferation, and dermal remodeling [7].

1.2.1. Hemostasis

After an injury, the process initiates with hemostasis within the first few hours and comprises three stages: vasoconstriction, primary hemostasis, and secondary hemostasis. Hemostasis is triggered by skin damage and represents the reparative response to prevent bleeding following damage to blood vessels [3,11]. Rapid vasoconstriction occurs to reduce blood flow, followed by primary hemostasis, where platelets aggregate to form a plug by adhering to exposed collagen. Secondary hemostasis then activates the coagulation cascade, converting fibrinogen into fibrin strands that stabilize the clot, collectively forming a thrombus that halts bleeding and initiates wound healing [11].

1.2.2. Inflammation

After hemostasis and coagulation, the inflammatory phase occurs, with neutrophils being the first immune cells to arrive at the wound site. The inflammatory phase, typically lasting 1 to 3 days, involves a coordinated immune response aimed at minimizing deeper tissue damage, closing the wound, and facilitating cellular migration. Neutrophils play a crucial role in defending against infection by phagocytosing bacteria and eliminating necrotic tissue. Additionally, they generate reactive oxygen species (ROS) and hydrogen peroxide through the activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. During this process immune cells release various mediators and cytokines that facilitate angiogenesis, thrombosis, and reepithelialization [12,13]. After wound cleansing, the body releases anti-inflammatory mediators and growth factors to suppress inflammation and initiate the proliferative phase of healing [14]. This transition is crucial for effective tissue repair and regeneration ensuring the timely progression to subsequent healing stages. On the other hand, prolonged inflammation can disrupt the normal differentiation and activation of keratinocytes, resulting in an impaired healing process and scar formation [3].

1.2.3. Proliferation

Proliferation phase lasts from 4 to 21 days and aims to rebuild the vascular network, restore the epithelial barrier, and lead to granulation tissue development. Restoring the blood vessel network is initiated by local environment and different growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and others depending on the type of tissue that is injured. This phase is a crucial process for wound repair, as it ensures the supply of nutrients and oxygen [3,15]. Granulation tissue, formed during the proliferation phase, is composed of macrophages, fibroblasts, blood vessels, collagen, and other extracellular matrix (ECM) components, and ensures filling the wound space while providing support for cells to migrate, grow, and develop properly during healing [16].

1.2.4. Remodeling

The remodeling phase begins after granulation tissue has formed, can extend from 21 days to up to a year and involves the reorganization and degradation of the ECM ultimately restoring tissue strength and structure. As the wound closes, type III collagen is degraded and substituted with type I collagen with the increase in matrix metalloproteinases activity and decrease in the levels of hyaluronic acid [17]. Any disruption in these steps can lead to impaired healing, such as chronic ulcers or excessive scarring [3].

1.3. Local and systemic factors affecting wound healing process

Wound healing is affected by a range of factors, generally classified into local and systemic categories. Local factors influence the wound's specific characteristics, while systemic factors, including overall health and comorbidities, impact the body's healing capacity. Abnormal repair processes arise from environmental, genetic, and epigenetic factors, which exacerbate the pathophysiological complications of chronic wounds [10,18].

Various local factors that disrupt wound healing include desiccation, maceration, infection, excessive or prolonged pressure on the wound site, necrosis etc. While desiccation delays healing because a moist environment is crucial for tissue regeneration, maceration caused by excess moisture also impedes healing thus highlighting the importance of maintaining proper skin care for effective wound management [19]. Infection further complicates the healing process and prolongs the recovery period, with common bacteria such as *Staphylococcus aureus (S. aureus)*, *Pseudomonas aeruginosa*, and various *Streptococcal* species being responsible. Chronic wounds infected for four weeks or more are commonly colonized by *Proteus*, *Escherichia coli (E. coli)*, and *Klebsiella*, which can penetrate deeper skin layers, leading to significant tissue damage and making the infection more challenging to treat [18,20].

Systemic factors that impact wound healing include age, gender, and sex hormones, along with conditions like diabetes mellitus (DM), obesity, immunosuppression, venous stasis and stress. Moreover, corticosteroids use and lifestyle factors such as alcohol consumption, smoking, and inadequate nutrition can hinder immune response, blood flow, and tissue repair, leading to delayed healing [17,20].

The rising prevalence of chronic conditions such as obesity, diabetes and vascular insufficiency has significantly increased the burden of chronic wounds, posing a substantial challenge to both patients and the healthcare system. Alarming data indicates the lifetime incidence of chronic ulcers in diabetic patients can reach as high as 19-34% [21]. Impaired wound healing in diabetic patients is influenced by a variety of intricate factors, including vascular, immune, and biochemical elements. DM alters immune response, diminishes angiogenesis, and interferes with the function of keratinocytes and fibroblasts, leading to delayed tissue repair and extended inflammation. Moreover, hyperglycemia results in increased blood vessel stiffness, reduced circulation, and microvascular issues [21–23]. Prevalent foot ulcerations in diabetic patients often require hospitalization, lead to high recurrence rates and importantly result in lower limb amputations in 31% of cases [24]. As the diabetic population increases, managing diabetic wounds becomes a significant healthcare challenge, highlighting the urgent need for effective chronic wound treatment strategies [23].

Literature also suggests that wound healing is impaired in obese individuals as chronic inflammation, triggered by excess adipose tissue, hinders the immune response and slows the healing process. Nowadays obesity affects 1.7 billion people globally which possesses high risk of chronic ulcers development. Obesity can be linked to alterations in both the macro- and microvasculature, reduced production of growth factors, and the formation of inadequate granulation tissue, all of which contribute to impaired wound healing [25].

Vascular insufficiency, including both Peripheral Arterial Disease (PAD) and Chronic Venous Insufficiency (CVD), also has detrimental effects on the rate of wound resolution. On one hand, PAD leads to low oxygen and nutrient levels at the wound site, slowing down energy-demanding processes such as collagen synthesis and cell migration, required for re-epithelization [26]. On the other side, CVD-induced stasis impairs the effective removal of metabolic waste from the wound bed, exacerbating the local oxidative environment and favoring bacterial colonization [27,28]. Localized ischemia and failure in removal of metabolic waste can also be triggered by sustained pressure over one part of the body due to prolonged immobility, a frequent condition among elderly population and bedridden patients. Such conditions impair the wound healing process through exacerbation of

inflammation and delay of the proliferative phase [29]. Given the global aging of the population, the identification of novel strategies to promote wound healing is urgently needed.

1.4. Current wound treatment modalities

Current therapeutic approaches for chronic wound management include surgical debridement, wound dressings, antibiotic therapy, hyperbaric oxygen therapy, and other adjunctive treatments. Frequently utilized agents for wound care consist of antiseptics (e.g., biguanide, silver, chlorhexidine, povidone iodine) and antibiotics (e.g., bacitracin, mafenide, mupirocin, neomycin, silver sulfadiazine). While topical antimicrobials are crucial for managing infected wounds and preventing infection progression, they are accompanied by several limitations, including a high risk of side effects and the potential for antimicrobial resistance. These issues highlight a significant global health concern and underscore the need for more effective and safer alternatives [30].

It has been estimated that over 5000 wound care products are commercially available on the market each with distinct advantages and limitations [18]. Conventional wound dressings such as bandages and gauze are designed to provide a moist environment, protect the wound from infection, and promote wound healing. Nevertheless, these dressings often face challenges, such as frequent application, limited drainage capacity and adherence to granulation tissue causing pain during dressing changes [31,32]. To address these issues, modern wound dressings such as foams, hydrogels, alginates, hydrocolloids, and films have been developed [32]. Commonly used biomaterials for wound dressings such as chitosan, collagen, hyaluronic acid, and silicone, help retain moisture at the wound area, absorb excess exudate and prevent microbial growth [33]. The shortcomings of many wound care products in achieving optimal therapeutic results have driven the development of nanotechnology-based treatments. These nanotherapeutic approaches, utilizing materials at the nanoscale (1–100 nm), are designed to enhance wound healing, reduce complications in chronic wound care, and provide sustained, controlled release of therapeutics to accelerate the healing process. Nanocarriers may enable targeted and controlled release of therapeutics, thus providing the aforementioned advantages [34].

In this review, following a brief overview on the general advantages of nanocarriers in the context of wound healing, we will systematically analyze the recent literature dedicated to the fabrication and preclinical assessment of liposomes and nanofibers as examples of (I) an established nanoparticle-based delivery system and (II) a modern platform that bridges the gap between drug delivery and structural scaffolding, respectively.

2. Nanocarriers as delivery strategy

2.1. Definition and types of nanocarriers

Nanocarriers are a rapidly advancing strategy in wound healing, providing localized, targeted, and sustained drug delivery that enhances tissue repair and regeneration. Their nanoscale dimensions, tunable physicochemical properties, and capacity for functionalization enable them to protect bioactive molecules, increase penetration, and allow controlled release at wound sites, thereby improving efficacy and minimizing systemic side effects.

Nanocarriers for wound therapy can be broadly categorized as lipid-based, surfactant-based, polymer-based and metal-based (Fig. 1; modified with permission from Refs. [35,36]). Lipid-based nanocarriers include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nanoemulsions [37]. Surfactant-based carriers, primarily niosomes, are widely studied for their stability and cost-effectiveness [38]. Polymeric nanosystems include polymeric

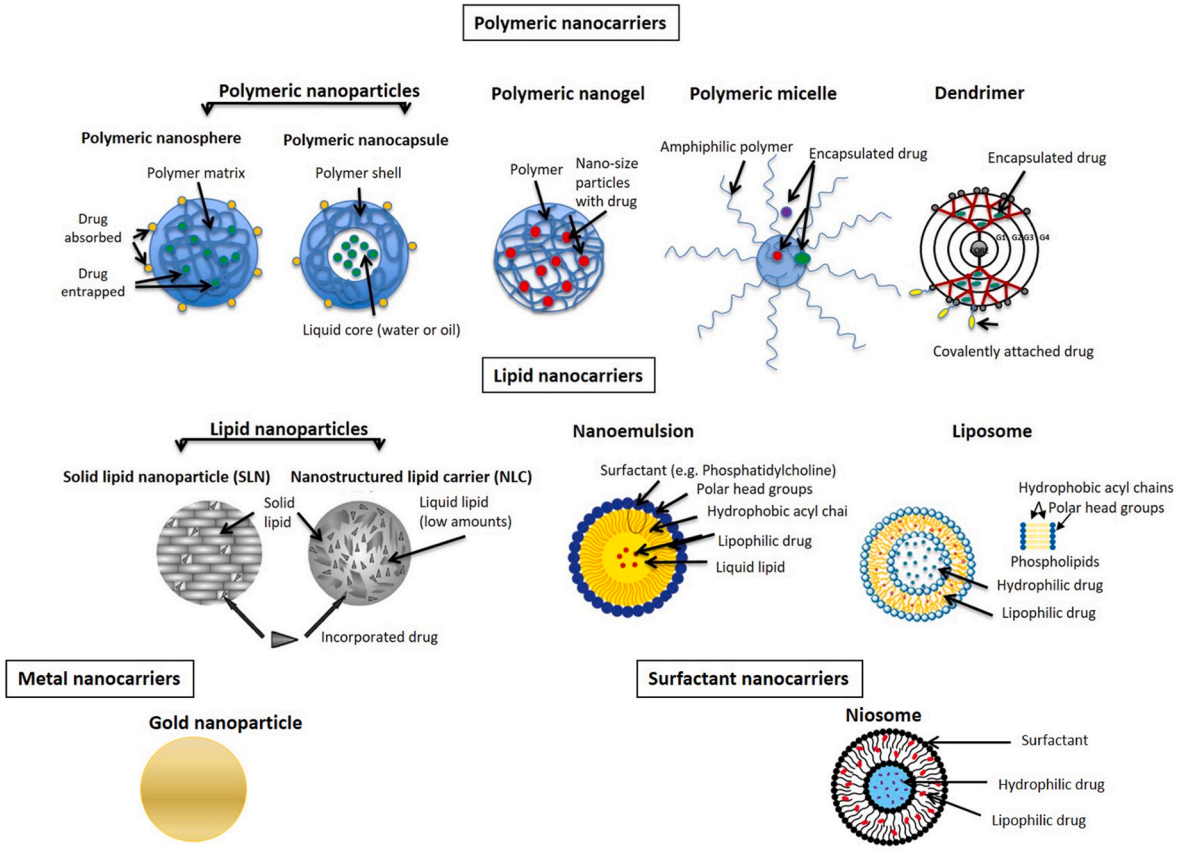

Fig. 1. Shematic representation of different nanocarriers used in wound healing (modified with permission from Refs. [35,36]).

nanoparticles (PNPs), i.e., nanospheres (matrix-type) or nanocapsules (reservoir-type) [39–42], polymeric micelles [43–45] and dendrimers [46–49] Among these, nanofibers produced by electrospinning are the most promising [50–54], as they combine peculiar scaffold properties with drug delivery capabilities. Hybrid lipid–polymer systems further exploit complementary features, enhancing stability and controlled release [55]. Metal-based nanoparticles (MBNPs), such as silver (AgNPs), gold (AuNPs), and copper (CuNPs) [56–59] NPs are also intensively studied due to their intrinsic antimicrobial and anti-inflammatory effects.

From a functional standpoint, nanocarriers can be divided into those with intrinsic therapeutic activity provided by the biological action of their components or their structural cues (e.g., AgNPs, chitosan nanofibers, etc.) and those that act as delivery vehicles for bioactive agents. Ideally, wound-healing nanocarriers should be easily engineered, biodegradable, biocompatible, chemically stable in physiological environments, and capable of reducing toxicity of loaded drugs.

Liposomes are the most extensively studied nanocarriers and represent the first generation of nanosystems in topical and transdermal drug delivery. Structurally, they are vesicles composed of phospholipid bilayers enclosing an aqueous core, enabling encapsulation of hydrophilic drugs in the core and lipophilic drugs in the bilayer [60,61]. Commonly used phospholipids include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), and phosphatidylglycerol (PG), often combined with cholesterol for membrane stability. Liposomes enhance dermal drug delivery by increasing penetration, targeting appendages, and forming depots for sustained drug release [62–67]. In wound healing, they have been used to deliver antimicrobials, anti-inflammatory agents, and growth factors, improving wound repair, while minimizing systemic side effects [68–70]. Several elastic liposomal systems have been designed to further enhance percutaneous drug penetration: Transfersomes®, composed of PC and edge activators (e.g., sodium cholate, polysorbates) [71], ethosomes containing PC and ethanol besides water [72], invasomes enriched with ethanol and terpenes in addition to PC and water [73] and penetration enhancer vesicles (PEVs), composed of PC and enhancers, such as Transcutol® or Labrasol® [74]. These additives (terpenes, penetration enhancers and ethanol) confer elasticity to vesicle membranes, enabling better drug penetration into or through the skin.

Nanofibers are ultra-fine polymeric fibers with high surface area-to-volume ratios and tunable porosity, structurally mimicking the skin ECM. These properties make them particularly suited for drug delivery systems and scaffolds in wound healing [50–54]. Produced by high-voltage electrospinning, they form porous scaffolds that support gas exchange, exudate absorption, and wound hydration while providing mechanical integrity [75] Nanofiber systems allow efficient encapsulation of therapeutic agents, protect them from premature degradation, and enable controlled and localized release, while reducing systemic side effects [50–54]. Drugs may be incorporated via polymer blending, coaxial spinning (core–shell fibers), surface adsorption, or post-spinning modifications, which allow tailored release profiles. Their ECM-mimicking architecture promotes cell adhesion, proliferation, and migration, and functionalization with ECM proteins, growth factors, or nanomaterials further enhances regenerative capacity [52,76–78]. Polymers used include U.S. Food and Drug Administration (FDA)-approved synthetic excipients, such as polycaprolactone (PCL), poly(lactic acid) (PLA), cellulose acetate (CA), polyethylene glycol (PEG), poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), polyurethane, polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA), known for mechanical strength and ease of processing. Natural polymers like silk fibroin or chitosan offer superior biocompatibility and biodegradability, but may be more difficult to process. Hybrid blends leverage both advantages. Nanofibers are particularly effective in treating chronic wounds, such as diabetic foot ulcers and in burn management [75,79,80].

2.2. Properties of liposomes and nanofibers relevant to wound healing

The unique properties of liposomes and nanofibers, which underpin their application in wound therapy will be discussed in the following paragraph.

Liposomes are nanosized vesicles (typically 100–300 nm) with tunable surface charge. Their physicochemical properties strongly influence dermal drug delivery and wound healing outcomes. While smaller vesicles have been hypothesized to penetrate skin more effectively, evidence is mixed: some studies show no correlation between reduced particle size and penetration [81–83], whereas others suggest an optimal size range for delivery [84–86]. Smaller liposomes, however, generally improve tissue retention and drug localization, enhancing wound healing. For instance, deformable liposomes of 300–350 nm successfully retained human epidermal growth factor (hEGF) within skin layers while avoiding systemic absorption [87]. Importantly, hEGF-loaded anionic deformable liposomes demonstrated sustained *in vitro* release, depot formation in *ex vivo* human skin, and enhanced mitogenic activity in fibroblasts and keratinocytes compared with neutral or cationic counterparts, highlighting their promise for chronic wound therapy [87]. Surface charge plays a key role in liposomal performance. Cationic elastic liposomes loaded with a low-molecular-weight protamine (LMWP)-fused growth factor–hyaluronic acid complex, significantly enhanced skin penetration, improved *in vitro* wound recovery, and reduced wound size in a diabetic mouse model, outperforming both vehicle and native growth factors formulations [88]. These findings align with earlier evidence that positively charged liposomes penetrate skin more efficiently than neutral or anionic systems [89–91]. A critical factor for efficient wound treatment with liposomes is linked to their retention on the wound site. Indeed, liposomes are usually diluted water-based dispersions, prone to dripping away due to their low viscosity, resulting in poor adherence to the injury site and necessitating frequent applications. Such limitations have been tackled incorporating liposomes in hydrogels [92], film forming solutions [93] and ointments [94]. As to the mechanism of action of liposomes in wound healing, they mainly serve as carriers for bioactive agents, which exert therapeutic effects in wound healing. In addition, liposomes improve hydration and create favorable wound microenvironments. Liposomes are considered safe due to their primary composition of biodegradable phospholipids, classified as Generally Recognized as Safe (GRAS). Non-hydrogenated soybean lecithin, rich in linoleic and linolenic acid, is a common source, contributing to both liposome safety and skin barrier integrity [95].

Nanofibers possess unique structural properties that make them highly effective for wound healing [96,97] Their nanometer-scale fiber diameter closely mimics the dimensions of collagen fibers (typically 50–500 nm) in native skin extracellular matrix, providing a large surface area for cell attachment [98]. This high surface-to-volume ratio and the porous architecture of nanofiber mats facilitate cellular adhesion and proliferation, while also enabling gas exchange, moisture retention, and absorption of wound exudate – creating a moist, oxygenated environment conducive to healing [99]. Moreover, surface functionalization strategies—such as electrostatic interactions, hydrogen bonding, or covalent bonding—allow immobilization of bioactive ECM molecules (e.g., chitosan, hyaluronic acid, decorin, perlecan) onto nanofibers made of synthetic polymers, enhancing their biological relevance. Nanofiber dressings are generally biocompatible and biodegradable. Nanofibers use materials (e.g., collagen, chitosan, PLGA, PCL) that avoid toxicity and are gradually absorbed or broken down into non-toxic byproducts in tandem with tissue regeneration [100,101]. This helps eliminate the need for dressing removal and supports uninterrupted tissue repair. Moreover, being flexible solid films, nanofibers provide better coverage and adherence to irregular wound surfaces without the risk of leakage, which is a common drawback with liposomal formulations.

Natural polymer nanofibers (e.g., chitosan, alginate, gelatin) inherently promote hemostasis and exhibit antimicrobial activity with low

immunogenicity, but generally lack mechanical strength [102]. Conversely, synthetic nanofibers (e.g., polycaprolactone, polyesters) provide robust mechanical support and tunable degradation rates, though they may require surface modifications or blending to enhance cell affinity [98,102]. Composite nanofibers combining natural and synthetic components leverage the strengths of both, yielding scaffolds with improved structural integrity and biofunctionality that accelerate wound closure [98]. Thus, nanofibers may possess intrinsic therapeutic properties, which initiate the healing process, but can also contain encapsulated drugs. Drug-loaded nanofiber systems further augment healing by serving as delivery vehicles for antimicrobials, growth factors, anti-inflammatory agents, natural compounds or nucleic acids, enabling sustained drug release at the wound site to reduce infection and stimulate cell migration, angiogenesis, and tissue regeneration [98,102]. Thus, the general mechanism of action of nanofibers relies on the modulation of cellular responses through their mechanical and pharmacological actions, encouraging fibroblast proliferation and keratinocyte migration, promoting granulation tissue formation and re-epithelialization, ultimately expediting wound closure and improving the quality of healed tissue [98,99]. Notably, electrospinning core-shell (coaxial) nanofibers enable sequential delivery strategies (e.g., rapid antibiotic release followed by sustained growth-factor delivery), offering an ideal feature in the context of wound healing, a process characterized by sequential biological phases [98]. Lastly, nanofibers can be also designed to be stimuli-responsive, when they evolve to “smart” drug delivery systems for advanced therapeutic applications [103].

3. Liposomes and nanofibers in wound healing

Liposomes and nanofibers have the potential of transforming chronic wound care providing targeted, prolonged, and effective treatment. These vehicles can deliver antibiotics, growth hormones, anti-inflammatory drugs, nucleic acid therapies, and natural compounds directly to the wound site, accelerating recovery and reducing systemic effects [104,105].

In the following paragraphs, recent preclinical studies on liposomes and nanofibers applications in wound healing will be reviewed and classified based on the type of active molecule(s) employed: antibiotics, anti-inflammatory agents, growth factors, nucleic acids and natural compounds. The studies discussed in this section were selected based on their relevance to wound-healing applications, prioritizing recent contributions (published between 2020 and 2026) as well as seminal or highly innovative works that provide robust *in vivo* evidence or mechanistic insights of translational significance.

3.1. Delivery of antibiotics

Antibiotics are frequently included in wound dressings and topical formulations to eradicate existing infection and/or prevent new bacterial colonization. However, they are accompanied by several limitations, including the limited permeation through the bacterial biofilm and potential for antimicrobial resistance. Nano-encapsulation can be beneficial for both aspects, as nanocarriers can promote drug penetration across biofilms and, by co-loading two or more antimicrobials, allow additive or synergistic effects to tackle resistance and improve safety [106,107] (Table 1). In this regard, the ability of liposomes in loading both hydrophilic and hydrophobic agents is extremely useful. Moreover, liposomes can (I) support the targeting of intracellular pathogens by increasing the cell uptake of antimicrobials and (II) improve their delivery by direct fusion with the bacterial membranes [120,121].

Following a bacterial infection on wounded skin, there is a significant loss of fluids and a decline in the body's innate immunity, which can result in sepsis. With the aim of absorbing these fluids while releasing an antimicrobial, Wang et al. developed a double network hydrogel wound dressing composed of PEG, α-cyclodextrin, and cross-linked acrylamide

Table 1
Selected wound healing studies on liposomes and nanofibers loaded with antibacterial agents. Acronyms: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)-2000] (DSPE-PEG-MAL), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), chorioallantoic membrane (CAM), Methicillin-resistant *Staphylococcus aureus* (MRSA), phosphatidylcholine (PC), polycaprolactone (PCL), polymyxin B-DSPE-PEG2000 conjugate (PMB-DSPE-PEG2000), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP).

Composition/ Preparation	Active Compound(s)	Key results (model)	Ref
Hydrogels with PEG, α-cyclodextrin, acrylamide loaded with liposomes/ Thin-film hydration	Amoxicillin	Sustained drug release up to 12 days, high antibacterial activity (*in vitro*, *S. aureus*), adjustable mechanical strength	[108]
Maleimide-conjugated liposomes (egg PC, cholesterol, DSPE-PEG-Mal, oleic acid)/Thin-film hydration, high pressure microfluidization, extrusion	Ceftriaxone, cephalexin, doxycycline, piperacillin, ampicillin, and ceftazidime	MIC values reduced by 9.33-fold (*E. coli*) and 8-fold (*K. pneumoniae*) compared to bare antibiotics *(in vitro)*. Reduced toxicity against human dermal fibroblasts *(in vitro)*.	[109]
Liposomes (PC, cholesterol, Tween 80, stearylamine)/ Thin-film hydration and sonication	Bacteriophage MR-5 and MR-10	2 log higher phage titer on the wound site; 4 log CFU/ml lower bacterial load on the wound site; higher wound closure rate and faster reduction of inflammatory markers (myeloperoxidase) compared to free phages (*in vivo*, diabetic BALB/c mouse model with excision wounds infected with MRSA)	[110]
Polymixin B-targeted liposomes (DPPC, DOTAP, cholesterol, DSPE-PEG2000, PMB-DSPE-PEG2000)/Thin-film hydration, extrusion	Hematoporphyrin monomethyl ether	Higher photodynamic antibacterial efficacy (*in vitro*, MDR *A. Baumanni*). Accelerated wound healing via macrophage polarization; complete eradication of MDR *A. baumannii* at day 2 post-inoculation; improved granulation, angiogenesis, and collagen deposition (*in vivo*, mouse burn wound infection model)	[111]
Carbon dot liposomes (triolein)/		Superior photodynamic antimicrobial activity against gram + bacteria (*in vitro*, MRSA). Wound area reduced to 18% at day 9 vs ~80% of control; bacterial viability at the wound site at day 9 was <10%; collagen deposition was increased (*in vivo*, BKS.Cg–7m+/+ Leprdb/J diabetic mice infected with MRSA)	[112]
Nanofibers or transparent films	Ciprofloxacin	Both nanofibers and films were active against gram + and	[113]

(*continued on next page*)

Table 1 (*continued*)

Composition/ Preparation	Active Compound(s)	Key results (model)	Ref
(PVP)/ Electrospinning		gram – bacteria (*in vitro*, *E. Coli* and *B. Subtilis*). Nanofibers absorbed wound exudate faster than films (*in vivo,* full-thickness wound in BALB/c mice)	
Simple and core-shell nanofibers (Eudragit® S100)/ Electrospinning	*Nitrofurazone*	The pH-sensitive polymer allowed fast drug release and efficient antimicrobial activity only at pH > 7for core-shell nanofibers (*in vitro, E. Coli*)	[114]
Crosslinked nanofibers (hyaluronic acid-ethylenediamine)/ Electrospinning	Ciprofloxacin and graphene oxide nanoparticles	NIR light-triggered drug laser. Increased antibacterial activity and biofilm eradication due to the combined phototermal-antibiotic action (*in vitro, S. Aureus and P. Aeruginosa*)	[115]
Core-shell nanofibers (shell: PCL/gelatin, core: gelatin)/ Electrospinning	*Gymnema sylvestre* extract and minocycline	Reduction in bacterial viability >99 % (*in vitro, S. Aureus, S. Epidermidis, P. Aeruginosa, E. Coli, MRSA).* Increase in cell density by 5-fold and 10-fold after 7 days (*in vitro*, human fibroblasts and keratinocytes, respectively). Enhanced blood vessel formation and re-epithelization compared to untreated control (*in vivo*, porcine second-degree burn model)	[116]
Crosslinked nanofibers (gelatin, crosslinker: glutaraldehyde vapor)/ Electrospinning	Ciprofloxacin Hydrochloride, Gentamicin Sulfate	Non-inferior antibacterial properties vs free antibiotics (*in vitro, P. Aeruginosa* and *S. Aureus*). 2.1-2.7-fold increase in new vessel number vs control (*in vivo*, CAM test). Enhanced epidermis maturation, reduced numbers of inflammatory cells, ordered arrangement of collagen fibers (*in vivo*, burn wounds on Wistar albino rats)	[117]
Core-shell nanofibers (shell: gelatin, core: PCL)/Coaxial electrospinning	Ciprofloxacin (core), Tetracycline Hydrochloride (shell)	Dual release: within 12 h (tetracycline) and for 5 days (ciprofloxacin). Synergistic antimicrobial effect for 5 days (*in vitro*, *E. coli* and *S. aureus)*	[118]
Nanofibers (PVA/ chitosan)/ Electrospinning	Colistin, meropenem	Antibacterial activity against ATCC strains and clinical isolates (*in vitro, A. Baumanni, P. Aeruginosa, E. Coli*). No signs of inflammation, rejection or tissue reaction following a subcutaneous implantation for 21 days (*in vivo*, NMRI male mice)	[119]

and enriched with amoxicillin-loaded liposomes [108]. The multicomponent approach allowed to tune the mechanical properties of the formulation, that exhibited remarkable swelling capacity, controlled release of amoxicillin over 12 days and robust antibacterial activity *in vitro*.

Ladva et al. suggested that surface decoration of liposomes with maleimides could enhance the interactions with bacterial envelopes through the reaction with exposed thiols [109]. Thus, PEG-maleimide-decorated liposomes loaded with different antibiotics were developed and characterized, showing uniform size, but sub-optimal encapsulation efficiency (35-43%). Nevertheless, antimicrobial encapsulation in decorated liposomes reduced the MIC *in vitro* compared to free and untargeted liposomes-loaded antibiotics in several strains of *E. Coli* and *Klebsiella pneumoniae*, typically encountered in septic wounds.

Liposomes were also employed as carriers for bacteriophage cocktails, to improve phage persistence in the wound site and tackle diabetic wound infection [110]. The approach was validated *in vivo* using diabetic BALB/c female mice with wound infected by a methicillin-resistant strain of *S. aureus* (MRSA), showing faster healing due to lower bacterial load when compared to animals treated with an unencapsulated phage cocktail.

Like diabetic wounds, burn wounds are also hard to treat as they break the skin's barrier, letting bacteria invade and cause sepsis and organ failure. In a recent work, polymyxin B-decorated liposomes were employed to deliver a potent photosensitizer for the antibiotic photodynamic therapy (aPDT) of multi-drug-resistant *Acinetobacter baumannii* infections in burn wounds [111]. This formulation destroyed bacteria *in vitro* and *in vivo* by targeting cell membranes and producing ROS, while facilitating wound healing through macrophage polarization towards anti-inflammatory M2 phenotype and inducing angiogenesis, granulation and collagen regeneration.

In another work, photoactivable carbon dot liposomes were employed to combat MRSA-infected wounds [112]. Light irradiation induced the production of hydroxyl radicals, key mediators of the antibacterial action demonstrated *in vitro* and *in vivo*. Importantly, the treatment showed limited toxicity towards mammalian cells due to the higher susceptibility of bacteria to oxidative stress, while it stimulated angiogenesis and collagen deposition.

Antibiotics have also been loaded on nanofibrous scaffolds to combine the pharmacological effect with the peculiar mechanical and functional properties of these formulations.

For instance, the water-insoluble antibiotic ciprofloxacin was co-loaded with povidone in polyvinylpyrrolidone (PVP) nanofibers mats. Antibacterial assays validated the efficacy of the mats against *E. coli* and *Bacillus subtilis*. Next, *in vivo* investigations utilizing a full-thickness excisional skin wound murine model revealed that nanofiber mats absorbed wound exudate faster than flat films with the same composition (used as a control), highlighting the importance of the fibrillar network in the wound environment [113].

Nanofibers can be engineered to have a stimuli-responsive release mechanism. By employing Eudragit® S100 as polymer, Rivero et al. produced pH-responsive nanofibers able to quickly release nitrofurazone at pH > 7 - typical of a contaminated environment - maintaining their structural integrity at lower pH [114]. An external light source in the near infrared (NIR) region can also be employed as a

trigger for drug release, as proven in a recent paper where graphene oxide nanoparticles were co-loaded with ciprofloxacin in crosslinked hyaluronic acid nanofibers. NIR irradiation not only promoted the on-demand release of the antibiotic, but also triggered a photothermal reaction that significantly enhanced the antibacterial and anti-biofilm activity *in vitro* [115].

Mechanical properties of the nanofibers are a critical aspect to consider when designing a formulation. Incorporating components that resemble the properties of the extracellular matrix at the wound site proved to be beneficial for boosting the healing process. To this aim, gelatin was co-spun with poly-ε-caprolactone to produce nanofibers loaded with a *Gymnema sylvestre* extract and minocycline hydrochloride. In addition to reduce bacterial colonization and biofilm formation, such formulation markedly increased skin cell proliferation and expedited wound healing in a pig model of second-degree burns [116]. Similarly, crosslinked gelatin scaffolds infused with ciprofloxacin hydrochloride and gentamicin sulfate showed significant antibacterial efficacy against *Pseudomonas aeruginosa* and *S. aureus*, while promoting wound healing in a full-thickness burn wound rat model. Histological analysis revealed accelerated re-epithelialization and increased collagen synthesis, indicating improved tissue regeneration [117].

Other authors explored the possibility to co-load two antibiotics in nanofibers for synergistic antibacterial action. Polycaprolactone/gelatine core-shell nanofibers loaded with tetracycline hydrochloride and ciprofloxacin were produced by co-axial spinning. Resultantly, a dual release mechanism could be achieved with tetracycline being released within 12 h to treat early-stage bacterial infections whilst ciprofloxacin CIP providing a prolonged effect due to its sustained release over 5 days [118]. In another study, chitosan/polyvinyl alcohol nanofibers enabled the release of colistin and meropenem for up to seven days, resulting in a robust antibacterial efficacy against *Acinetobacter baumannii* from clinical isolates *in vitro*, while maintaining high biocompatibility *in vivo*, with no negative tissue reactions observed in an animal model [119].

3.2. Delivery of anti-inflammatory agents

Inflammatory processes involved in chronic wounds establish a proteolytic environment, facilitated by the infiltration of inflammatory cells over the wound site and sustained production of pro-inflammatory cytokines and chemokines. If sustained for too long, such environment hampers natural healing. Anti-inflammatory agents, either topically applied on the wound or systemically administered, aim to mitigate excessive inflammation while preserving the balance with the necessary biochemical and cellular cues required for wound healing. Such therapeutics can benefit from being formulated as nanomedicines, that can modulate their release, adhesion and intracellular delivery properties, thereby contributing to the aforementioned goal (Table 2). Nanotechnology-based strategies could be coupled with commercially available medical textiles to combine controlled release-properties with wound protection. For instance, Ferreira et al. optimized a polymeric functionalization of nonwoven gauze to incorporate liposomes loaded with piroxicam, showing how liposomes lamellarity and lipid concentration impact on the release of the drug from the gauze [122].

Liposomes can also be exploited for their targeting ability towards phagocytic cells. A seminal application of this concept was provided incorporating dexamethasone phosphate into liposomes to favor its internalization by primary macrophages. Indeed, the presence of glucocorticoids receptors on numerous cell types is linked to high risk of unwanted effects. Specifically in the context of localized wound treatment, glucocorticoids (exogenously administered or endogenously synthesized) lead to thinning of the epidermal layer, loss of elasticity, disruption of the skin barrier function and dermal atrophy. Liposomes formulated using phosphatidylserine led to enhanced macrophage uptake over fibroblasts and keratinocytes and reduced inflammation markers such as IL6 and TNFα. The macrophage targeting was also demonstrated in a wounded 3D full thickness skin model, paving the

Table 2
Selected wound healing studies on liposomes and nanofibers loaded with anti-inflammatory agents. Acronyms: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG-2000), 1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), near-infrared (NIR), phosphatidylcholine (PC), polycaprolactone (PCL), poly (diallyldimethylammonium chloride) (PDDA), reactive oxygen species (ROS).

Composition/ Preparation	Active Compound (s)	Key results (model)	Ref
Liposomes (egg PC) adsorbed on PDDA-functionalized gauzes/Thin-film hydration and sonication	Piroxicam	Cationic polymer functionalization enhances liposomes' attachment to the fabric and controls the release (*in vitro*)	[122]
Liposomes (DPPC, cholesterol, DSPE-PEG-2000 or DPPC, cholesterol, DOPS)/ Thin-film hydration and extrusion	Dexamethasone phosphate	DOPS-containing liposomes demonstrated superior macrophage targeting (*in vitro*, primary human monocytes differentiated into macrophages vs primary dermal fibrorlasts and keratinocytes and 3D skin equivalent model). Enhanced expression of anti-inflammatory markers (e.g., MERTK, CD163) and decreased pro-inflammatory cytokine release (IL-6, TNFa) (*in vitro,* primary human monocytes)	[123]
Nanofibers (PCL)/ Electrospinning	11β-HSD1 Inhibitor (BVT2733)	Migration area more than doubled vs control in a scratch assay (*in vitro*, dermal fibroblasts and keratynocytes). 70% wound closure after 7 days vs 50-60% in control groups; number of vessels in wounds after 14 days more than doubled vs control (*in vivo*, diabetic C57BL/6 mice, full-thickness wound model)	[124]
Nanofibers (PCL/ gelatin)/ Electrospinning	4-Octyl Itaconate-chitosan conjugate	Promotion of M2 polarization, reduction of the intracellular ROS, reduced pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) (*in vitro*, murine macrophages and *in vivo*, full-thickness wound on diabetic mice). Enhanced angiogenesis, re-epithelialization, and collagen deposition (*in vivo*, full-thickness wound on diabetic mice)	[125]
Graphene oxide-functionalized nanofibers (PCL)/ Electrospinning	Ibuprofen, Ketoprofen, Vancomycin	NIR-light-triggered drug release, increased biodegradability due to graphene oxide coating (*in vitro*). Increased cell adhesion vs non-functionalized nanofibers (*in vitro*, human dermal fibroblasts)	[126]

way for future *in vivo* experimentation [123].

A different strategy to tackle the glucocorticoid unwanted effects on the wound was recently explored by Ding et al. With the aim of reducing the levels of endogenous glucocorticoids in diabetic ulcers - known to impair collagen synthesis and angiogenesis – they fabricated nanofibers loaded with an inhibitor of 11β-Hydroxysteroid dehydrogenase (11β-HSD), a key enzyme involved in glucocorticoid activation. The nanofibers enhanced the migration and proliferation of fibroblasts and activated the pro-angiogenic HIF1-α/VEGF signaling pathway in endothelial cells. When applied to the wounds of diabetic mice, the scaffold promoted wound closure by neovascularization, collagen deposition, and skin regeneration, surpassing 90% of healing in 10 days [124]. Nanofibers proved useful also in reprogramming macrophage polarization from an M1 (inflammatory) to an M2 (pro-healing) phenotype. Promoting such transition – that normally happens in a physiologically healing wound around day 7 – could expedite tissue regeneration in the proliferation phase [127]. A conjugate between 4-octyl itaconate -a derivative of the immune modulator itaconic acid- and chitosan was covalently linked to PCL/gelatin nanofibers to obtain resistant and slow-releasing dressings. Their application to inflamed macrophages *in vitro* successfully shifted their polarization towards an M2 phenotype, suppressing the expression of common inflammatory cytokines and reducing the intracellular ROS. Such molecular mechanisms were assessed also *in vivo*, where the nanofibers ultimately led to a faster wound closure rate, with reduced inflammation and control of the oxidative status [125].

Endowing nanofibers with on-demand release properties represents an attractive strategy to better adhere to the natural phases of wound healing. In this context, Mauro et al. described a near-infrared light-activated wound healing patch made of graphene oxide (GO) and electrospun PCL. The GO-PCL nanofibers allowed the precise release of three model drugs (ibuprofen, ketoprofen and vancomycin), under the control of light irradiation. Moreover, the presence of GO in the matrix boosted water adsorption, expediting the biodegradation of the dressing compared to the PCL-only nanofibers. Despite being only tested *in vitro*, with promising biocompatibility results, such system holds promise for the high level of controlled release, that might be extended to other drug combinations [126].

3.3. Delivery of growth factors

Growth factors (GFs) play a vital role during all stages of wound healing. Chronic and infected wounds are characterized by diminished concentrations of growth factors, which can be ascribed to their premature degradation due to the proteolytic environment and/or to alterations in cellular phenotype leading to their reduced expression [128]. Hence, supplementation of exogenous GFs represents a promising approach for treating chronic wounds. However, the inherently limited stability of GFs would impose frequent administrations to maintain an effective concentration at the site of action. Drug delivery systems might support the localized activity of GFs by protecting them from enzymatic and hydrolytic degradation, and spatially and temporally controlling their release [129]. This section summarizes the most recent developments in GFs delivery to the wound site through liposomes and nanofibers (Table 3).

Basic fibroblast growth factor (bFGF) was loaded into liposomes characterized by a hydrogel core of silk fibroin, designed to prolong the release and protect the GF from enzymatic degradation in the wound fluids. Indeed, encapsulation into hydrogel-core liposomes led to significantly higher retention of bFGF and prolonged activity compared to conventional liposomes. When tested in a mouse model of second-degree burns, the platform accelerated the healing time, promoting re-epithelization and vascular regeneration [130].

To maximize local retention of liposomes, Değim et al. incorporated epidermal growth factor (EGF)-loaded multilamellar vesicles into a chitosan gel. The gel applied to rats injured with a burn wound led to

Table 3
Selected wound healing studies on liposomes and nanofibers loaded with growth factors. Acronyms: 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), Basic Fibroblast Growth Factor (bFGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), hydrogenated phosphatidylcholine (HPC), Insulin-like Growth Factor I (IGF-I), phosphatidylcholine (PC), Platelet-derived Growth Factor-A (PDGF-A), Platelet-Derived Growth Factor-BB (PDGF-BB), Platelet-rich plasma (PRP), polycaprolactone (PCL), poly(ethylene oxide) (PEO), poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol (PVA), Vascular Endothelial Growth Factor (VEGF).

Composition/ Preparation	Active Compound (s)	Key results (model)	Ref
Liposomes with silk fibroin core (PC, cholesterol)/Reverse-phase evaporation and sonication	bFGF	Improved stability of bFGF in human wound fluids (*ex vivo*). Accelerated wound closure and more pronounced vasculature regeneration than free bFGF and other controls (*in vivo*, Balb/c mice with second degree scald)	[130]
Chitosan gel containing liposomes (DPPC, cholesterol)/Thin-film hydration and sonication	EGF	Increased epidermal thickness after 14 days of treatment vs controls; no signs of neutrophil infiltration (*in vivo*, second-degree burn wounds in Sprague Dawley rats)	[131]
Chitosan-based film-forming spray containing liposomes (soy lecithin, cholesterol)/Thin-film hydration	EGF	Complete healing on day 6, vs day 8 for EGF liposomes without the film forming solution (*in vivo*, surgical wound on Swiss Webster mice)	[132]
Anionic, neutral or cationic elastic liposomes (soy PC + polysorbate 20, stearylamine or sodium deoxycholate)/Thin-film hydration and extrusion	EGF	Anionic elastic liposomes provided a skin depot of EGF (*ex vivo,* human skin) and had the highest mitogenic effect (*in vitro*, human fibroblasts and keratinocytes)	[133]
Liposomes (HPC, cholesteol, DOTAP)/ Microfluidic	EGF, IGF-I, PDGF-A fused with a low molecular weight protamine and complexed with hyaluronic acid	Enhanced cell proliferation and rate of scratch wound closure (*in vitro*, human fibroblasts). Wound area at day 9 of treatment was 185% smaller than control; epidermal covering was completed after 11 days, with denser collagen fibers and thinner granulation tissue vs control (*in vivo*, diabetic C57/BL6 mice with full thickness wound)	[88]
Nanofibers (chitosan/ PEO) loaded with PLGA nanoparticles (loaded with PDGF-BB) and VEGF/ Electrospinning	VEGF, PDGF-BB	Promotion of proliferation (*in vitro*, human dermal fibroblasts). Dual release kinetics from the nanofibers and the nanoparticles-in-nanofibers (*in vitro*). Higher wound healing rate and collagen deposition than controls (*in vivo*, surgical wounds on Sprague–Dawley rats)	[134]

(*continued on next page*)

Table 3 (*continued*)

Composition/ Preparation	Active Compound (s)	Key results (model)	Ref
Interwoven nanofibers (collagen, hyaluronic acid)/Electrospinning	VEGF, PDGF-BB, bFGF, EGF	Sequential release pattern (*in vitro*). Increased proliferation and tubes formation vs controls (*in vitro*, human endothelial cells). Enhanced angiogenesis and collagen deposition leading to faster wound healing vs controls (*in vivo*, full thickness wounds on diabetic Sprague–Dawley rats)	[135]
Bilayer nanofibers (PCL, upper layer and chitosan/PVA, lower layer)/ Electrospinning	EGF	Wound closure rate and histopathological score higher than control and in line with a commercial wound dressing (*in vivo,* full thickness wounds on mice).	[136]
Nanofibers (PVA)/ Electrospinning	EGF, FGF	Enhanced cell attachment and proliferation (*in vitro*, human dermal fibroblasts). Significant reduction in wound size by day 21 vs nanofibers loaded with a single GF (*in vivo*, Sprague Dawley rat burn model)	[137]
Core–shell nanofibers (core: quaternary ammonium salt grafted sulfonated chitosan, gelatin; shell: PCL) coated with polydopamine/ Electrospinning	EGF, bFGF	Bacteriostatic activity (*in vitro, E. Coli, S. Aureus*). Non hemolytic (*in vitro*) and non-cytotoxic (*in vitro*, human fibroblasts). Faster healing rate, higher CD31 and lower TNFa expression than controls at 14 days (*in vivo*, full thickness wounds on Balb/c mice)	[138]
Nanofibers (chitosan/ PEO)/Electrospinning	PRP	Stimulation of cell proliferation (*in vitro*, keratinocytes and fibroblasts).	[139]

significant reepithelialization, fibroblast proliferation and increase in epidermal thickness compared to the EGF solution and EGF-liposomes, underlining the role of the gel [131]. With the same aim of increasing the residence time on the wound, EGF-loaded liposomes were embedded in a film-forming spray based on chitosan as a potential scaffold for wound treatment. A wound healing study performed on mice revealed that the combined formulation significantly accelerated wound healing compared to the soluble EGF and EGF-liposomes alone [132].

Elasticity of the bilayer is a critical attribute of liposomes intended for wound healing. Indeed, deformable liposomes have shown improved ability to cross bio-barriers, including the stratum corneum and bacterial biofilms [140]. As such, deformable liposomes bearing different surface charges and entrapping EGF were developed and compared for their skin permeation ability. Importantly, all formulations exhibited similar size (300-350 nm) and a high entrapment efficiency (80%). While all delivery modalities showed high skin retention *ex vivo*, anionic liposomes also showed sustained release and demonstrated enhanced mitogenic activity in human fibroblasts relative to neutral and cationic liposomes [133].

Elastic liposomes also boosted the wound healing activity of a GFs combination including EGF, insulin-like growth factor-I (IGF-I), and platelet-derived growth factor-A (PDGF-A). GFs were initially fused with low molecular weight protamine to yield skin-permeable derivatives, that were subsequently combined and loaded into elastic vesicles for enhanced skin permeation and fibroblast delivery. Such strategy increased the wound closure rate in a diabetic mouse model by 65%, promoting fast and extensive re-epithelialization [88].

In terms of promoting local retention of GFs while protecting them from enzymatic degradation, nanofiber mats could prove useful. Xie et al. employed chitosan and polyethylene oxide (PEO) to fabricate nanofibers incorporating vascular endothelial growth factor (VEGF) and poly(lactic-co-glycolic acid) nanoparticles loaded with platelet-derived growth factor-BB (PDGF-BB). Such hierarchical system allowed for differential release of the two GFs, facilitating fibroblast proliferation *in vitro* and matching the different phases of wound healing in a full-thickness rat skin wound model *in vivo* [134].

Biopolymers naturally occurring in the skin's extracellular matrix could also be employed as starting materials to yield biomimetic nanofibrous scaffolds. With this vision, an interwoven nanofiber network composed of hyaluronic acid (HA) and collagen (Col) was combined with multiple angiogenic growth factors (including bFGF, VEGF, PDGF, EGF) either directly incorporated within the nanofibers or encapsulated in gelatin nanoparticles (particle-in-fiber configuration). The early release of EGF and bFGF is believed to enhance epithelialization and vascular growth, whereas later release of PDGF and VEGF promotes the maturation of blood vessels. When cultivated on such platform, endothelial cells proliferate more rapidly and form a thread-like tubular network. Furthermore, the scaffold expedited wound closure and vascular maturation in wounded streptozotocin-induced diabetic mice [135].

To better mimic the skin structure, bilayer nanofibrous scaffolds were developed. In a first example, a bilayer dressing loaded with EGF was fabricated employing polycaprolactone (upper layer) and a combination of chitosan and polyvinyl alcohol (lower layer). The scaffold expedited wound closure and enhanced histological healing in a mouse model of full-thickness skin damage [136]. Shortly after, a multi-layered formulation composed of PVA nanofibers embedding EGF and FGF in alternating layers was developed. Its *in vitro/in vivo* efficacy was compared to a single-layer system co-entrapping the two GFs. Interestingly, both the multilayer and single layer dressings increased cell proliferation and adhesion of human dermal fibroblast *in vitro* and accelerated wound size reduction in a rat burn wound model, with no significant differences between the two configurations, indicating the simultaneous presence of the two GFs as the most crucial feature for successful healing [137].

Coaxial electrospinning provides a core-shell structure to nanofibers, allowing for encapsulation of GFs in the inner layer to better modulate the release and achieve lasting effects. In a recent paper, a cationic sulfonated chitosan, gelatin and polycaprolactone were employed to fabricate core-shell nanofibers loaded with EGF/bFGF. Nanofibers lowered inflammatory cytokines, increased collagen deposition and promoted angiogenesis in a rat full-thickness skin wound model. Moreover, the dressing showed a potent antibacterial activity due to the presence of the quaternary ammonium salt grafted sulfonated chitosan, highlighting its role as a bio-active component [138].

If using individual GFs could target specific pathways involved in wound healing, employing a natural combination could lead to synergistic effects. With this view, platelet-rich plasma (PRP) could be used as a source of blood-derived natural GFs. PRP was thus incorporated into chitosan/PEO nanofibers, proving that the fabrication process did not alter its bioactivity. The PRP nanofibers showed promising properties for wound healing, including increased metabolic activity and proliferation of dermal keratinocytes [139].

3.4. Delivery of nucleic acids

The wound healing process can be finely modulated using advanced

therapeutics, including nucleic acids such as DNA, microRNA, short interfering RNA (siRNA) and, more recently, circular RNA [141–143]. By knowing the pathways involved in the different stages of wound healing, nucleic acid sequences can be designed to upregulate or silence the expression of target genes, speeding up the recovery. However, it is known that nucleic acids do not have drug-like properties, since they are hydrophilic, anionic macromolecules with poor cell uptake, hampered cytosolic delivery and fast enzymatic degradation [144]. Hence, numerous delivery systems have been specifically developed to tackle these challenges and transport nucleic acids in the difficult context of wound healing. While these systems have been comprehensively reviewed elsewhere [145], the next section will focus on recent examples using liposomes (including lipid nanoparticles, LNPs) and nanofibers (Table 4).

Lipofectamine ™ 2000, a commercial mixture of cationic and helper lipids, was employed to form lipoplexes with a plasmid encoding for Stromal Cell-Derived Factor-1α (SDF-1α), an angiogenesis mediator. The lipoplexes were adsorbed in a crosslinked hyaluronan/collagen scaffold, that was next tested on diabetic rats' wounds. The treatment with the loaded scaffold led to an increase in SDF-1α expression in the wounds that promoted angiogenesis, induced tissue remodeling and expedited wound closure [146]. In another report, a microRNA 21 (miR-21) plasmid was co-encapsulated with simvastatin in PEGylated liposomes to tackle different phases of wound healing. Specifically, miR-21 is known to inhibit the pro-inflammatory and activate anti-inflammatory pathways, while simvastatin has pleiotropic effects on angiogenesis, re-epithelization and radical scavenging. Such combination strategy led to increased collagen deposition and epidermal proliferation, as well as a considerable reduction in inflammatory markers and accelerated wound closure in an excisional wound rat model [147].

Compared to DNA, RNA therapeutics have the advantage of not requiring nuclear entrance to exert their action. Moreover, short interfering RNA (siRNA) can be designed to target potentially any messenger RNA, providing an extremely versatile tool for molecular therapy. In this context, a lipoproteoplex (LPP) consisting of lipids and a cationic coiled-coil protein were developed to encapsulate a siRNA targeting Keap1, a repressor of Nrf2 which is involved in normalizing oxidative status in diabetic wounds. The application of LPP in a humanized mouse diabetic wound model reinstated Nrf2 antioxidant functionality, expedited tissue regeneration and enhanced redox homeostasis within the wound environment [148].

In the last years, some notable examples of wound healing therapies based on circular RNA (circRNA) -a promising alternative to linear mRNA for its increased stability-were reported. In the first paper, circRNA encoding VEGF was encapsulated in ionizable LNPs produced by microfluidics. *In vitro* transfection of LNPs proved the prolonged VEGF-A expression of circRNA compared with linear mRNA. A single topical administration on the wound of diabetic mice resulted in almost complete wound recovery on day 12 without significant toxicity or immunogenicity, while other conditions (linear mRNA-LNPs, recombinant VEGF and negative controls) lagged behind [149]. Similar results were achieved using a circRNA for another growth factor, FGF2, proving the robustness of the circRNA strategy. Also in this work, the prolonged expression of FGF2 by circRNA compared to mRNA was proved *in vitro*, also showing an increase in fibroblast proliferation and endothelial cell tube formation. The stability of circRNA allowed to detect FGF2 expression in the wound up to 13 days after a single administration, leading to faster wound healing due to an increase in collagen expression, higher myofibroblast count and enhanced angiogenesis [150].

In contrast to lipid-based nanoparticles, polymeric nanofibers do not promote the cytosolic delivery of nucleic acid therapeutics per se; thus, they require combination with cell penetrating peptides or nanoparticles to allow functional delivery. As such, Mulholland et al. developed a crosslinked alginate/PVA - chitosan/PVA bilayered nanofibers platform, subsequently soaked with a complex between siRNA targeting FK506-binding protein-like (FKBPL) and a cationic, amphiphilic 30-mer

Table 4
Selected wound healing studies on liposomes and nanofibers loaded with nucleic acids. Acronyms: 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-distearoylsn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (DMG-PEG-2000), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG-2000), ((4-hydroxybutyl)azanediyl) bis (hexane-6,1-diyl) bis (2-hexyldecanoate) (ALC-0315), bis(9-heptadecanyl)-6,6′-((3-(bis(2-ethanol))-aminopropyl)-azanediyl)bis(hexanoate) (U-105), circRNA (circular RNA), Fibroblast Growth Factor 2 (FGF2), heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102), poly{(2-dimethylaminoethyl methacrylate)-co-[N-(2-hydroxypropyl) methacrylamide]} (COP), matrix metalloproteinase-9 (MMP-9), polycaprolactone (PCL), polyvinyl alcohol (PVA), Vascular Endothelial Growth Factor (VEGF).

Composition/ Preparation	Active Compound (s)	Key results (model)	Ref
Liposomes (Lipofectamine™ 2000) embedded in collagen-hyaluronic acid crosslinked scaffolds/Direct mixing	pDNA encoding SDF-1α	Enhanced tubes formation vs empty vehicle and control (*in vitro*, human endothelial cells). Wound healing by day 15, improved re-epithelialization, promotion of angiogenesis (*in vivo*, full thickness wounds on diabetic Sprague-Dawley rats)	[146]
Liposomes (DSPC, DOTAP, cholesterol, DSPE-PEG2000)/ Thin-film hydration, freeze-thawing, extrusion	miR-21- encoding plasmid, simvastatin	Enhanced tube length vs simvastatin-liposomes and control (*in vitro*, human endothelial cells). Faster wound closure, reduced infiltration of inflammatory cells, higher collagen density than controls determined by histology (*in vivo*, excisional wounds on Wistar rats)	[147]
Liposomes (DOTAP, sodium cholate, coiled-coil cationic protein)/Thin-film hydration and extrusion	siRNA targeting Keap1	Reduction of Keap1 mRNA and protein with no cytotoxicity (*in vitro*, murine fibroblasts). Average wound healing time reduced from 31 days (control) to 22 days, reduction of ROS in the wound bed (*in vivo*, full thickness wounds on Male diabetic Lepr $^{db/db}$ mice)	[148]
LNPs (U-105 or ALC0315, DMG-PEG-2000, DSPC, cholesterol)/ Microfluidic	VEGF circRNA	Prolonged VEGF-A expression triggered by circRNA compared with linear mRNA (*in vitro*, human endothelial cells). Faster wound closure than recombinant VEGF and free circRNA. No difference in immunogenicity compared to controls (*in vivo*, C57BL/6 diabetic mice full-thickness cutaneous wound model)	[149]
LNPs (SM-102, DSPC, cholesterol, DMG-PEG-2000)/ Microfluidic	FGF2 circRNA	FGF2 expression induced for 13 days by circRNA vs 3 days for linear mRNA (*in vitro*,	[150]

(*continued on next page*)

Table 4 (*continued*)

Composition/ Preparation	Active Compound (s)	Key results (model)	Ref
		human embryonic kidney cells). Promotion of proliferation and migration (*in vitro*, murine fibroblasts) and increased tube formation (*in vitro*, human endothelial cells), vs FGF2 protein and linear mRNA. Residual wound area at day 15: 13.3 % vs 48.3-78.1% for controls; enhanced collagen deposition (*in vivo*, full-thickness skin wounds in db/db diabetic mice)	
Bilayered nanofibers (alginate/PVA - chitosan/PVA) crosslinked with glutaraldehyde/ Electrospinning	siRNA targeting FKBPL complexed with a cationic 30-mer peptide (RALA)	Induction of cell migration and endothelial tubule formation (*in vitro*, human microvascular endothelial cells). Increased vessel density compared to all other treatments, including a commercial dressing (*in vivo*, full thickness wound on C57BL/6J mice)	[151]
Nanofibers (PVA/PCL)/ Electrospinning	siRNA targeting MMP-9 in COP-coated nanodiamonds	Reduced healing time by 6 days vs untreated (*in vivo*, excisional wounds on diabetic C57BL/6 mice). 2.5-fold decrease of MMP-9 expression in scar tissue vs non-silencing control; no local toxicity (erythema, rash, papules) nor liver damage (*in vivo*, excisional wounds on C57BL/6 mice)	[152]

peptide. FKBPL is a potent antiangiogenic protein, thus its inhibition could represent a potential pro-angiogenic approach. Indeed, the siRNA-peptide complexes improved cell migration and endothelial tubule formation *in vitro* due to efficient protein silencing. Results were confirmed *in vivo*, where two local applications of the nanofiber mat containing the siRNA-peptide complexes led to an over 3-fold increase in angiogenesis compared to controls [151]. Another recent report describes the development of nanofibers containing siRNA against matrix metalloproteinase-9 (MMP-9), a proteolytic enzyme overexpressed in chronic wounds. siRNA were initially complexed with polymer-coated nanodiamonds as a non-toxic and effective transfection reagent, then electrospun with PVA to yield the functional layer of the nanofibrous mat (supported by a PCL layer). Topical application in diabetic wounded mice led to significant reduction in MMP-9 expression in the scar tissue and a faster scar formation [152].

3.5. Delivery of natural compounds

Despite recent advances in wound management and the development of innovative pharmacological agents for wound healing and skin regeneration, traditional approaches based on herbal and natural therapeutics continue to represent promising alternative strategies. This is largely attributable to the wide spectrum of bioactive constituents they contain, including alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, fatty acids, and phenolic compounds, which exert anti-inflammatory, antibacterial, and antioxidant properties. Furthermore, natural products are often favored over conventional therapies due to their widespread availability, relatively low cost, and reduced incidence of adverse effects [153]. Beyond the intrinsic benefits of medicinal plants in wound care, their therapeutic efficacy can be further enhanced through nanosizing techniques or by incorporating plant-derived bioactive compounds into nanostructured delivery systems, such as liposomes and nanofibers (Table 5). Particularly, these strategies are advantageous for molecules characterized by low aqueous solubility or stability and limited permeability across lipid-based cellular membranes, which may otherwise compromise their bioavailability and therapeutic performance [164].

In this context, over recent decades, considerable research has focused on curcumin, a natural polyphenol derived from turmeric, which exhibits several promising properties for wound treatment. Curcumin acts as a potent antibacterial agent, effective against pathogens such as *S. aureus* and *E. coli*, which are frequently found in diabetic wounds. Moreover, it promotes angiogenesis, keratinocyte migration, and the production of anti-inflammatory cytokines as well as growth factors. Despite these promising characteristics, curcumin faces significant challenges in both formulation and clinical application due to its poor solubility, limited stability, and low bioavailability.

Based on the considerations outlined above, Poornima et al. have pursued a dual approach to wound healing by developing an exudate-absorbing, infection-resistant polyacrylamide/alginate composite hydrogel patch loaded with liposome-encapsulated curcumin to mitigate its low water solubility and stability, thus enhancing antibacterial efficacy. Briefly, the lipogel dermal patch was tested for its wound healing properties using the DPPH assay, while its antibacterial characteristics were assessed against *E. coli* and *S. aureus* by the Kirby Bauer assay. To check new blood vessel growth, they also carried out an in-ovo CAM (Chorioallantoic Membrane) assay. Overall results demonstrated that liposomal encapsulation significantly enhanced the solubility of curcumin and provided sustained drug release, resulting in increased antibacterial efficacy. The hydrogel also demonstrated good adhesion and water retention capacity, essential for effective wound healing and infection prevention [154]. Liposomal-encapsulated curcumin was also investigated in a recent *in vivo* study employing an innovative antibacterial approach such as photothermal therapy (PTT). This medical treatment relies on laser-induced activation of photothermal agents to generate localized heat, which eliminate bacteria with limited side effects. More in detail, by J. Liu et al. developed a new antibacterial platform, specifically designed for the treatment of drug-resistant bacterial infections in diabetic wound ulcers. Firstly, they synthesized a novel organic photothermal agent (IRC) with absorption in the second near–infrared region (NIR-II, 1000–1700 nm), with high efficacy in PTT due to its deep tissue penetration and low tissue damage. Then, by encapsulating curcumin and IRC within phase-change material (PCM) liposomes, they obtained IRC-CUR@PCM thermosensitive nanoparticles. Under 980 nm laser irradiation, IRC-CUR@PCM exhibited effective PTT and controlled curcumin release. The nanoparticles were tested in a diabetic mouse model infected with MRSA and the obtained results showed that IRC-CUR@PCM promoted cell proliferation, M2 macrophages polarization, and deposition of collagen, thereby accelerating wound healing. Moreover, IRC-CUR@PCM demonstrated excellent biocompatibility. Thus, this NIR-II-activated smart nano-antibacterial platform presents a promising solution for efficiently treating and improving the prognosis of bacterial infections in diabetic wounds, with potential clinical applications in various other deep-seated drug-resistant bacterial infections [155].

Similarly, Wu et al. developed a dermal hydrogel for diabetic wound dressing with anti-inflammatory, antibacterial, and antioxidant properties. The formulation incorporates phlorizin, a flavonoid derived from non-edible parts of the apple tree, known for its antimicrobial, antioxidant, hypoglycemic, and anti-inflammatory activities. Phlorizin

Table 5
Selected wound healing studies on liposomes and nanofibers loaded with natural compounds and extracts. Acronyms: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG-2000), (2-Hydroxypropyl)-gamma-cyclodextrin (HP-γ-CD), chorioallantoic membrane (CAM), matrix metalloproteinase-2 (MMP-2), phosphatidylcholine (PC), polyacrylamide (PAM), polycaprolactone (PCL), polylactic acid (PLA), polyvinylpyrrolidone (PVP).

Composition/ Preparation	Active Compound(s)	Key results (model)	Ref
Hydrogel (PAM/ alginate, crosslinker: calcium chloride) containing liposomes (PC, cholesterol)/Thin-film hydration and sonication	Curcumin	Sustained (10 h), first-order kinetic drug release showing curcumin Fickian diffusion (*in vitro*). Enhanced antibacterial activity (*in vitro*, *E. coli* and *S. aureus)* and angiogenesis promotion (*in vivo*, CAM assay)	[154]
Phase-change material liposomes (lauric acid, stearic acid, PC, DSPE-PEG-2000)/	IRC (a NIR-II phototermal agent) and curcumin	30+°C temperature rise and complete drug release after 6 min of irradiation at 980 nm (*in vitro*). Promotion of M2 polarization (*in vitro*, murine macrophages). Complete healing of the outer epidermal wound and complete bacteriostasis by day 15 (*in vivo*, MRSA-infected diabetic ICR mice and diabetic foot Goto–Kakizaki rats)	[155]
Hydrogel (oxidized sodium alginate and carboxymethyl chitosan) loaded with liposomes (PC, cholesterol)/ Thin-film hydration and sonication	Phlorizin	Controlled drug release up to 2 days at pH 5.5, high water absorption and swelling within the first 2 h (*in vitro*). Enhanced diabetic wound healing by: activation of Nrf2 signalling and suppression of TLR4/ NF-κB/MyD88 pathways, improved collagen deposition and re-epithelialization (*in vivo*, diabetic ICR mice)	[156]
Nanofibers (PCL/ gelatin)/ Electrospinning	*Indigofera aspalathoides*, *Azadirachta indica, Memecylon edule* and *Myristica andamanica*	Lack of cytotoxicity, no impairment of metabolic activity, especially with *Memecylon edule* nanofibers (*in vitro,* human dermal fibroblasts). Promotion of epidermal differentiation through increased expression of early (Ker 10) and intermediate (filaggrin) differentiation markers by *Memecylon edule* nanofiber (*in vitro*, human adipose derived stem cells)	[157]
Nanofiber (cellulose acetate)/ Electrospinning	Crude annatto extract (rich in bixin and norbixin)	Lack of cytotoxicity and high biocompatibility (*in vitro*, primary mouse fibroblasts from C57BL6 mice). Reduction of inflammation, promotion of tissue regeneration and no scarring after 60 days of implantation (*in vivo,* full thickness wounds on Wistar rats)	[158]
Nanofibers (PLA)/ Electrospinning	Hydroethanolic extract from *Teucrium ramosissimum* leaves (flavonoids, terpenoids, phenolic acids)	Significant wound closure (95% by day 15), enhanced re-epithelialization, reduced necrosis, and improved tissue regeneration observed by histology (*in vivo*, mouse pressure ulcer model)	[159]
Nanofibers (chitosan/HP-γ-CD)/ Electrospinning	Quercetin	Enhancement of quercetin solubility (20-fold) due to complex inclusion (*in vitro*). Potent antibacterial activity (*in vitro, E. Coli, S. Aureus*). Reduction of inflammatory markers (IL-6, NO secretion) (*in vitro*, mouse fibroblasts, human macrophages)	[160]
Core-shell nanofibers (shell: cellulose acetate; core: PVP)/Coaxial electrospinnig	Rhubarb Anthraquinones, Honey, Borneol	Healing Promotion of MRSA-infected surgical wounds and severe burn injuries; mitigation of scar formation by modulation TGF-β1/ Smads/EN1 signaling (*in vivo,* Sprague Dawley and Wistar rats)	[161]
Nanofibers (PLA-PCL)/ Electrospinning	Naringin	alanced absorbency, moderate hydrophobicity, and appropriate moisture vapor transmission (*in vitro*). Sustained release over three days (*in vitro*). Prolonged antifibrotic effect induce by the downregulation of fibrotic markers (growth factor β1, collagen type 1 alpha 1 chain, α-smooth muscle actin) (*in vitro*, human dermal fibroblasts)	[162]
Nanofibers (Poly (octanediol-co-citric acid)-gelatin)/ Electrospinning	Curcumin	Skin biomechanics mimicry & adhesion to moving wounds (*in vitro*), MMP-2-responsive release (*in vitro*). Enhancement of scarless wound healing in diabetic and hypertrophic wound models (*in vivo*, diabetic db/db mice); Reduced inflammation by modulating MCP-1 and EMMPRIN	[163]

(*continued on next page*)

Table 5 (*continued*)

Composition/ Preparation	Active Compound(s)	Key results (model)	Ref
		expression (*in vitro*, activated fibroblasts and *in vivo*).	

enhances skin wound healing by inhibiting the PI3K/Akt/mTOR signaling pathway and upregulating autophagy-related proteins. Since phlorizin water solubility is very low, they produced phlorizin-liposomes (PL) and then incorporated them into an oxidized sodium alginate (OSA) and carboxymethyl chitosan (CMCS) hydrogel scaffold, yielding an OSA/CMCS/PL (PLOCS) composite hydrogel adopting Schiff base reaction. The study evaluated the swelling properties, antibacterial efficacy, and biocompatibility of the PLOCS composite hydrogel, as well as its role in promoting diabetic wound healing. The findings indicated that PLOCS efficiently regulates drug release, exhibits advantageous swelling and degradation traits, and displays notable antioxidative capabilities alongside *in vitro* biocompatibility. Histopathological investigations of streptozotocin-induced diabetic mouse wounds indicated that PLOCS increased healthy epithelial tissue proliferation and collagen synthesis. Western blotting exposed that PLOCS reduces inflammation by blocking the TLR4/NF-κB/MyD88 pathway. In conclusion, the authors state that PLOCS composite provides a new generation of dressings for the treatment of diabetic wounds, alleviating the pain while reducing medical treatment costs and the risk of infection [156]. The results obtained in these studies support the efficacy of novel nanotechnologies combined with advanced therapeutic treatments in expanding the therapeutic potential of natural molecules used in traditional medicine.

Beyond liposomes, electrospun nanofibers offer a promising strategy for the delivery of natural extract as well as bioactive compounds, as they can incorporate molecules with diverse physicochemical properties and enhance their bioactive efficacy.

One of the earliest studies on this topic, more than two decades ago, aimed to address the drawbacks of ointments or hydrogels in the treatment of exuding wounds. The authors, Jin et al., used the electrospinning technique to incorporate four individual plant extracts including *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylon edule* and *Myristica andamanica* along with a biodegradable polymer, polycaprolactone (PCL), to produce nanofibers and evaluated the proliferation of human dermal fibroblasts (HDF) on the scaffold by cell proliferation assay. Obtained results suggested that the HDF were metabolically active on plant extracts containing nanofibers, especially PCL/Memecolyn (PCL/ME). Moreover, F-actin and collagen staining studies further confirmed that the PCL/ME was the most suitable substrate for skin tissue engineering. Finally, the expression of early and intermediate epidermal differentiation markers was observed by performing the differentiation of human adipose derived stem cells to epidermal lineages on PCL/ME scaffolds. This study highlighted the potential therapeutic applications of plant extract-based scaffolds for wound healing and skin reconstitution and, subsequently, numerous studies have been carried out to further investigate this area [157].

Among the many studies, one of the most significant investigated the incorporation of annatto (*Bixa orellana* L.), a natural dye with antimicrobial, antioxidant, and anti-inflammatory properties, into cellulose acetate nanofiber scaffolds via electrospinning. To evaluate their *in vivo* performance, the scaffolds were surgically implanted into dorsal incisions of Wistar rats. Two weeks post-implantation, the nanofibers remained in the subcutaneous tissue without signs of inflammation or scarring, demonstrating biocompatibility. By day 60, the scaffolds had begun to naturally degrade; however, an increase in mast cells suggested that the annatto extract effectively modulated the immune response, thereby mitigating inflammation. Furthermore, the scaffolds promoted fibroblast proliferation, reduced inflammation, and supported tissue regeneration without visible scarring. The gradual degradation of the nanofibers allowed ongoing healing, while the annatto extract acted as a plasticizer, enhancing fiber flexibility and structural integrity [158].

Plant-derived metabolites are widely acknowledged for their immunomodulatory and anti-inflammatory properties, as well as for their ability to promote fibroblast proliferation and accelerate tissue regeneration. In this context, Bouhajeb et al. developed implantable electrospun PLA nanofiber scaffolds loaded with *Teucrium ramosissimum* extract to improve the treatment of pressure ulcers. In a rodent ischemia–reperfusion injury model using Swiss albino mice, the fabricated dressing significantly enhanced wound contraction, achieving 95.17% healing within two weeks, compared to 68.89% in the untreated group and 55% in the placebo group. Moreover, macroscopic and histological evaluations confirmed enhanced collagen deposition, improved re-epithelialization, and effective skin remodeling, while the nanofibrous scaffolds reduced scarring and prevented infection risk. The structured dressing demonstrated a regulated release profile, to address early inflammation, succeeded by a prolonged release over 15 days to preserve bioactivity. Taken together, PLA nanofibers loaded with *Teucrium ramosissimum* represent a biocompatible and implantable wound dressing particularly suitable for the treatment of chronic wounds and pressure ulcers [159].

As already emphasized previously, addressing the problem of poor solubility of an active molecule makes it bioavailable and therefore effective. To this end Alishahi et al. developed a biofunctional wound dressing composed of chitosan-based nanofibers containing cyclodextrin–quercetin inclusion complexes on nonwoven cotton substrates to mitigate the low water solubility of quercetin, a natural antioxidant with antibacterial and anti-inflammatory properties, by the creation of inclusion complexes with hydroxypropyl-beta-cyclodextrin (HP-β-CD) and hydroxypropyl-gamma-cyclodextrin (HP-γ-CD). The antibacterial assessments of the resultant dressing demonstrated that HP-γ-CD/Quercetin nanofibers injected with chitosan effectively eradicated the tested microorganisms and also imparted anti-inflammatory effects by diminishing nitric oxide and IL-6 synthesis in regenerative and immunological cells [160].

Although wound closure is the primary goal, excessive scar formation is another significant issue following deep trauma, severe burns, or chronic wounds, often caused by an imbalanced wound microenvironment. Uncontrolled fibroblast activation and excessive collagen deposition can lead to hypertrophic scars and keloids, which negatively impact both aesthetics and tissue function. Therefore, regulating key signaling pathways, such as TGF-β1/Smads/EN1, is crucial for inhibiting fibrosis and promoting effective tissue repair. Modern wound dressings that modulate inflammation and support organized tissue regeneration can significantly reduce the risk of scarring [165]. In this regard, Zeng et al. developed a multi-drug loaded electrospun nanofiber wound treatment to improve healing and minimize scar formation. The dressing was fabricated through coaxial electrospinning, encapsulating rhubarb anthraquinones and honey within a polyvinylpyrrolidone core, while borneol (a natural bicyclic monoterpene) was integrated into a cellulose acetate shell, resulting in enhanced porosity, wettability, and a biphasic drug release profile for superior dissolution. The designed dressing contributed to increased biocompatibility, and migration of fibroblasts and endothelial cells, and revealed evidence of sustained antibacterial action against MRSA *in vitro*. Furthermore, in male Sprague-Dawley rats also they distinctly expedited wound closure in MRSA-infected wounds and severe burns, accelerated hair follicle regeneration, and lessened scar formation by reducing skin thickness and improving collagen orientation. The therapy inhibited transforming growth factor beta 1, small mothers against decapentaplegic (Smad) proteins, and engrailed 1 (a transcription factor involved in fibrosis regulation) expression while enhancing the inibitory Smad7, so positively modulating fibrotic pathways [161].

With the continued aim of minimizing hypertrophic scarring, innovative wound dressings that modulate inflammation and support organized tissue regeneration have been proposed by Tottoli et al. More in

detail, they developed Biofiber a biodegradable electrospun dressing composed of PLA-PCL fibers loaded with naringin (NG), a natural anti-fibrotic agent. Its performance was evaluated in terms of exudate management, mechanical properties, and prophylactic efficacy. The dressing exhibited optimal fluid-handling behavior, with balanced absorbency, moderate hydrophobicity, and appropriate moisture vapor transmission. Its circular texture conferred flexibility and conformability, leading to improved mechanical properties after exposure to simulated wound fluid. *In vitro* studies demonstrated a sustained release of NG over three days. This controlled delivery induced a prolonged antifibrotic effect in normal human dermal fibroblasts by down-regulating key fibrotic markers, including growth factor β1, collagen type 1 alpha 1 chain, and α-smooth muscle actin. No significant effect was observed in hypertrophic scar-derived fibroblasts, highlighting Biofiber potential as a prophylactic approach [162].

Recently, Nie et al. created a matrix metalloproteinase-2 (MMP-2)-responsive drug-releasing nanofibrous mat composed of curcumin-entrapped POCA-gelatin nanofibers for scarless wound healing. The dressing responds to elevated MMP-2 levels in inflamed wounds by releasing curcumin to stimulate fibroblasts and restore immunological equilibrium.

This technique not only reduce inflammation but also facilitates basement membrane renewal and collagen orientation, redirecting the wound healing process towards genuine tissue regeneration instead of merely removing fibrosis. This engineered material mimics the mechanical properties of skin, adheres effectively to wounds, and promotes basement membrane regeneration by modulating immune responses. Further research on diabetic and tension-loaded wound models revealed faster healing, reduced inflammation, and better tissue regeneration with well-aligned collagen fibers and less scarring [163].

The overall outcomes of the reviewed studies support advances in regenerative medicine by limiting inflammation and promoting wound healing toward a scarless repair, suggesting a potential future focus for wound care strategies.

4. Recent advances and future perspectives

4.1. Production and scalability

Over the past decade, research in nanomedicine has greatly expanded our understanding of its potential in wound healing, leading to the development of innovative formulations with promising preclinical results. The transition from laboratory-scale formulations to industrial production remains challenging, particularly in terms of achieving batch-to-batch consistency, scalability, regulatory compliance, and cost-effectiveness.

For liposomes, commonly used methods such as thin-film hydration, ethanol injection, and reverse-phase evaporation are well suited for laboratory-scale preparation but present limitations at larger scale. These include difficulties in ensuring reproducibility and homogeneity across batches, as well as the need for additional size-reduction steps (e.g., extrusion or ultrasonication), which increase process complexity, time, and costs. In this context, microfluidic mixing has emerged as a promising alternative, as it is based on a relatively simple and well-controlled mixing process that enables precise tuning of particle size and distribution, while remaining cost-effective and compatible with scalable and continuous manufacturing [166,167]. However, some limitations remain, including the need for organic solvent removal and the requirement for case-by-case process optimization depending on formulation parameters. In this regard, recent advances in computational modeling and simulation tools are increasingly facilitating process optimization and accelerating the development of robust and reproducible microfluidic formulations [61,168].

For nanofibers, several fabrication techniques have been developed, including electrospinning, melt spinning, centrifugal spinning, wet spinning, and drawing. Among these, electrospinning is the most widely used due to its ability to produce fibers with very small diameters and high surface-area-to-volume ratios [169]. Significant advances have been made with the development of multi-needle and needleless electrospinning systems, which enhance productivity and scalability. In this context, production costs are mainly associated with raw materials (e.g., polymers and solvents) and equipment, but the availability of industrial-scale technologies supports the feasibility of large-scale manufacturing [170].

4.2. Marketed products and regulatory challenges

Despite the remarkable advances, the successful translation of such technologies into approved and commercially available therapies still faces several regulatory challenges.

Even though liposomes represent one of the earliest and most commercially successful nanocarrier technologies, with the highest number of approved nanomedicine products to date [171], only a single liposomal formulation has been specifically approved for wound-healing applications. Repithel®, a povidone-iodine liposomal hydrogel, combines antimicrobial activity with a moist wound environment to accelerate epithelial regeneration and reduce inflammation in both acute and chronic wounds [172,173]. On the other hand, nanofiber-based scaffolds have progressed further in terms of clinical implementation in wound care, with multiple electrospun dressings already approved by the FDA. Examples include Restrata® Sheet™ (Acera Surgical), designed to emulate the native extracellular matrix and promote cellular infiltration and tissue regeneration, and Phoenix™ and Anthem™ Wound Matrices (RenovoDerm®), composed of biodegradable polymers such as poly(glycolic acid) and poly(l-lactide-co-caprolactone). These electrospun matrices are indicated for both acute and chronic wounds, offering a versatile and bioresorbable alternative to traditional wound dressings [174]. In parallel, portable electrospinning technologies have emerged as a promising frontier in wound care, enabling the in-situ deposition of nanofiber scaffolds directly onto the wound surface using gun-like devices, resulting in a rapid and patient-specific therapy [175,176]. Among them, the Spincare™ system stands out as a clinically approved portable device capable of generating and applying a nanofibrous, skin-like matrix directly onto the wound bed. This technology exemplifies a new generation of dynamic, on-demand wound dressings, delivering a biomimetic structure that accelerates epithelialization, reduces pain, and enhances patient comfort compared with standard therapies. Its non-invasive application offers distinct advantages in clinical settings, and its integration into routine practice marks a paradigm shift toward more personalized and adaptive wound care solutions [177].

While liposomes excel in optimizing drug delivery to the wound site and nanofibers function as multifunctional scaffolds guiding tissue regeneration, growing evidence supports the integration of these platforms into hybrid systems, such as liposome-loaded nanofibers [178–182]. These composite systems aim to combine the controlled and efficient delivery capabilities of liposomes with the structural, biomimetic, and regenerative properties of nanofibrous matrices, thereby maximizing therapeutic efficacy [104].

Despite these advancements, the significant structural and functional complexity of these products makes their regulatory approval pathway particularly challenging [183]. For liposomal formulations, the regulatory authorities require extensive physicochemical characterization, along with *in vitro* evaluation and, when necessary, proper *in vivo* correlation [184]. Nevertheless, the guidelines are not specifically intended for topical liposomal products; therefore, the specifications are often extrapolated from parenteral guidelines, making regulatory pathways uncertain [185]. While wound dressings and scaffolds are generally regulated as medical devices facilitating faster market access [186–188], particular attention must be given when nanotechnology-based manufacturing processes are involved [189]. Moreover, when such dressings incorporate bioactive compounds or drugs, they can be

defined as combination products, and their classification as drug products or medical devices depends on the determination of the principal mode of action [190,191]. This classification is often difficult to establish, as both the bioactive agent and the polymeric or nanofibrous matrix can contribute synergistically to the therapeutic outcome [192,193]. Consequently, the complexity of these products – coupled with fragmented regulatory guidance – hinder clinical translation, highlighting the need for clearer, more specific guidelines and harmonization across regulatory authorities.

5. Conclusions

Nanocarrier-based strategies have demonstrated significant potential in advancing wound-healing therapies by addressing both biological and technological limitations of conventional treatments. Among the various nanocarriers, liposomes and nanofibers have emerged as two of the most extensively studied systems, each fulfilling distinct yet complementary therapeutic roles. Liposomes primarily function as delivery systems, enhancing the local availability and stability of antimicrobial agents, growth factors, and other bioactive molecules. By contrast, nanofibrous systems provide a biomimetic structural framework that closely resembles the native extracellular matrix of the skin, promoting tissue regeneration. In addition to their structural function, nanofibers may exhibit intrinsic antimicrobial activity and enable sustained, localized release of therapeutic agents, thereby exerting a dual biological and delivery function.

Despite encouraging preclinical and early clinical evidence, the translation of nanocarrier-based wound-healing technologies remains constrained by regulatory complexity and limited product-specific guidance. While liposomes have achieved broad regulatory success in other therapeutic areas, their application in wound care is still scarce. Conversely, nanofiber-based dressings have progressed further toward clinical adoption, including FDA-approved electrospun scaffolds and emerging portable electrospinning systems that enable personalized, in situ wound treatment.

Emerging combinatorial strategies, including nanofibrous platforms incorporating liposomes, underscore the potential of integrated approaches to address the multifactorial nature of wound healing. The rational design of such hybrid systems, together with clearer and harmonized regulatory pathways, may represent a decisive step toward more effective, multifunctional, and clinically translatable wound-healing therapies.

CRediT authorship contribution statement

Luca Casula: Conceptualization, Writing – original draft. **Yasmin Adeela:** Writing – original draft. **Francesco Lai:** Writing – review & editing. **Jovana Bradić:** Writing – original draft. **Michele Schlich:** Writing – original draft, Writing – review & editing. **Nina Dragićević:** Writing – original draft. **Chiara Sinico:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

Data availability

this article is a review and does not report new experiment data. All data discussed are availabale in the cited literature.

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