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Recent advances in coaxial electrospun nanofibers for wound healing

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ABSTRACT

The skin is the body's primary immune barrier, defending it against pathogenic invasion. Skin injuries impose a significant physiological burden on patients, making effective wound management essential. Dressings are commonly employed in wound care, and electrospun nanofiber dressings are a research hotspot owing to their ease of fabrication, cost-effectiveness, and structural similarity to the extracellular matrix. Coaxial electrospinning offers considerable advantages in drug delivery, fiber structure transformation, and enhanced interaction with the host. These attributes make coaxial electrospun materials promising candidates for precision and personalized wound dressings in medical treatments. This review provides a comprehensive overview of wound healing and its influencing factors. It also outlines coaxial electrospinning's production principles and benefits in wound dressings. Guided by the factors affecting wound healing, coaxial electrospun nanofiber dressings have different application modalities. Furthermore, we discuss the current limitations and future directions for enhancing the current coaxial electrospun dressing technologies.

1. Introduction

The skin, the largest human organ, covers approximately 2 m^2 in adults and serves multiple critical functions [1–3]. It protects the body against external threats and acts as the first line of immune defense, preventing pathogen invasion [4]. The skin also prevents excessive loss of water and nutrients, senses environmental changes, and regulates body temperature [4–6], highlighting the importance of maintaining skin integrity. Skin wounds caused by physical injuries, surgical procedures, or exposure to extreme temperatures and chemicals [7] markedly impact human health. Skin wounds contribute to approximately 5.8 million deaths annually, accounting for one-tenth of global mortality [8]. Wounds can become chronic under conditions such as diabetes or infections [6,9]. Chronic wounds affect 1–2% of the population in developed countries and worldwide [10]. Their point prevalence is 1.47 per 1000 in the UK [11]. By 2022, China alone reported approximately 30 million individuals with chronic wounds [12]. Chronic wounds are categorized into pressure ulcers, vascular ulcers, and diabetic ulcers [13]. Prevalence rates of pressure ulcers, which are chronic ulcers caused by sustained pressure, ranged from 3.4 % to 32.4 % worldwide, according to a cross-sectional study in 2019 [14]. It is believed that prevalence rates of venous leg ulcers are between 1.5 ‰ and 3 ‰ [11]. Moreover, 20–25 % of diabetic patients will develop foot ulcers [15,16]. Given this prevalence, promoting the regenerative healing of skin wounds is crucial [7]. While debridement and skin grafting are the gold standard for managing severe wounds, the scarcity

Abbreviations: Coaxial electrospinning, (CES); coaxial electrospun nanofiber, (CEF); Platelet-rich fibrin, (PRF); reactive oxygen species, (ROS); growth factor, (GF); extracellular polymeric substances, (EPS); Extracellular matrix, (ECM); Epidermal growth factor, (EGF); nano particles, (NP); matrix metalloproteinases, (MMPs); epidermal stem cells, (EPSCs).

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of available skin sources and potential donor site damage limit their widespread application [3,17].

Wound care primarily aims to promote scarless healing by shielding the wound from mechanical forces and microbial infiltration while establishing a microenvironment that fosters cellular proliferation and migration [18]. Wound dressings are suitable for this purpose. Traditional dressings like gauze are non-occlusive and inert [19], with limitations in controlling drug release and short-term antibacterial efficacy [20]. Nanofiber membranes, a type of bioactive dressing, are particularly suitable for wound dressings as their structure resembles the extracellular matrix (ECM) [8,21]. Various methods, such as drawing processing, template-assisted synthesis, self-assembly, and electrospinning, have been employed to fabricate nanofibers. Among them, electrospinning is particularly notable for its low cost, high efficiency, and higher yield compared to other techniques [2,22]. Electrostatic attraction in liquids was observed in the 1600s by William Gilbert. John Francis Cooley filed the first electrospinning patent in the 1900s [23]. In 1969, Geoffrey Ingram Taylor developed a mathematical formula for electrospinning [23], and the technique was further advanced in the 1980s [24]. By 1977, electrospun nanofibers were successfully used as wound dressings [25]. Nevertheless, monoaxial electrospinning has limitations, including difficulties in controlling sustained drug release and challenges in creating complex structures, which hinder its application. Coaxial electrospinning (CES) was developed to overcome these issues. CES offers advantages such as a simple production process and high drug-loading capacity, rendering it an effective option for wound healing [26]. Recently, several CES membranes have been applied to heal wounds.

Herein, we comprehensively review coaxial electrospun nanofiber (CEF) dressings, focusing on CEF dressings' forms and their unique activities in wound healing. First, we briefly summarized the physiological phases and factors affecting wound healing. Then, the fundamental principles of CES and its distinct advantages as a wound dressing are discussed. We specifically summarize the special structures of CEF dressings and drug-delivery systems for sustained drug release during wound healing. Additionally, we discuss the current challenges and advancements in CEF dressings, as well as future research directions.

2. Factors influencing wound healing and features of ideal wound dressings

2.1. Factors influencing wound healing

Wound healing is an intricate biological process [27], unfolding in four overlapping phases: hemostasis, inflammation, proliferation (re-epithelization), and remodeling (scar maturation) (Figc 1A) [28,29]. Hemostasis commences immediately after skin damage, persisting for minutes to hours [30]. During this phase, injured blood vessels contract, and platelets activate to form a fibrin clot with fibrinogen, effectively halting bleeding [31]. Neutrophils are the first immune cells to migrate to wound sites, which marks the beginning of the inflammatory phase. Subsequently, monocytes are recruited to the wound site by chemotactic factors such as platelet-derived growth factor (PDGF), stromal-derived factor 1 (SDF-1/CXCL12), and transforming growth factor-β (TGF-β) expressed by neutrophils and platelets within 48–96 h after injury. The monocytes then differentiate into macrophages [27,32]. The acute inflammatory phase typically lasts 1–3 days [30]. In this phase, M1 macrophages are predominant, releasing tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, and matrix metalloproteinases (MMPs) to clear damaged tissue and neutrophils while supporting antibacterial actions and antigen presentation [33]. By the third day, the counts of M2 macrophages increase; they become the dominant immune cells by the seventh day [34]. M2 macrophages are crucial for angiogenesis and ECM deposition. As the wound progresses into the proliferation stage, fibroblasts become the main effector cells [27]. Typically, this stage lasts from several days to one month [30]. Following re-epithelialization, the remodeling phase ensues, which can last several months to years, involving skin remodeling and scar formation [30].

High redundancy and compensatory mechanisms prevent minor alterations that delay wound healing [35]. However, sufficient

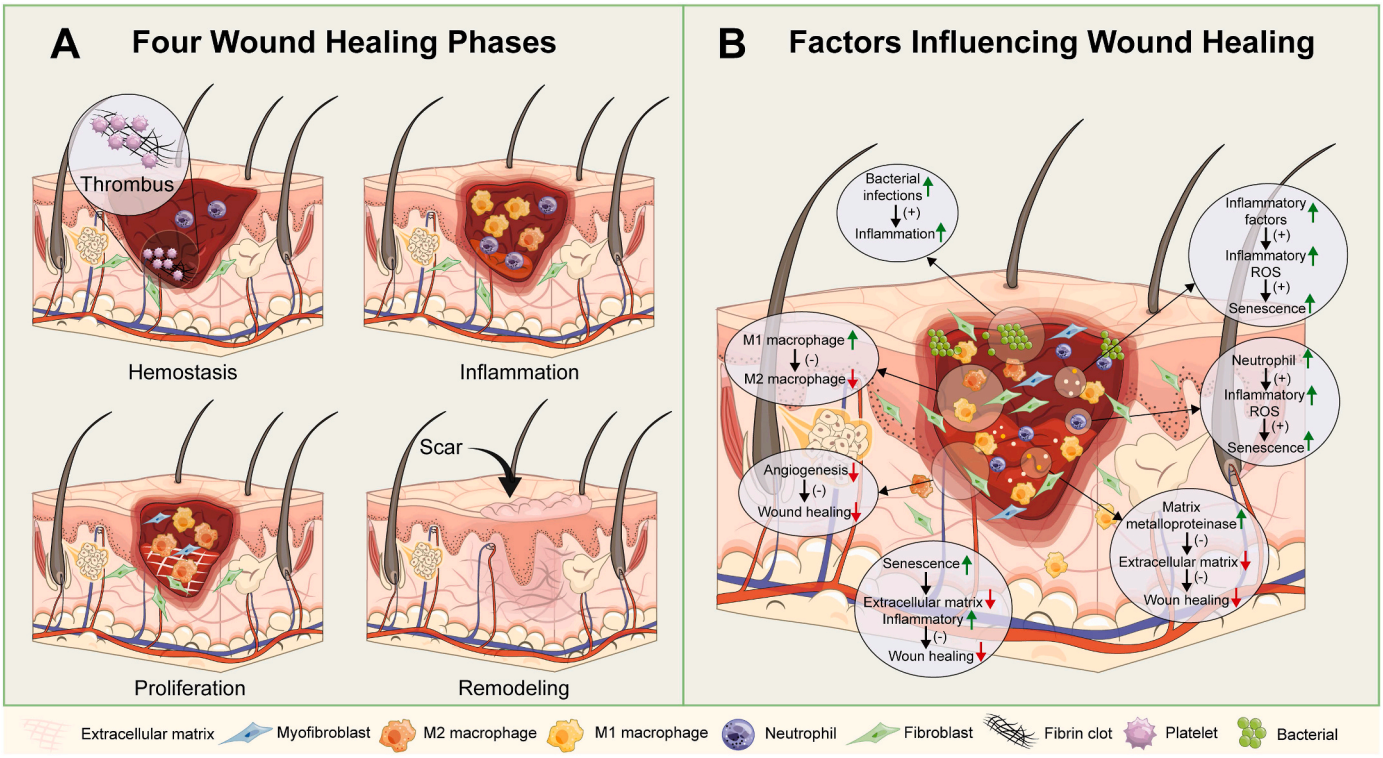

Fig. 1. Diagram of the four wound-healing phases and influencing factors. (A) Diagram depicting the four successive and overlapping phases of wound healing: hemostasis, inflammation, proliferation, and remodeling. (B) Factors that inhibit wound healing.

perturbations in the wound-healing system can lead to distortions, manifesting as pathological scarring or chronic wounds [35]. The hallmark features of hard-to-heal wounds include persistent inflammation, recurrent infections, elevated MMP and reactive oxygen species (ROS) levels and impaired angiogenesis and tissue epithelialization (Fig. 1B) [36].

Immune dysregulation significantly impedes the intricate process of wound healing. Chronic wounds typically exhibit a pronounced influx of M1 macrophages, a decrease in M2 macrophage counts, and an upregulation of inflammatory mediators, such as TNF-α, hypoxia-inducible factor 1-α (HIF1-α), and IL-1β [30,37]. Numerous M1 macrophages produce high levels of proteases, including MMP1, MMP3, and MMP11, which contribute to ECM degradation and hinder wound-healing progress [37]. Prolonged and intense inflammation leads to increased ROS levels. Although modest ROS concentrations can stimulate cell migration and angiogenesis, excessive ROS concentrations can trigger oxidative stress, lipid peroxidation, and substantial cellular damage, thus delaying wound closure [38]. A persistently elevated inflammatory milieu and oxidative stress culminate in cellular senescence.

Senescent cells exhibit functional impairment and epigenetic alterations in pro-inflammatory phenotypes, amplifying inflammation within the wound site [35,39]. The regenerative and reparative capabilities of the skin are intricately linked to epidermal stem cells (EPSCs) [40]. However, the regenerative potential of senescent EPSCs is compromised, hindering their angiogenic and wound-healing properties [41]. Additionally, immune cells undergo senescence, resulting in impaired cellular functions and diminished clearance capabilities, rendering wounds more susceptible to microbial colonization.

Bacterial infections are prevalent and pose a significant challenge, impeding wound recovery [9]. The warm and moist environment of the wound provides a natural culture medium for microorganisms [29]. Additionally, prolonged exposure to wounds renders them susceptible to microbial invasion, complicating the wound environment and impeding healing. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the predominant pathogens in skin wounds [42]. *S. aureus* is typically found as an isolated, single colony in infected foot ulcers and diabetic wounds, delaying wound healing, and endemic in healthcare settings globally [43]. Microbial cells produce extracellular polymeric substances (EPS) to form protective biofilms, effectively shielding themselves from host immunity and antimicrobial agents [44]. Disrupting these biofilms is a critical aspect of CEF dressings.

Impaired angiogenesis is a crucial factor contributing to delayed wound healing [45]. Neovascularization is typically initiated as early as three days post-injury, with capillary formation supplying oxygen and nutrients, particularly during the proliferation phase of wound healing [46]. CEF dressings engineered to promote angiogenesis, such as those incorporating vascular endothelial growth factor (VEGF) [47], are a common strategy in dressing design.

Additional factors, including age [48] and hyperglycemic microenvironments [36], significantly influence wound recovery. Treatments that address two or more damaging factors during wound healing are more effective than those targeting a single causative factor. Ideal wound dressings are tailored to address the factors mentioned above.

2.2. Features of ideal wound dressings

Ideal wound dressings should mimic the ECM of the target tissue [8,49], absorb excess fluids [50,51], shield wounds from the external environment [50,52], support gas exchange [29,53], exhibit non-immunogenic properties, not provoke allergic reactions [29], and ensure comfort, flexibility, and adaptability to wound contractions (Fig. 2) [2,43]. Furthermore, enhanced dressing adaptability across various stages of wound healing requires high biocompatibility [49], minimal biotoxicity [54], and non-toxic degradation byproducts. Optimal adhesion [29] is crucial for secure attachment to the wound surface [43] and easy removal [55]. Maintaining moisture within the wound is recognized as speeding healing compared to traditional dry dressings [56–58]. Excellent hemostatic properties [50] aid in transitioning the wound from the hemostatic to the inflammatory phase. Besides, dressings must have appropriate mechanical properties similar

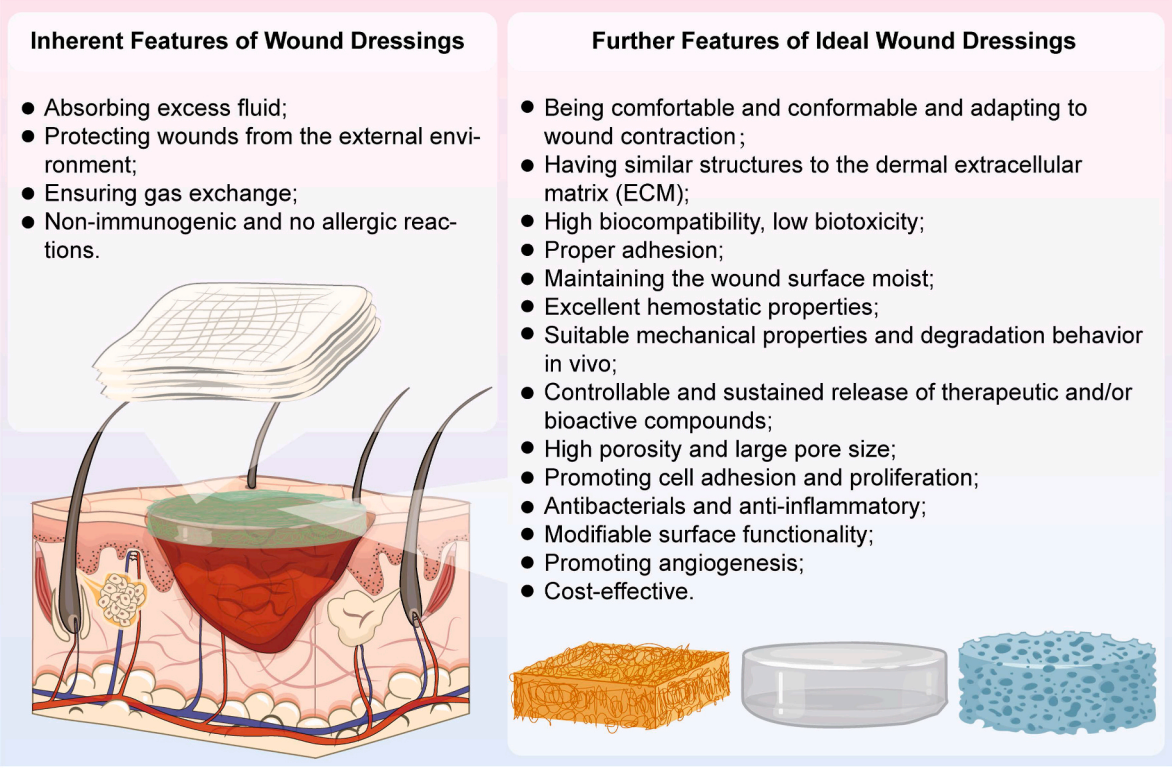

Fig. 2. Features of ideal wound dressings.

to those of natural skin, with degradation rates matching the wound-healing speed [43,59]. The ability to control and sustain the release of therapeutic or bioactive agents into wounds is also critical [2,3,43]. High porosity and large pore size facilitate cell adhesion, migration, angiogenesis, and exudation [60]. Thus, dressings should stimulate cell adhesion and proliferation, guide cellular behavior to promote re-epithelialization [2,61], possess antibacterial and anti-inflammatory properties [50–52], possess modifiable surface functionality [54,62], promote angiogenesis [63], and be cost-effective [54]. CEF dressings have unique advantages in simulating the structure of ECM and are expected to become ideal wound dressings.

3. CES manufacturing principles and advantages of CEF dressings

3.1. CES manufacturing principles

Electrospinning involves using electric fields to draw fibers from a polymer solution or melt [64]. The standard configuration comprises a collector connected to a grounded or negatively charged electric field, a spinneret connected to a positive electric field, a high-voltage power supply, and a syringe pump (Fig. 3A) [65]. The polymer solution is pushed through a syringe pump at a consistent rate and extruded from the needle tip. When an electric field is applied, a cone structure known as the "Taylor cone" forms, as electrostatic repulsion overcomes the solution's surface tension. Subsequently, fibers are ejected from the Taylor cone and collected by the collector to form fiber membranes with the required topology [66,67].

The principle of CES largely mirrors that of monoaxial electrospinning. Introduced by Sun et al., in 2003, CES employs a spinneret composed of two concentric capillaries linked to independent syringe pumps (Fig. 3B) [2,68]. The electric field force acts on the shell solution to induce the ejection of shell polymers, while shear forces on the core solution, resulting from adhesion and friction, draw the core solution into the cone, forming a double jet (coaxial) [69].

CEF production requires precise adjustments to various parameters. Environmental parameters, such as temperature and humidity; equipment parameters, including external electric field and the solvent flow rate; and solvent parameters, including polymer type and concentration, are crucial for determining the characteristics and morphology of electrospun nanofibers [64]. For instance, elevated humidity levels can disrupt solvent evaporation during electrospinning, affecting the formation of porous fibers [70]. However, low humidity accelerates the evaporation rate of the solvent, leading to insufficient extension of the jet, thus forming thicker nanofibers and even blockage at the needle [71]. Adjusting the collector's rotation speed enables the production of randomly oriented or aligned fibers [72]. Longer distance between the needle tip and collector [73], higher rate of liquid pump injection [42], and lower applied voltage [74] require a larger fiber diameter [75]. The voltage should also be adjusted within a suitable range because voltages that are too low and too high make core and sheath jets split [76]. Fine-tuning the liquid flow rate of the core-shell syringe pump can control fiber and fiber shell thicknesses [77]. The flow rate of the shell should be higher to entrain the core solution completely [78]. When the core solution has a higher velocity than the sheath, fibers have a thick sheath and a buckled core [76]. Nozzles can be positioned horizontally or vertically, with vertical placement typical in wet electrospinning processes [79]. By adjusting the position of the inner and outer nozzle tips [80] or even removing the inner nozzle [81], CEFs of different shell thickness/core diameter ratios and different diameters can be produced.

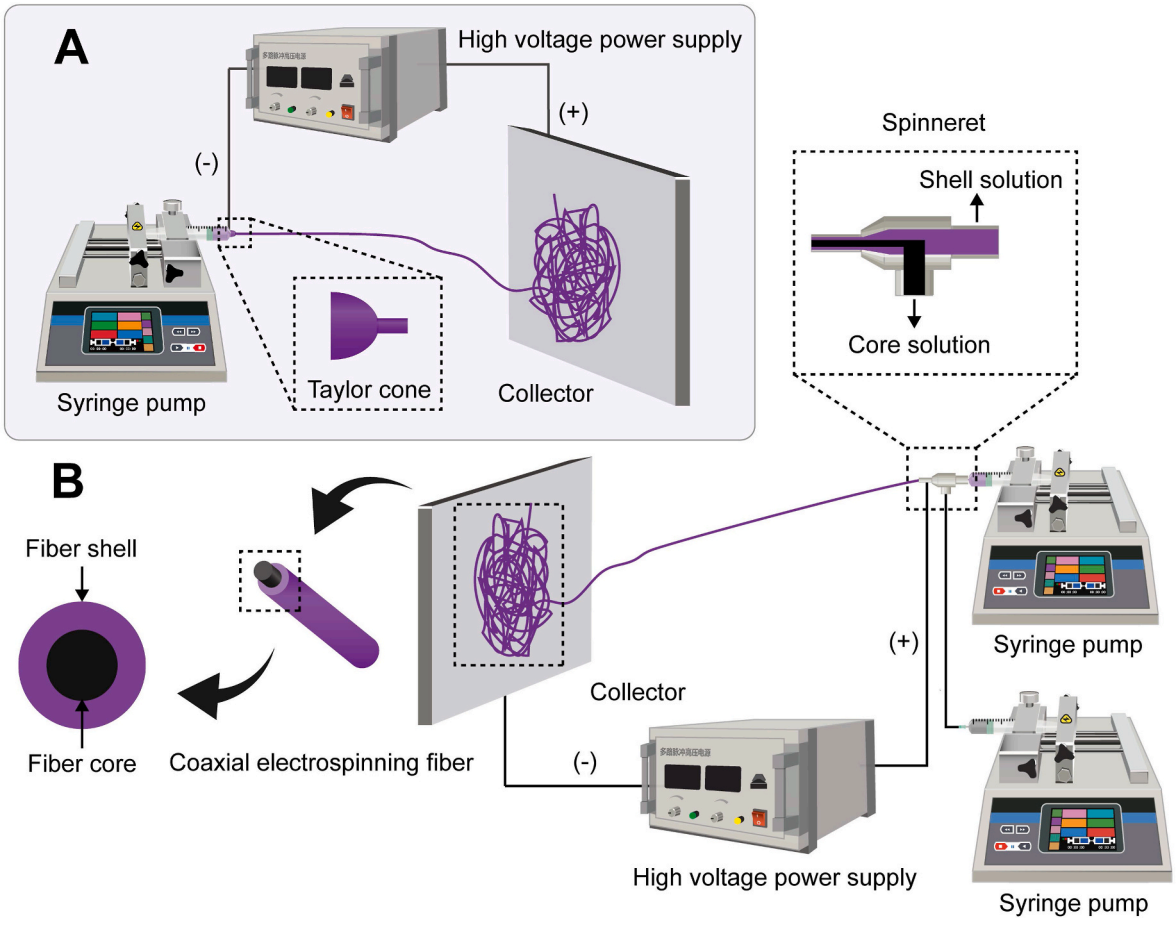

Fig. 3. Diagram of the principles of monoaxial electrospinning and coaxial electrospinning (CES). (A) Monoaxial electrospinning process. (B) CES fabrication process.

CEF production is influenced by the polymer and solvent properties of the core and shell. Core and shell polymers converge at the nozzle outlet and co-deposit on the receiver to form fibers. When employing polymers dissolved in different types of solvents, including organic solvents, such as dimethylformamide and chloroform, and inorganic solvents, such as distilled water, the polymer solution, may crystallize and obstruct the nozzle [82]. For a given polymer, lower molecular weights correspond to smaller fiber diameters [83], whereas high polymer solution concentrations result in thick fibers [75]. In traditional CEF processes, the shell solution is the driving solution, and it should be electrospinnable and more viscous than the core solution to entrain the core solution in the compound jet by the viscous shear stress. However, an electrospinnable driving solution as a core solution is also feasible [78].

3.2. Advantages of CEF dressings

Electrospun nanofiber wound dressings mimic the ECM [84]. The diameter of type I collagen in the dermis ranges from 50 to 500 nm, closely aligning with that of electrospun nanofibers, which are thinner than 1000 nm [85]. Nano dimensions significantly enhance the surface-area-to-volume ratio of electrospun nanofiber dressings [85], facilitating cellular adhesion [86]. Electrospinning also allows for precise morphological control of nanofibers [8], enhancing guidance capabilities for cellular activities. For instance, highly aligned CEF dressings promote cell migration, re-epithelialization, and wound healing [87–89].

The interconnected porous structure of electrospun nanofiber dressings supports cellular activities, including angiogenesis [45], gas exchange [8,90], and absorption of wound exudates [90], thereby maintaining a moist environment conducive to wound healing [64]. Although the ideal pore size for optimal cell growth and wound healing varies, most researchers agree that sizes ranging from tens to hundreds of microns are optimal, matching the pore sizes of electrospun nanofiber dressings [60]. Manipulating fiber diameters can direct exudate flow out efficiently, with thicker inner and thinner outer fibers being effective [91].

Furthermore, compared with monoaxial electrospinning, side-by-side electrospinning, and multiple jet electrospinning, CES can separate the shell and core polymers until the solution is ejected, enabling the production of electrospun materials with opposing properties and amalgamating the advantages of both materials to produce multifunctional dressings [92]. For instance, combining poly (ε-caprolactone) (PCL), known for its excellent spinnability and mechanical properties but poor cell adhesion owing to its hydrophobic nature [52,93,94], with gelatin (Gel), a biocompatible and hydrophilic material lacking spinnability [8,93,95], as core and shell solutions, respectively, enhances the mechanical performance, hydrophilicity, and tissue compatibility of the resulting CEF dressings [93].

CEF dressings also offer unique advantages as drug-delivery vehicles. CES can directly electrospun drug solutions, resulting in high drug loading and encapsulation efficiency [29]. Its large area-to-volume ratio provides a large host contact area, which facilitates drug diffusion. Furthermore, easily inactivated drugs and bioactive compounds can maintain their biological activity when incorporated into the core [8,64]. An initial burst release of the drug occurs when drug-loaded basic electrospun nanofibers are implanted into wounds [45]. This phenomenon is attributed to the movement of the drug to the fiber surface as the solvent evaporates, leading to rapid release upon contact with body fluids [96]. CEFs with drugs loaded in the core can mitigate this initial burst effect, ensuring sustained release [45,97]. Conversely, CEFs with drugs loaded in the shell can utilize the early burst release of drugs after implantation, resulting in short-term increases in drug concentration, which is useful for drugs requiring high concentrations, such as antibiotics [93,94]. These advantages make CEF ideal for wound dressing.

4. Materials used in CEF dressings

4.1. Synthetic polymers commonly used in CEF dressings

Electrospun wound dressings utilize two main types of materials: natural and synthetic polymers [56]. Table 1 outlines the common core-shell substrates for CEF wound dressings from 2013 to 2024, with certain materials frequently employed as both core and shell components.

4.1.1. Poly (ε-caprolactone)

PCL, a commonly used synthetic material in electrospun dressings [98], is a semi-crystalline, linear aliphatic polyester. Increasing its relative molecular mass decreases crystallinity [99]. PCL exhibits favorable characteristics, including excellent spinnability, high solubility, and a low melting point range (59–64 °C). It has also been approved for clinical use by the U.S. Food and Drug Administration (FDA) [18,99–101], and shows remarkable biocompatibility, good mechanical properties, high flexibility, low toxicity, and low antigenicity [94,100]. PCL biodegrades under physiological conditions over 2–4 years [29,101] and occurs in two stages: non-enzymatic hydrolysis initially cleaves aliphatic ester groups via surface and bulk degradation pathways. Subsequently, when the polymer attains a lower molecular weight, it is engulfed by macrophages, giant cells, and fibroblasts, leading to intracellular degradation and the formation of hydrolytic intermediates, specifically 6-hydroxycaproic acid and acetyl coenzyme A, which are subsequently excreted from the body [29]. Owing to their hydrophobic nature [100], the water contact angle of PCL dressings is approximately 90° [102], which can impede cell adhesion. Fortunately, the formation of hydrophilic surface functional groups in the surface hydrolysis phase *in vivo* relatively improves cell adhesion and proliferation [103]. PCL cores provide mechanical support to CEFs [104,105]. In PCL shells, PCL grafted with maleic anhydride improved the coverage of the fiber core by enhancing the interfacial compatibility between two components of core and shell [106].

4.1.2. Polyvinyl alcohol

Polyvinyl alcohol (PVA) is a hydrophilic polymer with hydroxyl groups on its molecular chains and is prominently employed in wound dressings [54]. This environmentally friendly and cost-effective material exhibits commendable biocompatibility [20,107], biodegradability [108,109], flexibility [66], swelling properties [110], a broad range of crystallinity [66], and chemical resistance [108]. PVA is non-toxic [111] and non-carcinogenic [108,110]. Owing to the hydroxyl groups, PVA can be modified by attaching growth factors (GFs) and other biomolecules [54,108] and can improve cell adhesion [112]. With its excellent spinnability, PVA is often blended with other materials, such as polysaccharides-*Bletilla striata* polysaccharide [113], licorice extract [1], and alginate [114], to enhance its spinnability along with serving as the core material of CEFs to bolster their mechanical properties [1,115,116]. Despite its relatively lower mechanical strength (compared to PCL), different concentrations of PVA are utilized in conjunction with PCL to meet different wound situations [24,103]. With high hydrophilicity [66,115] and water solubility [10,110], PVA can be combined with collagen [69] and gel [117] to improve spinnability while preserving its water solubility. When sustained drug release is required, PVA is utilized as the core material for drug loading [24,118]. Conversely, CEFs with drugs loaded within the PVA shell commonly exhibit burst release in the early stages of dressing implantation [105]. Wu et al. employed the coaxial electrospinning technology to integrate small molecule sugar alcohols (SAs), including xylitol (Xyl), sorbitol (Sor), and erythritol (Ery), within silver (Ag) nanoparticles (NPs) loaded PVA nanofiber matrix. The CEF dressings thus produced exhibited self-adhesive properties, the ability to scavenge ROS, and remarkable antimicrobial activity [112]. Although they comprehensively treat thermal injuries, animal experiments verifying the functionality of these dressings are

Table 1
Brief characteristics of common materials used for coaxial nanofiber wound dressings.

Material Source	Materials	Features and Functions	Ref.
Natural Materials	Gel	A hydrolyzate of collagen with high biocompatibility, water absorbency, hydrophilicity, biodegradability and affinity to drugs, non-immunogenic, poor mechanical properties and spinnability.	[1,4,5,8,15,42,45,50,55,59,63,93,95,115,117,130,146,147, 155–158,160,162,165,176,193,200,207,208]
	CS	A natural cationic polysaccharide with low cost, good biocompatibility, biodegradation, moisture retention, hemostatic abilities, anti-inflammatory and antioxidant effects, nontoxicity, nonimmunogenicity, poor mechanical properties and poor spinnability.	[4,15,26,56,58,67,116,120,122,124,143,145,160–162,164–168, 201,202,204]
	Col	The most abundant component of the extracellular matrix, with high biocompatibility, water retention, biodegradability, and poor mechanical properties.	[56,69,85,136,137,144,151,152]
	zein	A polyprotein, which is the main storage protein of corn, has nontoxicity, low cost, flexibility, good biocompatibility, biodegradability, amphiphilicity, antibacterial properties, antioxidant properties, water-swellability, high spinnability, low mechanical properties and low nutritional value.	[38,95,121,125,175,195]
	HA	A hygroscopic glycosaminoglycan with unique viscoelastic properties, good biocompatibility and biodegradability.	[49,139,172,185]
	CA	A polysaccharide polymer, which is an acetate derivative of cellulose, has biodegradability, biocompatibility, chemical stability, thermal stability, nontoxicity and no water solubility.	[42,129,134,199]
	Alginate	A natural anionic polysaccharide polymer with nontoxicity, low cost-effectiveness, hydrophilicity, water absorbency, moisturizing property, high biocompatibility, high biodegradability, poor spinnability and poor mechanical properties.	[53,67,92,114,123,173]
	SF	A proterin extracted from *Bombyx mori* silkworm cocoons with excellent mechanical strength and toughness, biocompatibility, rapid hemostatic ability, controllable degradation rate and low immunogenicity.	[16,173]
Synthetic Materials	PVA	A hydrophilic polymer with hydroxyl groups on its molecular chains, a wide range of crystallinity, high biocompatibility, biodegradable ， water solubility, environmentally friendly, low-cost, good mechanical properties, flexibility, swelling properties, chemical resistance, nontoxicity, non-carcinogenic, ease of functionalization, high spinnability and high water solubility.	[1,5,10,20,24,54,62,66,67,69,103,105,107–109,111–113,115–118, 127,130,131,183,186,187,196,201]
	PLA	An environmentally friendly, non-toxic material, and it has good biocompatibility, biodegradability, high hydrophobicity and suitable mechanical properties.	[9,47,61,66,70,77,82,111,113,127,131,136,143,144,152,177]
	PCL	A semi-crystalline linear aliphatic polyester with high spinnability, high solubility, low melting point, high biocompatibility, good mechanical properties, high flexibility, low toxicity, low antigenicity, biodegradability, hydrophobicity and low cost.	[4,5,18,20,22,26,29,38,42,50,54,55,58,59,62,69,77,79,84–86,93, 98,101–103,105,106,109,124,125,144,155–158,163–168,172,176, 178,180,182,183,186,189,193,196,197,199,200,202,207]
	PEO	A water-soluble polymer with high biocompatibility, hydrophilicity, spinnability and nontoxicity.	[12,15,17,18,85,95,99,102,120–125,136,172,173,180,197]
	PEG	A non-toxic and water-soluble polymer, which is a commonly used porogen.	[24,62,63,70,97,107,178]
	PGS	A tough biocompatible elastomer with nontoxicity, good biocompatibility, flexibility, linear hydrolytic degradation properties, similar to collagen and elastin, suitable for drug release, with low specific surface area and can Spinnability.	[3,21,182,189]
	PU	A semi-crystalline polymer, combining hard and soft segments, with non-biodegradability, biocompatibility, moderate blood-compatibility, low toxicity, elasticity, great barrier properties, oxygen permeability, water absorption and drainage, abrasion resistance, chemical resistance, hydrophobicity and low cell affinity.	[9,59,82,99,139,162]
	PVP	A highly water-soluble polymer with high biocompatibility, suitable tensile strength, hydrophilicity, detoxification, hemostasis and good spinnability can inhibit the recrystallization of crystallized drugs and promote blood sedimentation.	[15,29,38,86,92,96,98,116,127,129–132,134–137,164,177,179, 185]
	PLLA	A synthetic material with good biocompatibility, high mechanical strength, adjustable degradability, high recyclability, good stability, good spinnability, and breathability.	[21, 45, 175, 208, 212]
	PLGA	An easily processable polymer with controllable microstructure, mechanical properties, degradation cycle, and crystallinity, good biocompatibility, and poor water solubility.	[43,47,49,63,122,145–148,181]

Abbreviations: PLA, polylactic acid; PVA, polyvinyl alcohol; PU, polyurethane; Gel, gelatin; PCL, poly(ε-caprolactone); PEO, polyethylene oxide; PLLA, poly(l-lactide); PLGA, poly(L-lactide-co-glycolide); PVP, Polyvinylpyrrolidone; Col, collagen; CS, chitosan; CA, cellulose acetate; PGS, polyglycerol sebacate; HA, hyaluronic acid; PEG, polyethylene glycol; SF, silk fibroin.

lacking.

4.1.3. *Poly(ethylene oxide)*

Poly(ethylene oxide) (PEO) is utilized extensively in medical and pharmaceutical applications for its nontoxicity and biocompatibility [119]. PEO, a water-soluble polymer, improves the hydrophilicity of electrospun fibers used with hydrophobic polymers by forming hydrogen bonds with these polymers [18]. The non-ionic nature of PEO contributes to its high spinnability [119], enabling its blending with materials possessing poor spinnability, such as chitosan [120] and zein [121]. By forming hydrogen bonds with chitosan, PEO enhances its spinnability [122]. PEO and alginate blending as a shell solution exhibits high spinnability and can maintain the gel-like nature of alginates [123]. The introduction of PEO shows minimal interference with plate and

plasma proteins due to water interaction and steric repulsion [110], making it suitable for incorporation in the shell layer of CEFs to facilitate an appropriate wound-healing environment [15,124,125]. Stable jet electrospinning (SJES) is an effective method to produce aligned fibers. The key step in SJES for the production of aligned fibers is to add high molecular weight PEO to the spinning dope, effectively eliminating the jet-whipping motion in conventional electrospinning and enabling the easy collection of highly aligned fibers [88,126]. This method does not require complex collectors or electric field treatments, thereby simplifying its implementation [60].

4.1.4. Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a highly water-soluble polymer commonly used as a sacrificial material to fabricate hollow [96,127] and patterned fibers [86,128]. It has high biocompatibility, adequate tensile strength, good spinnability, and safety recognized by the FDA [129–131]. PVP is also used as a matrix carrier in various drug-delivery systems to enhance the water solubility of drugs and inhibit the recrystallization of crystalline drugs [52,116,129,132,133], having improved the solubility of over 160 poorly water-soluble drugs [134]. In 2023, Windbergs et al. demonstrated that the PVP shell of CEFs dissolved upon contact with small amounts of wound exudate, facilitating rapid and controlled phage release [135]. Similarly, Askari et al. used PVP to rapidly release collagen to improve wound healing [136,137]. PVP exhibits detoxification, hemostasis, and blood sedimentation-promoting properties, making PVP fiber dressings beneficial for wound hemostasis [38]. The PVP–iodine complex (PVP-I) has broad-spectrum bactericidal, antiprotozoal, and virucidal properties, gradually releasing active iodine to provide a sustained antibacterial effect. Notably, long-term use of PVP-I rarely induce microbial resistance [29].

4.1.5. Polyurethane

Polyurethane (PU) has a flexible design and shows rapid polycondensation at almost any temperature without releasing small molecules [138,139]. PU is a common biomaterial because it is biocompatible and has moderate compatibility with blood [139]. PU electrospun dressings also possess good barrier properties, oxygen permeability, solvent and abrasion resistance, impact strength, and low-temperature flexibility [138,140]. Interestingly, the excellent moisture transfer properties of PU can transport wound fluid away from the contaminated area [9]. PU can be endowed with different characteristics by modification. For example, waterborne PU has high hydrophilicity [102]. Silicone-containing PU exhibits better flexibility than PU, and PU-polydimethylsiloxane has been developed into dressings [99]. However, its stretchability is poor. Biodegradable block copolymer DegraPol® (DP) has been developed to improve the stretchability of PU. A surgeon-friendly, reversibly expandable bioactive tube made of DP can be easily applied to the wound site even after a conventional tendon repair in clinical settings [141]. Simultaneously, thermoplastic PU shows good stretching and mechanical performance [140,142]. They are expected to serve as wound dressing material for highly mobilized skin. Acrylate-end-capped urethane-based polymer precursors cross-link in a solid state upon UV irradiation, resulting in the formation of photo-cross-linkable CEF dressings [53].

4.1.6. Poly(lactic acid)

Poly(lactic acid) (PLA), one of the most widely used bioplastics globally, is produced by the controlled polymerization of lactic acid monomers obtained from bacterial fermentation with lactic acid bacteria and sourced entirely from renewable materials, such as rice, starch, sugar cane, corn, and wheat [9,82]. PLA is a safe, eco-friendly, non-toxic material exhibiting favorable biocompatibility, biodegradability, and suitable mechanical properties [9,66,113,119,136]. Biodegradation of PLA occurs through the hydrolysis of the ester group within its structure [82]. PLA, classified as an aliphatic thermoplastic polymer [143], is either found in an amorphous (D-lactic acid) or semi-crystalline (L-lactic acid) form. Important properties of PLA polymers, including crystallinity, mechanical properties, barrier properties, and thermal properties are determined by the ratio of the stereoisomer (D, L, and D-L) components used in production [82]. Despite its commendable properties, the undirected chain structure of PLA fibers renders it brittle and endows it with a low elongation percentage and brittler structure at room temperature [9], limiting the use of PLA in applications necessitating high flexibility. Consequently, PLA is frequently combined with other materials, such as PCL [77,144], PVA [111], and PU [82], in scenarios requiring high tensile strength. PLA has high hydrophobicity [111]. A water-soluble biocompatible polymer, such as PVA, exhibits reasonable chemical and thermal stability, electrospinning along with PLA can overcome this limitation [111].

4.1.7. Poly(L-lactide-co-glycolide)

Poly(L-lactide-co-glycolide) (PLGA) is a random copolymer of PLA and poly(glycolide) (PGA). Its mechanical properties and degradation cycle can be adjusted by the ratio of lactic acid/glycolic acid [145–147]. The degradation rate can be slowed by reducing the glycolic acid content and increasing the molecular weight [110]. It can be easily processed and is biocompatible with a controllable microstructure, exhibiting excellent mechanical strength and flexibility. It has been approved by the FDA for clinical use [148]. However, PLGA is insoluble in water, and organic solvents are commonly used for PLGA electrospinning [110]. PLGA and PLA are typical aliphatic polyesters, producing acidic degradation products during degradation [122,149]. On the one hand, lactic acid produced by PLGA can enhance angiogenesis, collagen synthesis, and recruitment of endothelial progenitor cells to promote wound healing [122]; on the other hand, too many acidic products can cause aseptic inflammation. CEFs with acid-neutralizing properties, i.e., “pH-neutral fibers,” can ameliorate inflammatory responses caused by the acidic degradation products of PLGA [150]. PLGA is an attractive copolymer for drug delivery. Zamani et al. loaded Gabapentin (GBP), a medicine aiding the recovery of neuropathic pain, and ciprofloxacin (CIP) in the PLGA shell and the Gel core. Drug release studies showed the sustained release of Cip and GBP within 64 days from the CEFs *in vitro* [147]. Homaeigohar et al. also synthesized PEO-chitosan (CS)/PLGA CEF dressings loaded with antibiotic levofloxacin and antioxidant quercetin and showed that the dressing drove the healing cascade of burn wounds [122].

4.2. Natural polymers commonly used in CEF dressings

Natural polymers generally exhibit high biocompatibility and biodegradability but poor mechanical properties (Table 1). Therefore, these materials are typically combined with synthetic polymers to produce electrospun wound dressings.

4.2.1. Collagen

Col 1 is among the most common natural polymers used in CEFs. Col 1 constitutes over 90 % [1] of the human body’s protein content and 70 %–80 % of the skin ECM [5,35]. Collagen provides strength and structural support to tissues and cells and can act as a signaling substrate for endothelial cell growth, further modulating cell phenotype and cell-ECM interactions [100,136,151]. Collagen plays a key role in inflammatory, proliferative, and remodeling phases [5]. Collagen has attracted great interest in regenerative medicine due to its remarkable biocompatibility, water retention, and biodegradability [152,153]. Numerous studies have demonstrated that using collagen can accelerate fibroblast migration and wound closure. For instance, Sun et al. produced a PLA (shell)/collagen (core) electrospun nanofiber dressing and confirmed its efficacy in improving cell migration *in vitro* and facilitating wound healing *in vivo* [152]. The triple helical structure of Col 1 can promote cell adhesion and bolster the mechanical strength of Col 1. However, it is often destroyed due to solvent issues when used as an

electrospinning raw material [5]. In an acidic solvent system comprising acetic acid/ultrapure water, collagen/PVA (PVA) electrospun nanofibers retain the main structure of Col1 (triple helix) [5]. Therefore, an acetic acid solution may serve as a superior solvent for collagen. Despite these advantages, collagen fibers suffer from poor mechanical properties and are susceptible to degradation at room temperature, which can impact their drug-release properties. This limitation can be addressed when it is spun with other stable polymers, such as PCL [154,155].

4.2.2. Gelatin

Gelatin, a hydrolysate of collagen with non-immunogenic properties, high biocompatibility, and biodegradability, and remarkable hydrophilicity, is among the widely utilized polymers in electrospinning [93,115,130]. Combining PCL as the core and Gel as the shell in CEF dressing enhances water absorption compared with PCL fiber dressing alone, leading to rapid wound closure [93]. The mixture of PCL and gelatin as the fiber shell improves the hydrophilicity [156]. However, gels typically lack the mechanical strength and spinnability seen in many natural polymers [115]. It is often spun with synthetic polymers to match the tissue stiffness of the skin. Moreover, gels demonstrate a high affinity for drugs and bioactive factors, as evidenced by electrospun dressings incorporating antibiotics [147,157], GFs [158], and non-steroidal anti-inflammatory drugs [42]. Gelatin methacrylate (GelMA) can be photo-crosslinked while maintaining the capabilities of Gel, including hydrophilicity, absorbing wound exudate, and promoting cell adhesion and angiogenesis [159]. Prajatelistia et al. modified the shell part of the CEFs by combining gelatin methacrylate (GelMA) with cerium oxide (CeO2). These CEF dressings significantly enhanced cell proliferation, resulting in suitable dressings for chronic wounds [117].

4.2.3. Chitosan

CS is a natural cationic polysaccharide obtained from crustaceans [160,161] known for its low cost [162], good biocompatibility, biodegradability [4,163,164], non-toxicity [162], and non-immunogenicity [162]. It possesses inherent hemostatic abilities [124,165], anti-inflammatory effects [16,166], antioxidant [116], and moisture retention properties [167], with a structure analogous to that of glycosaminoglycans in the ECM [168], rendering it ideal for wound-healing applications [145]. Compared to other natural polymers like collagen and gel, CS demonstrates a reduced degradation rate, which is contingent on its molecular mass [169]. Therefore, CS is particularly suitable for wounds that require prolonged degradation. CS also serves as an antibacterial agent owing to its mild antibacterial properties [152,158,163]. However, its antibacterial efficacy is limited in a neutral environment and cannot achieve satisfactory antibacterial effects during wound healing [4]. Various functional groups have been grafted onto chitosan chains to solve these critical issues. For example, sulfonate and quaternary ammonium salt graft-modified CS (QAS-SCS) demonstrate higher water solubility and mechanical strength, along with enhanced antibacterial properties than CS [4,152]. CS structure comprises active hydroxyl and amino groups, with intermolecular chains linked by hydrogen bonds [160]. Due to its polycationic nature and robust intramolecular forces, pure CS and its derivatives pose challenges for electrospinning [166]. Oroojalian et al. synthesized CS- poly(ethylene glycol) (PEG)-ZnO-*Astragalus arbusculinus*/SF CEFs and verified their effect on promoting diabetic wound healing, especially with exogenous adipose-derived stem cells [16].

4.2.4. Alginate

Alginate, a natural anionic polysaccharide derived from brown algae, comprises β-D-mannuronic acid and α-L-guluronic acid residues [92,114]. It can undergo ionic crosslinking to generate gels through interactions with polyvalent cations like calcium [51,53]. Composite materials based on alginate offer advantages such as non-toxicity, cost-effectiveness, high biocompatibility, and pronounced biodegradability [114]. Electrospun alginate dressings exhibit hemostatic properties [92], high absorption capacity for wound exudate [53,92], and support a moist wound environment [85], making alginate extensively used in wound dressings. However, insufficient chain entanglements and electrostatic repulsion among alginate polyanions impede fiber formation during electrospinning [170]. Incorporating polymers with suitable molecular weights, such as PEO and PVA, along with alginate can induce an entanglement effect, consequently mitigating this repulsion and facilitating the electrospinning process [67,92,123,171]. Furthermore, methacrylate alginate (AlgMOD) can enhance the mechanical strength of alginate-based dressings by modifying alginate with methacrylic anhydride to induce covalent crosslinking [53]. Introducing cosolvents into aqueous solutions is another strategy to enhance alginate's spinnability. For instance, glycerol disrupts the hydrogen-bonding network within and between alginate molecules, forming new hydrogen bonds between glycerol and sodium alginate. This change in viscosity enhances the solution's spinnability [110].

4.2.5. Hyaluronic acid

Hyaluronic acid (HA) is a glycosaminoglycan naturally present in the ECM with distinctive viscoelastic properties, good biocompatibility, and biodegradability [139,172]. HA is a hygroscopic macromolecule that controls hydration within the wound site and maintains proper moisture balance during wound healing, promoting cell proliferation and migration [172]. HA enhances fibroblast proliferation, consequently elevating collagen levels in wounds [139]. Moreover, HA is widely used in drug delivery systems [49]. Consequently, HA is a prevalent component in CEF dressings [139]. Han et al. developed a HA/PLGA core/shell fiber dressing loaded with epigallocatechin-3-O-gallate and demonstrated the significant impact of this dressing in improving the healing of diabetic wounds [49].

4.2.6. Silk fibroin

Silk fibroin (SF), a protein extracted from *Bombyx mori* silkworm cocoons by degumming the coating layer of sericin, shows excellent mechanical strength and toughness [173]. As a biomaterial, SF has highly satisfactory biocompatibility, rapid hemostatic ability, controllable degradation rate, and low immunogenicity [16,89,174] but lacks effective antimicrobial activity [174]. Chlorin e6 (Ce6) [174], zinc oxide (ZnO) NPs [173], and other antibacterial substances are loaded in the dressing to improve the antimicrobial properties of SF electrospun dressings. SF nanofibers from conventional electrospinning have worse mechanical properties than their pristine fiber forms. Post-electrospinning treatment with stretching and co-electrospinning with reinforcing nanocomponents have been demonstrated to effectively improve mechanical properties [89].

Other natural polymers, such as zein [95,121] and cellulose acetate (CA) [42], are commonly used in CEF dressings. Similar to other natural polymers, they have attractive biocompatibility, biodegradability, and safety, but poor water solubility [38,129,175] (Table 1).

5. Application forms for CEF wound dressings

CEF dressings, widely employed in wound care, exhibit diverse structures and functionalities that address factors inhibiting wound healing (Fig. 4). Various CEF dressing architectures have been used in wounds, each varying in structural configuration and functional attributes according to specific applications.

5.1. CEF dressings with special structure fibers

The unique characteristics of CES enable the easy production of multi-layer CEFs and hollow fibers with distinctive functionalities. Compared to solid fibers, hollow fibers offer a significantly higher surface-area-to-volume ratio, providing more sites for drug adsorption, improving drug-loading efficiency, and providing contact for exudate absorption [60,82]. CES employs two primary strategies for hollow-fiber

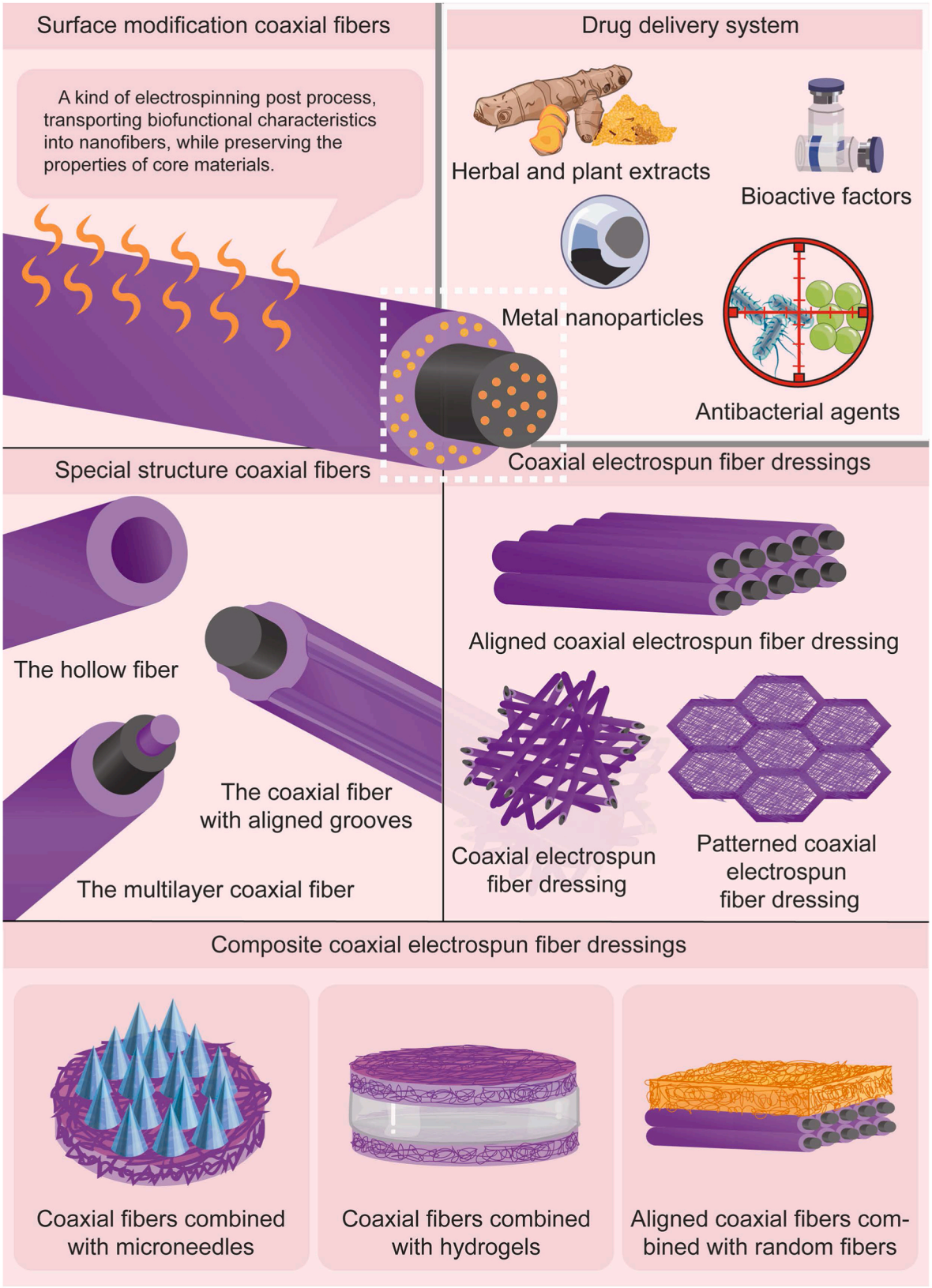

Fig. 4. Application forms of coaxial electrospun nanofiber (CEF) wound dressings.

fabrication: core decomposition (dissolving the core material using a solvent) and core extraction (removing the core material through heat treatment) [60]. Wound dressings are primarily produced through core decomposition. For instance, Aytac et al. spun PU shell and PVP core nanofibers using CES technology and then dissolved PVP in distilled water to fabricate PU hollow fibers (Fig. 5A) [82]. Similarly, Li et al. used core decomposition to produce hollow fibers by spinning PCL shells and PEO core fibers, subsequently removing PEO in ultrapure water

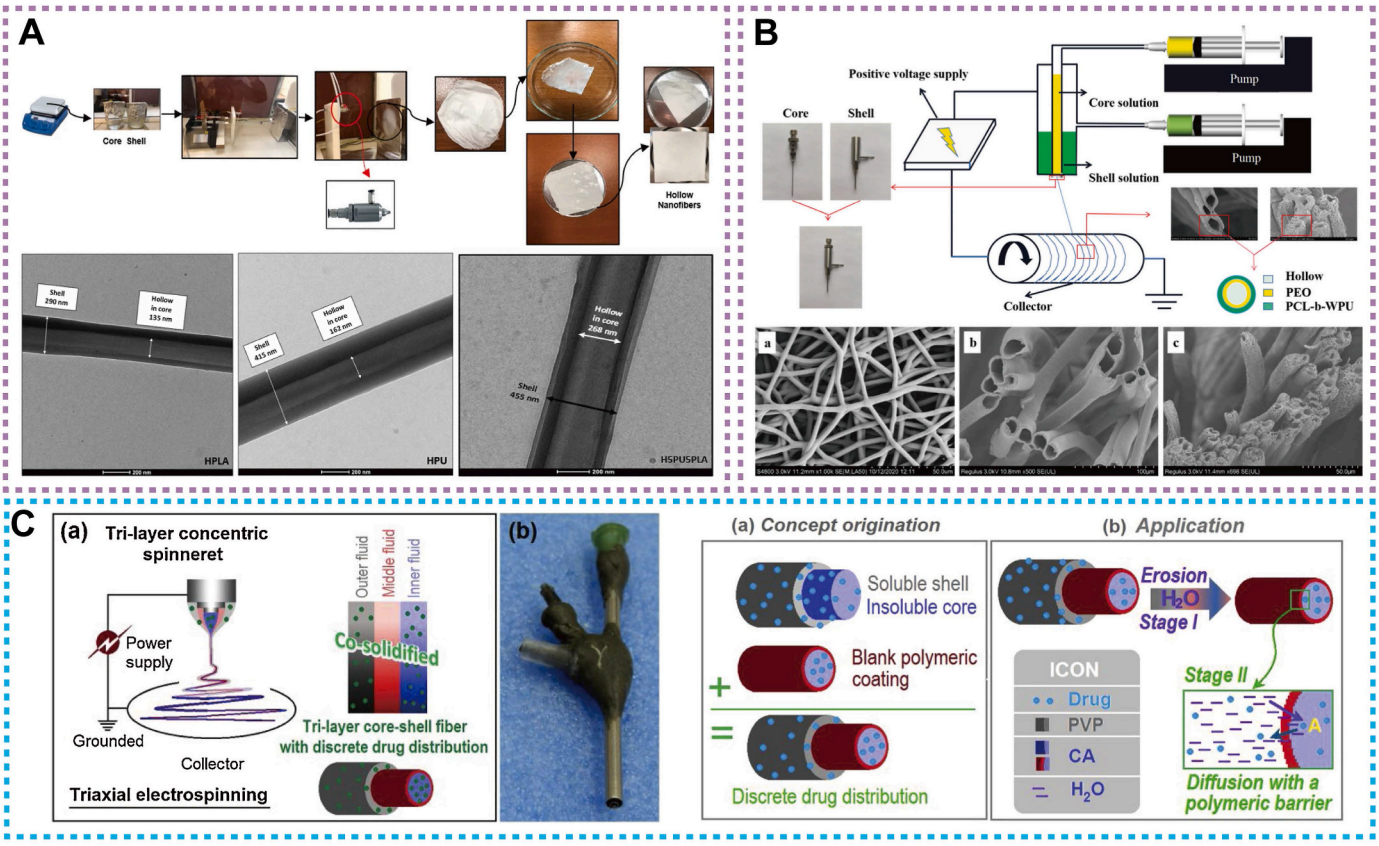

Fig. 5. Hollow and multi-layer coaxial electrospun nanofiber dressings for wound healing. (A) Polyurethane hollow fibers made of dissolved polyvinylpyrrolidone core. Reproduced with permission [82]. Copyright 2023, Springer Nature. (B) Polycaprolactone hollow nanofibers made of dissolved poly(ethylene oxide) core. Reproduced with permission [102]. Copyright 2021, Wiley. (C) Electrospun triaxial nanofibers with middle blank layers for accurate dual-stage drug release. Reproduced with permission [134]. Copyright 2020, Elsevier.

(Fig. 5B) [102]. Despite their larger surface area compared to solid fibers, hollow fibers exhibit drug-release characteristics similar to conventional electrospun fibers, potentially leading to a burst release of drugs immediately after dressing implantation.

Multi-layer coaxial fibers offer distinct advantages, unlike hollow fibers, for sustained drug release. Modified triaxial electrospinning can spin trilayer nanofibers for dual-stage drug release. Yu et al. employed ketoprofen (KET) as a model drug loaded within the CA core and a PVP shell (Fig. 5C) [134]. A blank CA layer inserted between the two layers effectively slows the diffusion rate of the drug molecules from the core. This design allows for the two-stage release of KET, with each stage exhibiting a distinct release profile [134]. During the first stage, KET is rapidly released to address patient symptoms effectively. In the second stage, KET is released in a sustained manner, reducing dosing frequency and improving patient compliance [134]. Electrospun nanofibers with multiple coaxial layers, each with differing water solubility and loaded with different drugs, enable precise control over drug release and facilitate multifunctionality.

5.2. Micropatterned and aligned CEF dressings

Aligned CEF dressings offer great potential for cell elongation and migration alignment along the fiber direction compared to disordered fiber membranes due to their "contact-guide" effect [60,166]. Human dermal fibroblasts extend into a spindle shape along the fiber direction on the aligned fibrous structure of CS/PCL electrospun membranes, showing enhanced migration capabilities compared to fibroblasts on randomly oriented fibrous membranes [166]. Furthermore, the aligned fibrous structure of the electrospun membrane facilitates the desired phenotypic switch in the cells and ECM deposition. However, they do not distinctly regulate cellular functions [88]. This shortcoming can be addressed by loading drugs into aligned fiber.

Various strategies exist for fabricating micropatterned electrospun dressings. For instance, laser ablation has been employed to create aligned grooves within random fiber membranes that serve as guides for cells [60]. Another method involves blending materials with varying water solubility for electrospinning; the highly water-soluble material dissolves quickly when dressings are applied to a wound, forming grooves that aid in cell guidance [86]. An innovative, aligned micropatterned CEF dressing composed of an n-CuO_2+PVP/PCL composite sheath and PCL core was described by Qi et al., in 2023 (Fig. 6) [86]. In this system, PVP gradually disintegrates upon insertion into a moist wound, creating nano grooves aligned with the nanofibers, thereby enhancing cell guidance and promoting skin regeneration. L929 fibroblasts cultured on this dressing exhibited enhanced migration compared to those cultured on random fibrous dressings, leading to faster wound closure [86].

Patterned electrospun dressings can be fabricated using structured collectors. Korsunsky et al. modified a fiber collector using laser ablation, resulting in a CEF membrane with a distinct pattern mirroring that of the collector [24]. Additionally, Xu et al. developed a template collector featuring uniformly spaced 500 μm-diameter orifices, which was subsequently employed for spinning fiber dressings. There were uniformly distributed holes in the final dressings where the cells gathered (Fig. 7) [155]. Furthermore, they created a more interesting collector comprising metal and insulating materials arranged in an orderly manner. During electrospinning, more fibers were deposited on the metallic protrusions of the collector, whereas the density of deposition was lower in the insulating regions. They ultimately spun a fiber membrane with a 500-micron-diameter "honeycomb" structure by this

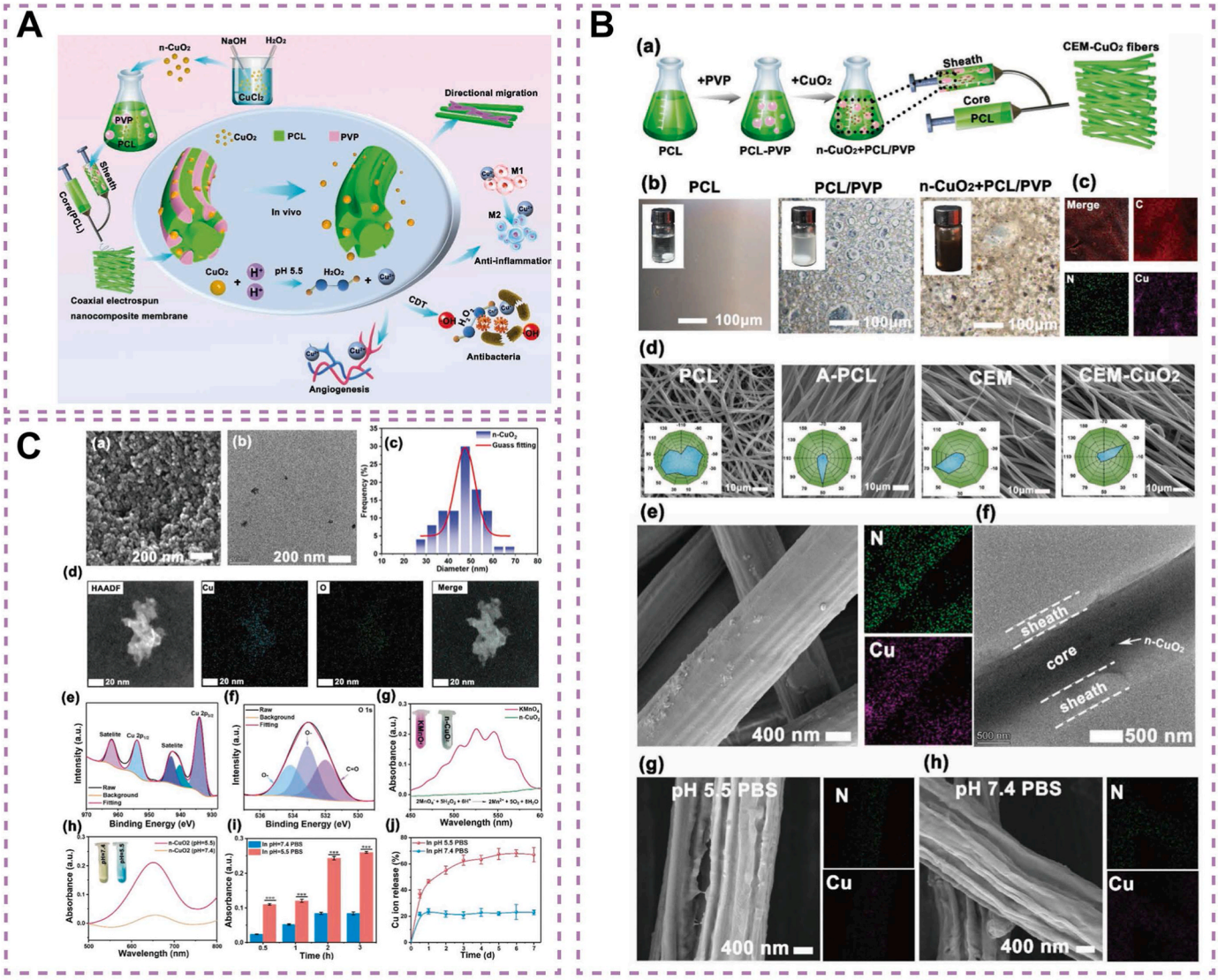

Fig. 6. Coaxial electrospun nanofiber (CEF) dressings with nano-grooved patterns and copper peroxide nanoparticles. (A) Diagram of coaxial electrospun fibers with nano-grooved patterns and copper peroxide nanoparticles. (B) Dissolution of polyvinylpyrrolidone (PVP) exposes nano-grooved patterns. (C) Copper peroxide nanoparticles. Reproduced with permission [86]. Copyright 2023, Wiley.

collector (Fig. 4) [45].

Numerous alternative techniques are available for fabricating micropatterned electrospun dressings, such as the ultralow-voltage continuous electrospinning patterning technique [74]. However, these methods have not been used to produce CEF wound dressings. Considering the beneficial effects of micropatterned dressings on wound healing, it is imperative to develop additional patterned CEF dressings using diverse techniques to accommodate various wound environments.

5.3. Surface modification of CEF dressings

Surface modification is an electrospinning post-process that transports biofunctional characteristics into nanofibers while preserving the properties of core materials [61,64]. Polycationic polylysine (PLL) molecules are coated onto fiber surfaces to create cationic sites that attract anionic sites on cell surfaces, facilitating cell adhesion and proliferation [29]. Epidermal growth factor (EGF) is a key GF in wound healing, stimulating keratinocyte proliferation and migration. Wounds treated with EGF-surface-modified nanofibers exhibited accelerated closure rates compared to untreated wounds [62]. Alongside exogenous GFs, endogenous GFs play critical roles in wound healing. Heparin-functionalized PCL core and gel shell CEFs demonstrated superior adsorption capacity for endogenous GFs compared to PCL/gel CEFs lacking heparin. Consequently, wounds treated with heparin-modified PCL/gel fiber dressings exhibited enhanced healing [176].

5.4. Drug-delivery system

CEF wound dressings are commonly used as drug-delivery vehicles to promote wound healing via multiple mechanisms. They provide three drug-delivery mechanisms: encapsulating drugs in the core, enveloping them with a shell for sustained drug release, incorporating multiple drugs in the required layers (core or sheath) to achieve controlled drug release, and enabling triggered or controlled release in response to external stimuli [177]; introducing porogens (typically water-soluble polymers like PEG) into the shell to create pores can accelerate drug release from the core [178,179]; when loaded with different drugs, the dressing can act as an antibacterial agent, promote collagen generation, enhance angiogenesis and so on.

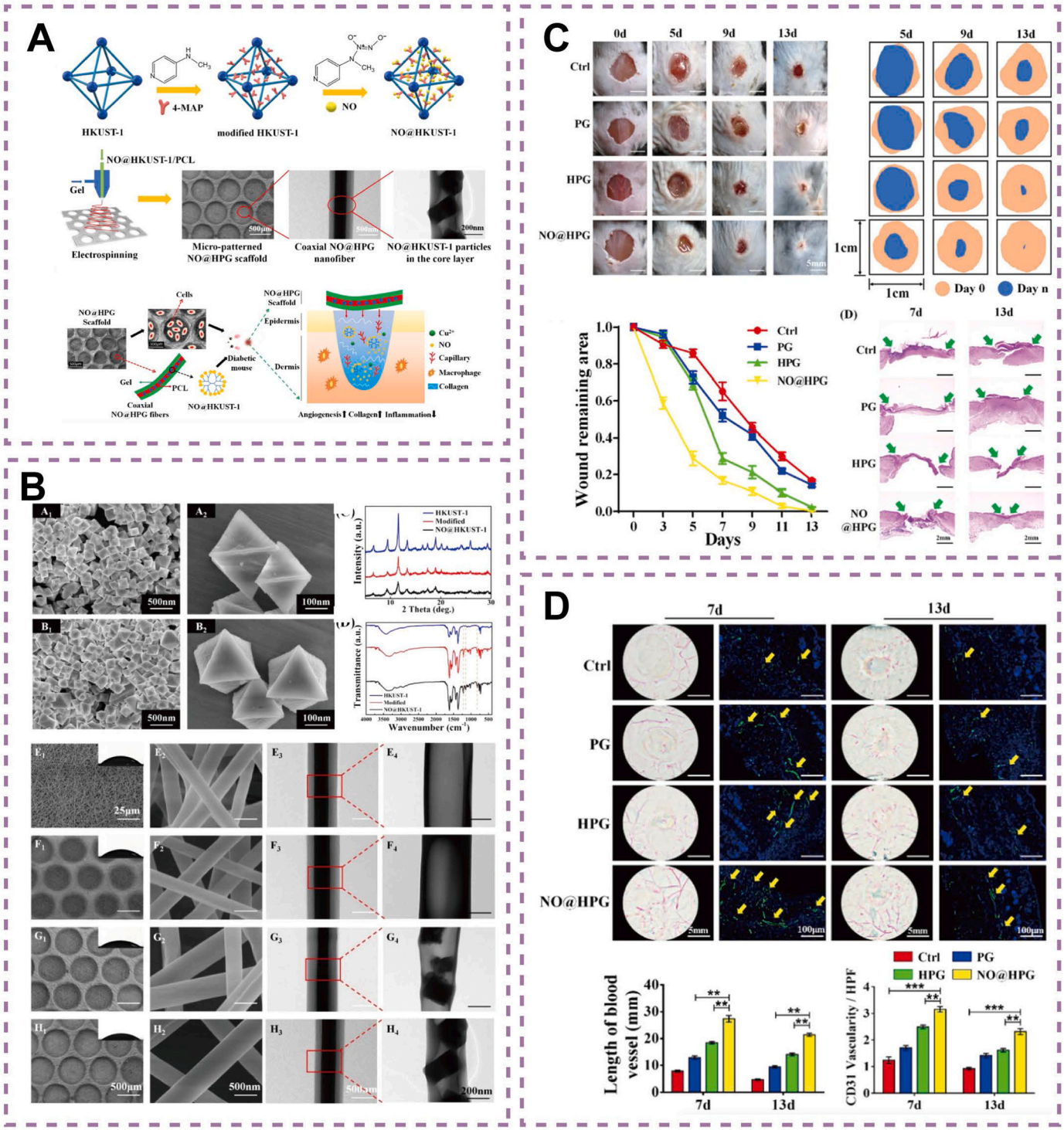

Fig. 7. Patterned electrospun fiber dressings made using patterned collectors. (A) Fabrication process of patterned electrospinning membranes with NO-loaded HKUST-1 (NO@HKUST-1) particles. (B) Scanning and transmission electron microscopy images of nanofibers and HKUST-1. (C) The dressing enhances wound healing. (D) The dressing promotes angiogenesis. Reprinted with permission from Ref. [155] Copyright 2020, American Chemical Society.

5.4.1. Bioactive factors

Bioactive factors, including GFs, chemokines, and antimicrobial peptides (AMPs), are commonly used in wound healing (Table 2). Angiogenesis can be enhanced by VEGF [167,176], basic fibroblast growth factor (bFGF) [180], peptides like angiopoietin-1-derived peptide (QHREDGS), 12-mer prominin-1-derived peptide (PR1P), glucagon-like peptide-1 (GLP-1), and its analog liraglutide (LG) [47]. Factors like bFGF [62], fibroblast growth factor-2 (FGF2), EGFs [62], and PDGF enhance cell migration, proliferation, and differentiation [43,152]. Chemokines like SDF-1α promote local vascularization and tissue regeneration by recruiting endothelial progenitor cells and smooth muscle progenitor cells [47]. However, the short half-lives of these bioactive factors, with VEGFs having a half-life of 90 min and LG lasting 13 h, coupled with their susceptibility to degradation by MMPs, necessitate repeated administration [47]. Utilizing CEFs to load drugs is preferred to reduce the number of drug administrations and maintain

Table 2
Coaxial electrospun fiber dressings with bioactive factors from 2013 to 2024.

Material		Bioactive Factors or Drugs		Animal model	Functions of Bioactive Factors	Ref.
Core	Shell	Core	Shell			
N/A	PLGA/ Gel	PR1P, SDF-1α, LG,	OEO	Healthy rat model and a diabetic rat model	PR1P increases VEGF binding to ECs and increases angiogenesis by potentiating endogenous VEGF; SDF-1α promotes in situ vascularization and neo-tissue regeneration by recruiting cells; LG promotes the migration of cells.	[47]
PVA	PCL, PEG	bFGF	EGF	Female diabetic C57BL/ 7 mice models	EGF increases the migration and proliferation of keratinocytes; bFGF maximizes the efficacy of wound healing.	[62]
PEO, PCL, PDLLA	PCL, PEO	bFGF, BSA	N/A	N/A	bFGF and BSA are encapsulated into the core to check the potentiality of the nanofiber and create a natural ECM-mimicking microenvironment.	[180]
PVA	PCL	PRP	ε-PL	Rat burn models	PRP promotes angiogenesis and cell proliferation; ε-PL antimicrobial.	[183]
PVA	Gel	N/A	A-PRF	Rat models	A-PRF slowly releases growth factors and cytokines to improve angiogenesis, repair and regeneration.	[115]
N/A	PCL, PEO	Insulin	N/A	N/A	Insulin acts as a growth factor and enhances the cellular sensitivity to EGF, VEGF, and FGF.	[18]
PHB	SA	Arginine	LB	Rat models	Arginine is an important precursor for collagen synthesis and cell building and stimulates the release of growth hormone and insulin-like growth factors; LB antimicrobial.	[114]
N/A	PLGA	Insulin	N/A	Diabetic rat models	Insulin signals the migration, proliferation, and secretion of growth factors through fibroblasts, ECs, and keratinocytes.	[181]
PA6	PGA	Alizarin	ε-PL, Cur	N/A	ε-PL antimicrobial.	[44]
PVA	PCL	TP	ε-PL	N/A	ε-PL antimicrobial.	[186]
PLLA	zein	N/A	RCSP	N/A	RCSP improves fibroblast proliferation.	[175]
PLGA	PLGA	PDGF	Van	Infect diabetic SD rat models	PDGF is an approved growth factor for the treatment of diabetic wounds.	[43]
PGS	PCL	PRP	N/A	N/A	PRP promotes angiogenesis and cell proliferation.	[182]
PVA	PLCL	VEGF	Amox	N/A	VEGF promotes endothelial cell proliferation and survival.	[118]
PCL	SF	N/A	TA	Rat models	TA has anti-oxidation, anti-aging, and elimination of free radicals.	[104]
PVA	PVA	Pleurocidin	N/A	N/A	Pleurocidin antimicrobial.	[187]
PVP	PVDF	IBU	LA	SD Rat models	LA is a temperature-controlled release phase change Materials.	[179]
N/A	PVP	CH, KH (the second layer)	N/A	N/A	KH maintains a moist wound environment; CH heals the wound.	[137]

Abbreviations: PR1P, 12-mer prominin-1-derived peptide; SDF-1α, stromal cell-derived factor)-1α; LG, liraglutide; HFIP, Hexafluoroisopropanol; PLGA, poly(L-lactide-co-glycolide); Gel, gelatin; OEO, organo essential oil; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; PCL, poly(e-caprolactone); PEG, Poly (ethylene glycol); PVA, poly(vinyl alcohol); PEO, polyethylene oxide; PDLLA, poly-DL-lactide; BSA, bovine serum albumin; PRP, platelet-rich plasma; A-PRF, advanced platelet-rich fibrin; PHB, poly-3-hydroxybutyric acid; LB, layered double hydroxidesbacitracin; Cur, curcumin; PGA, polyglycolic acid; PA6, Polyamide 6; RCSP, Rana chensinensis skin peptides; PLLA, poly(l-lactide); PDGF, platelet-derived growth factor; Van, vancomycin; Lev, levofloxacin; Amox, amoxicillin; VEGF, vascular endothelial growth factor; SF, silk fibroin; TA, tocopherol acetate; SA, Sodium alginate; PVDF, poly(vinylidene fluoride); LA, lauric acid; IBU, ibuprofen; CH, collagen hydrolysate; ECs, endothelial cells; KH, keratin.

the activity of various bioactive factors [158].

Insulin is widely recognized for its stimulatory effects on human tissue proliferation. Its primary role is to act as a growth factor that enhances cellular sensitivity to EGF, VEGFs, and FGFs [181]. Windbergs et al. showed that CEF dressings with an insulin solution core and PCL and PEO shells significantly boosted the migration rate of fibroblasts and keratinocytes and expedited the wound-healing process in an excised human skin model, including both the epidermal and dermal layers [18].

Platelet concentrate derived from blood is an autologous source of GFs. Self-derived platelet-rich plasma (PRP) is rich in GFs, and its composition varies between individuals, making PRP suitable for personalized treatment, thereby reducing the risk of allergic reactions [182]. However, PRP is susceptible to enzymatic degradation in the wound microenvironment, which can be prevented by incorporating PRP into electrospun fibers [183]. Platelet-rich fibrin (PRF) is a new-generation platelet concentrate obtained by blood centrifugation without additives [115]. PRF contains platelets trapped within a fibrin matrix that enables the slow release of GFs and cytokines [40,115]. Advanced PRF (A-PRF) is a more concentrated form of PRF that contains higher levels of GFs than PRF. PVA/gel CEF dressings with A-PRF enable sustained release of VEGF and PDGF, resulting in improved cell viability, angiogenic potential, and wound closure [115].

Liposomes are artificial vesicles that mimic natural membranes, typically comprising a phospholipid bilayer enveloping an aqueous medium [184]. They have been extensively studied as model membranes and carriers for drugs, proteins, and DNA. CES is a liposome-encapsulated system that shields liposomes from degradation at wound sites and prevents their rupture by lowering the relative shear force within the core fluid [185]. Huang et al. used hyaluronate (HA-Na) as the CEF core for loading liposomes, with PVP as the shell. Scanning and transmission electron microscopy reveal that liposomes are highly stable and maintain a consistent size when re-dissolved in water after one month, further extending the validity of dressing [185].

AMPs are natural macromolecules synthesized by various biological organisms and have emerged as antibacterial agents because of their efficacy against biofilms and broad-spectrum antibacterial activity [44,186,187]. The primary antibacterial mechanism of most AMPs involves electrostatic interactions between positively charged AMPs and the negatively charged microbial cell membrane, ultimately leading to membrane disruption [186]. This mechanism minimizes the risk of developing bacterial resistance. Epsilon-poly(L-lysine) (ε-PL), originating from *Streptomyces albus*, is a well-known unconventional AMP that exhibits broad-spectrum antibacterial properties, biocompatibility, biodegradability, high water solubility, non-toxicity, and cost-effectiveness [186,188]. Lan loaded ε-PL in the shell of CEFs and demonstrated its good antibacterial activity [186]. Bacitracin is a cyclic polypeptide with potent bacteriostatic and bactericidal properties. Its advantage lies in its compatibility with both hydrophobic and hydrophilic carriers [114]. *Rana chensinensis* skin peptides (RCSP) mainly

consist of peptides and proteins, including antibacterial and antioxidant peptides. These peptides, which have low toxicity in normal cells, have considerable potential for applications [175]. Nevertheless, challenges persist with AMPs, including low stability and rapid clearance from the body [44]. Loading AMPs into CEFs can overcome some of these challenges regarding *in vivo* stability.

5.4.2. Antibiotic, phage, and other antibacterial agents

Broad-spectrum antibiotics effective against both Gram-positive and Gram-negative bacteria are preferred for wound management [168]. Various antibiotics, including Cip [168,189], mupirocin (Mup) [190], and tetracycline hydrochloride (TH) [93,191], have been used for wound treatment (Table 3).

Table 3
Coaxial electrospun fiber dressings with antibiotics from 2013 to 2024.

Material		Antibiotic and other drugs or bioactive factors		Animal model	Ref.
Core	Shell	Core	Shell		
F127	Pec, Kr	Mup	N/A	Wistar rat models	[190]
PCL	Gel	Cur	TH	N/A	[93]
Zein, PEO	Gel, PEI	TH	PDA	N/A	[95]
Zein,	PEO, PCL	TH	N/A	N/A	[125]
PGS	PCL	SIM, Cur	Cip	Female rat models	[189]
PCL	Gel	CTG	Cip	Rat burn models	[55]
PCL	PCL	Rif	N/A	N/A	[101]
PCL	CS	Cip	N/A	Kunming mice models	[168]
PU	CS, Gel,	Cla	ZnO	N/A	[162]
N/A	F127-PCL	Van, Ag,Ga	N/A	N/A	[194]
PVP, Gel	PEO, CS	Imi, Cil	Van	N/A	[15]
PLGA	PLGA	PDGF	Van, Gen	Infect diabetic SD rat models	[43]
PLA	PVP	Lev	Nap	N/A	[177]
CL	PCL	MB, PS	N/A	N/A	[84]
PVA	PCL	Amo	N/A	N/A	[20]
Gel	PLGA	Cip	GBP	N/A	[147]
PCL	CA, Gel	Ind	Cip	N/A	[42]
PGS	PHB	SIM	Cip	N/A	[3]
CS	PCL	TH	N/A	N/A	[26]
Gel	PCL, Gel	Gymnema sylvestre	Mino	Pig burn models	[193]
PEO, zein	PEO	TH	N/A	N/A	[121]
PCL, Gel	PEO	N/A	DOX	N/A	[85]
N/A	PLGA	TH	N/A	N/A	[148]
PEO, CS	PLGA	Lev	QS	Rat burn models	[122]
PVA	PLCL	VEGF	Amo	N/A	[118]
PVP	PVP	Pir	Moxi, Fus	Diabetic Wistar rat models	[133]
PCL	Eudragit L100–55	TH, DOX, ROX, LNZ	N/A	N/A	[191]
PEG, PHB	PEG, PHB	Gen	N/A	N/A	[97]
PCL	Gel	CIP	TH	N/A	[157]

Abbreviations: Mup, mupirocin; F127, PluronicF127; Pec, pectin; Kr, Keratin; TH, tetracycline hydrochloride; PCL, poly(e-caprolactone); Gel, gelatin; Cur, curcumin; PEO, polyethylene oxide; PDA, polydopamine; PEI, polyethylene imine; PGS, poly(glycerol sebacate); Cip, ciprofloxacin; SIM, simvastatin; CTG, Centella Total Glucosides; Rif, rifampicin; CS, chitosan; Cla, clarithromycin; Van, vancomycin; F127-PCL, Pluronic F-127-poly(ε-caprolactone); Imi, imipenem; Cil, cilastatin; PLGA, poly (lactide-co-glycolide); PDGF, platelet-derived growth factor; Lev, levofloxacin; Nap, naproxen-sodium; CL, chitin-lignin; MB, methylene blue; PS, penicillin/streptomycin; Amo, amoxicillin; GBP, Gabapentin; CA, cellulose acetate; Ind, indomethacin; PHB, poly hydroxyl butyrate; PGS, poly (glycerol sebacate); SIM, simvastatin; Mino, minocycline; DOX, doxycycline; Gen, gentamicin; QS, quercetin; Moxi, Moxifloxacin; Fus, fusidic acid; Pir, Pirfenidone; ROX, roxithromycin; LNZ, linezolid; PEG, polyethylene glycol.

Cip, a third-generation fluoroquinolone antibiotic with minimal side effects and strong permeability, exhibits broad-spectrum antibacterial properties [55,147,192]. It prevents bacterial DNA synthesis by inhibiting DNA gyrase after penetrating the bacterial cell membrane [42]. Cip effectively treats a diverse range of wound infections and serves as a prophylactic agent. Cip is always loaded into the shells of CEFs and shows burst release in the early stages after dressing implantation to establish effective antibacterial concentrations and prevent infection [3,42,55].

TH is another broad-spectrum antibiotic that ranks second globally in terms of production and usage [148]. Highly water-soluble, TH is found in an amorphous state within fibers, enabling significant release to combat bacterial infections during the initial stages of skin repair [93,95,121]. TH enhances fibroblast adhesion, showing promising potential for wound healing applications. Minocycline hydrochloride (Mino), a second-generation tetracycline analog, is effective against both Gram-positive and Gram-negative bacteria, possesses anti-inflammatory properties, and may aid in scar prevention. Mino- and *Gymnema sylvestre* (Asclepiadaceae)-loaded PCL/Gel CEF dressings can promote scarless healing of pig burn wounds [193].

Doxycycline (DOX), a member of the tetracycline class of antibiotics, exhibits broad-spectrum antibacterial properties and can inhibit MMPs by chelating divalent metal ions [85]. Arzub et al. fabricated a three-layered DOX-collagen-loaded nanofiber wound dressing to enhance wound healing. The first layer comprised CEFs with a PEO and collagen core encapsulating DOX within the PEO shell [85]. The second and third layers comprised CS and alginate fibers, respectively, each serving distinct functions [85]. The first layer served as an antibacterial agent, preventing external exposure of the exudate, while the subsequent layers directly interacted with the wound. CS promotes cell migration to the wound site, and alginate fosters a moist environment, absorbs exudates, aids in hemostasis, and inhibits proteases [85]. However, animal studies have not yet been conducted to validate the efficacy of these dressings.

Vancomycin hydrochloride (Van) is a glycopeptide antibiotic that is approved for managing *S. aureus* infection [43,194]. It inhibits bacterial cell wall mucin precursor synthesis by binding to the l-Lys-d-Ala-d-Ala sequence [194]. Van is also used to treat drug-resistant gram-positive bacteria and methicillin-resistant *S. aureus* (MRSA) [43]. However, Van does not exhibit the same activity against MRSA when wounds are coinfected with gram-negative bacteria. To address this, Van is combined with other antibacterial drugs that are effective against gram-negative bacteria, triggering complementary killing mechanisms and demonstrating synergistic antibacterial effects [15,194]. The combination of the β-lactam antibiotic imipenem and Van exhibits optimal synergy and antibacterial activity [15]. However, large-dose Van injections can lead to nephrotoxicity, ototoxicity, and allergic reactions, while imipenem injections may cause gastrointestinal issues. Davani showed that the adverse effects associated with high doses of Van and Imipenem can be overcome by loading these drugs into the shell and core of CEFs for a two-stage sustained release [15].

In addition to antibiotics, bacteriophages are promising antibacterial agents, with bacteriophage-based therapies showing good tolerability in clinical trials. Windbergs et al. encapsulated *Staphylococcus* phage EBHT or *Pseudomonas* phage JG004 within a PVP shell in CEFs. The CEF dressing maintained good antibacterial properties even after storage at −20 °C for four weeks [135]. Furthermore, amphoteric surfactants, like dodecyl trimethylammonium chloride, exhibit potent broad-spectrum antibacterial activities suitable for controlling wound infections and have been incorporated into CEF dressings [96]. Other antibacterial agents, such as metal ions and essential oils (EOs), are utilized in CEF dressings, as described below. They all use the special drug-release characteristics of CEFs to achieve sustained drug release [195].

5.4.3. Metal nanoparticles

Metal NPs are also commonly used antibacterial agents (Table 4). Zinc (Zn) [16,162,166], silver (Ag) [9,10,164], and copper (Cu) NPs [86] are representative metal NPs.

Ag NPs have been in the spotlight for the past 19 years because of their broad-spectrum antibacterial properties at low doses [10,111,178]. Ag NPs increase bacterial membrane permeability, enter cells [9,164], disrupt DNA replication, denature proteins [164], and inhibit cellular respiratory enzymes by altering the hydrogen atom position in the thiol (-SH) group (-S-Ag-) [9,194,196]. Furthermore, Ag NPs have high non-toxicity, thermal stability, and low volatility, rendering them suitable antibacterial agents for CEF dressings [52]. Silver sulfadiazine (SSD) loaded CEFs slowly release the silver ions and sulfadiazine in the wound areas, reducing burn wound sepsis in patients [197].

Various Zn compounds, such as zinc phosphate (ZnP) [198] and ZnO [162], exhibit antibacterial properties. Specifically, ZnO NPs eradicate bacteria by destabilizing bacterial membranes through mechanical damage and oxidative stress [199]. They are non-toxic, modulate cellular interactions, improve cell metabolism, and upset GFs [16]. Hami et al. highlighted the high hydrophilicity of ZnO NPs and observed an increase in the swelling capacity of dressings by incorporating ZnO NPs [162].

Cu NPs are multifunctional particles. Cu^{2+} ions can simulate hypoxic conditions at the wound site, promoting the expression of HIF-1α and VEGF for angiogenesis and collagen deposition [86,155]. Furthermore, Cu peroxide (n-CuO_2) NPs are ideal chemodynamic therapy (CDT) agents due to their robust Fenton catalytic activity [86]. When CuO_2 NPs are present in the shell of PCL/PVP core/shell fibers under mildly acidic conditions typical of diabetic wounds, they decompose into Cu^{2+} and H_2O_2, further generating hydroxyl radicals (·OH)-, a type of ROS, which significantly affect sterilization (Fig. 6C) [86]. Cu NPs can also be used in gas delivery for wound healing (Fig. 7) [155]. Notably, nitric oxide (NO) is key in cellular signaling during wound healing. Cu ions can reduce nitrite to NO through redox reactions in the presence of glucose *in vivo*. Metal−organic frameworks (MOFs) with central Cu elements exhibit remarkable superiority in NO storage and delivery [155]. A type of NO-loaded HKUST-1 (NO@HKUST-1) particle in CEF dressing was reported by Xu et al., in 2020. In a diabetic C57BL/6J full-thickness wound model, the NO@HKUST-1 group exhibited a remarkable wound-healing rate of 99.57 % after 13 days, surpassing other groups [155].

Other metal NPs have also been used as CEF dressings. For example, cerium (III) nitrate delays the need for post-burn debridement. To address challenges related to burn treatment in regions lacking burn centers, Martinez et al. developed a coaxially spun PEO/cerium (III) nitrate dressing [17]. Zhao et al. incorporated Ti3C2Tx MXene, known for its electroactivity, into the shells of PCL CEFs to enhance wound healing through endogenous electric fields [200]. Fe_3O_4 NPs are embedded in the core of magnetothermal responsive CEFs for a controlled release of drugs [156]. Given the diverse characteristics of different metals, the development of multifunctional CEF dressings incorporating various metal NPs is anticipated.

5.4.4. Herbal and plant extracts

Herbal remedies are traditional wound treatments, with phytochemicals serving as valuable drug agents in dressings (Table 5). Herbs primarily exert antibacterial, anti-inflammatory, antioxidant, hemostatic, angiogenesis-stimulating, and re-epithelialization-promoting effects on wound healing [49,90,105,131,163]. They have few adverse

Table 4
Coaxial electrospun fiber dressings loaded with metal nanoparticles from 2013 to 2024.

Material		Metal, its existence form and its loading layer	Functions of the metal	Animal Model	Ref.
Core	Shell				
PCL	Gel	Cu, MOFs, core	As long shelf-life NO storage applications.	Diabetic C57BL/6J mice model	[155]
Gel	PLGA	Co, PCC, core	Promoting angiogenesis and being antibacterial.	Female Wistat rat model	[63]
CS, PEG	SF	Zn, ZnO-NPs, core	Regulating cellular interactions, metabolic, and the synthesis of key macromolecules.	Diabetic mice model	[16]
PLA	PU	Ag, PLA-Ag NPs, core	Being antibacterial.	N/A	[9]
PCL	PCL, Gel	Ti, $Ti_3C_3T_x$ MXene, shell	Providing excellent electroactivity, and antibacterial activity.	Sprague-Dawley rat model	[200]
PCL	PVP, PCL	Cu, CuO_2, shell	Promoting angiogenesis and being antibacterial.	Diabetic SD rat model	[86]
PCL.CS	PVP	Ag, Ag NPs, shell	Being antibacterial.	SD rat model	[164]
PVA	PSMA	Ag, Ag NPs, shell	Being antibacterial.	N/A	[10]
PU	CS, Gel	Zn, ZnO NPs, shell	Being antibacterial.	N/A	[162]
N/A	PEO	Ce(III), Ce(III) nitrate, core	Firming burn eschars to leather-like, slowing down the infiltration of toxic metabolites and delaying debridement.	N/A	[17]
N/A	F127-PCL	Ag, AgNO3, core; Ga, $Ga(NO3)_3$, core	Being antibacterial.	N/A	[194]
N/A	PCL, PEG	Zn, ZnO NPs, shell; Ag, Ag NPs, core	ZnO creates open pores with fiber stability; Ag NPs were used as a model drug.	N/A	[178]
PVA	PLA	Ag, Ag NPs, core	Being antibacterial.	N/A	[111]
PCL	PCL	Zn, ZnO NPs, shell	Being antibacterial.	N/A	[199]
PVP	SA, PVP	Ca, Ca^{2+}, core	Stabilizing fibers from melting in contact with liquids to form gels.	C57BL/6J mice model	[92]
PCL	CS, Col	Ag, Ag-NPs, shell	Being antibacterial.	N/A	[56]
SAs	PVA	Ag, Ag-NPs, shell	Being antibacterial.	N/A	[112]
PVA	GelMA	Ce, CeO2, shell	Being antibacterial and anti-inflammatory.	N/A	[117]
PCL	PVA	Ag, Ag-NPs, shell	Being antibacterial and anti-inflammatory.	SD rat model	[105]
PEO, SA	SF	Zn, ZnO NPs, core	Being antibacterial and anti-inflammatory.	N/A	[173]
PEO	PCL, PEO	Ag, SSD, core	Reduce burn wound sepsis and being antibacterial.	New Zealand white rabbits burn model	[197]
PCL, Gel	N/A	Fe, Fe3O4 NPs, core	Magnetothermal responsive.	Kunming mice model	[156]
PVA	PCL	Ag, Ag-CS, core	Being antibacterial.	N/A	[196]

Abbreviations: MOFs, metal−organic frameworks; PCL, poly(e-caprolactone); Gel, gelatin; Co, cobalt; PCC, PEGylated curcumin cobalt; PLGA, poly (lactide-co-glycolide); CS, chitosan; SF, silk fibroin; NPs, nanoparticles; PEG, polyethylene glycol; PLA, polylactic acid; PU, polyurethane; PVP, polyvinylpyrrolidone; PVA, polyvinyl alcohol; PSMA, poly(styrene-co-maleic anhydride); Ce(III), cerium(III); F127-PCL, Pluronic F-127-poly(ε-caprolactone) (F127-PCL); SA, Sodium alginate; Col, collagen; SAs, sugar alcohols; CeO_2, cerium oxide; GelMA, gelatin methacrylate; SF, silk fibroin; PEO, polyethylene oxide; SSD, silver sulfadiazine.

Table 5
Coaxial electrospun fiber dressings loaded with herbal and plant extracts from 2013 to 2024.

Herbal and Plant Extracts	Basic Information	Functions	material		Ref.
			Core	Shell	
Ast	Belonging to the Fabaceae family, Astragalus genus; a Native to Iran; the source of 'Anzaroot'; riching in saponins, alkaloids, flavonoids, anthraquinones, amino acids, polysaccharides and beta-sitosterol.	Anti-inflammatory; antioxidant; analgesic qualities; reducing tissue swelling.	CS, PEG	SF	[16]
BSP	A type of natural plant polysaccharide; extracted from Bletilla striata (Thunb.); comprising α-mannose, β-glucose, and β-mannose.	Promoting wound healing; antiinflammation; anti-fibrosis; biocompatibility; biodegradation; low cost; wide range of applications.	PVA	PLA	[113]
RA	A natural polyphenolic carboxylic acid; wide range of sources.	Antioxidant; anti-inflammatory.	PVA	PLA	[113]
Pec	A type of natural plant polysaccharide.	Biocompatible; biodegradable; antiinflammatory; antibacterial; complement system regulation properties.	F127	Kr	[190]
Cur	A type of natural polyphenol derived from turmeric; riching in pyrogallol and catechol groups.	Antibacterial; anti-inflammatory; antioxidant properties; ability of crosslinking with polysaccharides; favoring cell proliferation, migration, collagen deposition and wound re-epithelialization; low toxicity.	PCL	ChMA	[163]
			PGS	PCL	[189]
			PCL	Gel	[93]
			PA6	PGA	[44]
			Gel	PLGA	[63]
			N/A	CS, PVA	[201]
			PCL	CS, PEO	[124]
Tan	A type of natural polyphenol compounds; riching in pyrogallol and catechol groups.	Antibacterial; anti-inflammatory; antioxidant properties; ability of crosslinking with polysaccharide.	PCL	ChMA	[163]
Lic	A traditional therapeutic sweet and calming herb; having more than 20 triterpenoids and 300 flavonoids; a source of amino acids, proteins, simple sugars, polysaccharides, mineral salts, pectins, resins, starches, sterols, and gums.	Antiviral; antibacterial; sedation.	PVA	Col	[1]
PN	A traditional Chinese herb used in wound healing for hundreds of years; Saponins are the effective components.	Inhibiting the increase in capillary permeability, inflammatory exudation, tissue edema, leukocyte migration and granulation tissue proliferation; promoting angiogenesis; inhibiting the scar formation.	PCL, CS	PVP	[164]
Allantoin	A heterocyclic derivative of purine and the main metabolic intermediate from the comfrey plant and the urine of most mammals.	Anti-inflammatory; antioxidant; antisecretory; cytoprotective mechanisms; antiulcerogenic activity.	PVA	PSMA	[10]
EGCG	The major catechin from tea.	Antioxidant; anti-inflammatory, antibacterial; immunomodulatory properties; increase normal epidermal keratinocyte differentiation and proliferation.	N/A	PLCL, Gel	[8]
CTG	A total glucoside made from the whole herb of Centella asiatica, family Umbelliferae; light yellow to light brownish yellow powder; odorless, bitter, slightly moisture-attracting, soluble in water and ethanol, insoluble in trichloromethane and ether; triterpene saponins and their derivatives are the active ingredients.	Antioxidant; anti-inflammatory; inhibiting scar formation; promoting wound healing; promoting neovascularization; stimulating vascular endothelial growth factor production.	PCL	Gel	[55]
Sage	Belonging to the Lamiaceae family; riching in phenolic acids and flavonoids.	Antibacterial; antioxidant.	PLA	PVP, PVA	[131]
AV	Belonging to the Liliaceae family; riching in water (>98 %) in the mucilaginous gel and ~2 % minerals, vitamins, enzymes, anthraquinones, sterols, salicylic acid, amino acids and polysaccharides, such as hemicellulose, cellulose, mannose derivatives, pectin, glucomannan and acemannan.	Antioxidant; anti-inflammatory; antiviral; antiallergic; UV protection; cicatrizing; proving cell growth and proliferation.	Gel, PVA	PVP,	[130]
			N/A	PCL, Kr, CS	[202]
			PAAm	L-Arg, AloKr	[203]
Ab	An aldopentose sugar and structural isomer to xylose; in the l-form; the third most abundant sugar after glucose and xylose.	Antioxidant.	Gel, PVA	PVP,	[130]
G. sylvestre	Belonging to the Asclepiadaceae family; a common botanical.	Anticancer; anti-constipation; anti-obesity; anti-inflammatory; wound healing properties.	Gel	PCL, Gel	[193]
TP	Polyphenols in tea; are susceptible to light, heat, and oxidants.	Antioxidant; antibacterial.	PVA	PCL	[186]
Bromelain	A proteolytic enzyme derived from pineapple stem; a wound debriding enzyme.	Anti-inflammatory; anti-microbial; anticoagulant.	PCL	PVA, Gel	[109]
Sal B	the inhibitor of matrix metalloproteinase.	Antioxidant; stimulating angiogenesis.	PCL	PVA, Gel	[109]
FA	A hydroxycinnamic acid derivative found in plant cell walls, fruits, vegetables, cereals and in seeds of coffee.	Anti-cancer; anti-inflammatory; anti-diabetic; anti-microbial; stimulating angiogenesis.	CS	PCL	[167]
RSV	A non-flavonoid polyphenolic compound extracted from grapes, berries, and peanuts.	Antiinflammatory; chemopreventive; cardioprotective; hepatoprotective; antioxidant.	CS	PCL	[167]
Asiaticoside	A major triterpenoid component derived from Centella asiatica (L.).	Antioxidant, immunomodulatory; anti-inflammatory.	CS	CS, PVA	[67]
Emodin	1,3,8-trihydroxy-6-methyl-anthraquinone.	Antimicrobial; anticancer; antioxidant; anti-inflammatory; inhibition effect on *methicillin-sensitive S. aureus* and MRSA.	PVP	CA	[129]
Law	2-hydroxy-1,4-naphthoquinone.	Antioxidant.	Gel	PCL	[50]
TE	An aromatic plant; riching in Thymol and carvacrol.	Antioxidant; anti-inflammatory; antibacterial.	PVA	PLA	[54]
EGCG	The major polyphenolic compound found in green tea.	Antioxidative; cancer preventive; bactericidal; anti-inflammatory; stimulating angiogenesis.	HA	PLGA	[49]
Lemon balm Eos	Belonging to the Lamiaceae family.	Antimicrobial.	CS	CS, Col	[160]
Dill EOs	An annual aromatic herb; belonging to the family Umbelliferae.	Anti-inflammatory; analgesic.	CS	CS, Col	[160]

(*continued on next page*)

Table 5 (*continued*)

Herbal and Plant Extracts	Basic Information	Functions	material		Ref.
			Core	Shell	
S. mutica EOs	Riching in thymol and carvacrol.	Antimicrobial, antioxidant.	CS, PVA	PVP, MD	[116]
O. decumbens EOs	Riching in thymol and carvacrol.	Antimicrobial, antioxidant.	CS, PVA	PVP, MD	[116]
Ajwain EOs	Belonging to the family of Apiaceae; riching in thymol; volatility and low solubility in water.	Antibacterial; promoting hemostasis; anti-inflammatory; fastening wound closure and re-epithelialization.	Gel, PVA	PVP,	[130]
Nigella seed oil	A traditional herbal medicine; be known as "Black Cumin" and "Black Onion Seeds"; riching in proteins, carbohydrates, fibers, ashes, moisturizers, linoleic, oleic, palmitic, dihomolinoleic and eicosadienoic acids.	Antioxidant; anti-bacterial; treatment of dermatitis, eczema, skin rashes, tissue impairment.	N/A	PVA	[108]
OM oil	A natural oil plant.	Antibacterial.	CS	CS	[204]
EMB	A naturally occurring benzoquinone derivative obtained from the *Embelia ribes* plant.	Anti-inflammatory, antibacterial, and antioxidant.	PHB	PEO, Alginate	[123]
QS	A polyhydroxy flavonoid that is mainly found in flowers, leaves, and fruits of different plants.	Antioxidant.	PEO, CS	PLGA	[122]
Biobran	An immunomodulator phytochemical derived from the enzymatic modification of rice bran using carbohydrate hydrolyzing enzymes extracted from shiitake mushrooms.	Antioxidant and immunomodulatory effects.	PVA	PCL	[103]
ABE	A ubiquitous plant in the low-altitude mountains, whose roots extract triterpenoids, aromatic compounds, sterols, flavonoids, and stilbenes.	Antioxidant and anti-inflammatory.	PCL	PVA	[105]
Chalcone	An aromatic ketone that forms the central ring for many critical biological compounds and a natural genetic precursor of abundant flavonoids and isoflavones in plants.	Anticancer, antioxidant, anti-inflammatory, antihypertensive, antiviral	PBAT	PLA, PVA	[127]

Abbreviations: Ast, *Astragalus arbusculinus*; SF, silk fibroin; CS, chitosan; PEG, polyethylene glycol; BSP, Bletilla striata polysaccharide; RA, Rosmarinic acid; PLA, polylactic acid; PVA, polyvinyl alcohol; Pec, pectin; F127, Pluronic-F127; PCL, poly(ε-caprolactone); ChMA, methacrylate chitosan; Tan, tannic acid; Cur, curcumin; Lic, licorice; Col, collagen; PN, Panax nototoginseng; PA6, Polyamide 6; PGA, polyglycolic acid; Gel, gelatin; PSMA, poly(styrene-co-maleic anhydride); EGCG, epigallocatechin-3-O-gallate; PLCL, Poly(L-Lactic-cocaprolactone); PGS, polyglycerol sebacate; CTG, Centella Total Glucosides; PVP, polyvinylpyrrolidone; Ajwain EOs, Trachyspermum Ammi essential oil; AV, aloe vera; Ab, arabinose; Lemon balm EOs, Melissa officinalis L. essential oils; dill EOs, Anethum graveolens L. essential oils; G. sylvestre, Gymnema sylvestre; TP, tea polyphenols; S. mutica EOs, Satureja mutica; O. decumbens Eos, Oliveria decumbens essential oils; MD, MRSA, *maltodextrin; Staphylococcus aureus*; PEO, polyethylene oxide; Nigella, Nigella sativa Seed Oil; Kr, Keratin; PLGA, poly(L-lactide-co-glycolide); CA, cellulose acetate; TE, Thyme extract; OM oil, *Origanum Minutiflorum* oil; Sal B, salvianolic acid B; FA, Ferulic acid; PSV, Resveratrol; EGCG, epigallocatechin-3-O-gallate; HA, hyaluronic acid; EMB, Embelin; QS, quercetin; PAAm, polyacrylamide; L-Arg, L-Arginine; AloKr, keratin; ABE, *Ampelopsis brevipedunculata* extract; PBAT, polybutylene adipate terephthalate; Law, lawsone.

effects, are inexpensive, and have wide applicability [16]. Unlike antibiotics, bacteria are less prone to developing resistance to herbs [98]. However, most phytochemicals, like rosmarinic acid [113] and sage [131], are susceptible to light and oxygen degradation, particularly in the highly inflammatory environment of wounds. Loading them into CEFs is a promising strategy to safeguard their bioactivity and enhance their therapeutic efficacy.

Curcumin (Cur) is a plant extract commonly used in the production of CEF dressings (Table 5). Cur possesses antibacterial, anti-inflammatory, and antioxidant properties and promotes cell proliferation, migration, collagen deposition, and wound re-epithelialization [201]. Lu et al. developed a Cur-loaded CEF membrane with anti-biofilm and visual pH-sensing capabilities [44]. They incorporated Cur into a degradable PGA shell, facilitated by layer-by-layer assembled ε-PL, to disrupt EPS and provide antibacterial effects. They introduced alizarin, a pH-sensitive diagnostic reagent, into the polyamide 6 core for real-time visual in situ diagnosis [44]. They demonstrated the remarkable antimicrobial efficacy of this dressing against *S. aureus* and *P. aeruginosa*, achieving inhibition rates of 98.63 % and 99.30 %, respectively, in the *in vitro* antimicrobial experiments [44].

Aloe vera (AV) extract is another popular plant extract in CEF dressings. AV gel contains a high water content (over 98 %) along with minerals, vitamins, enzymes, anthraquinones, sterols, salicylic acid, amino acids, and polysaccharides [202]. AV was extracted in the shell of CEF dressings to harness its antioxidant and anti-inflammatory properties; it promoted wound healing in rats [130,203].

EOs are a distinct category of volatile plant compounds, making their incorporation into CEFs particularly significant. Lemon balm (*Melissa officinalis* L.) EOs [160], nigella seed oil [108], and *Origanum minutiflorum* oil [204] have been used in CEF dressings. Combining two or more EOs with different functions into one dressing is a noteworthy design approach. Dill (*Anethum graveolens* L.) EOs and Lemon balm EOs are known for their anti-inflammatory, analgesic properties and antimicrobial activity against nosocomial infections, resepectively. Loading them into CEFs can relieve pain and exert anti-inflammatory and antibacterial effects [160].

5.4.5. Other bioactive molecules

Additional bioactive compounds are incorporated into CEF wound dressings. For instance, silica is encapsulated within the PVA and PEG cores to serve as a drug-delivery vehicle because its high surface area facilitates targeted drug delivery. Graphene oxide in the PVA shell improves the mechanical properties of the fibers [24]. Bioglass, a Ca-Si-containing ceramic material that promotes angiogenesis [12], is also used in CEF wound dressings, demonstrating efficacy in wound healing, particularly in diabetic models [45].

Diagnostic agents are valuable for CEF dressings due to their monitoring capabilities. Alizarin is pH-sensitive and has been used in CEF dressings to monitor wound conditions in situ [44]. Prussian blue nanocrystals, as diagnostic reagents, monitor bacterial infections and guide dressing changes while enhancing anti-inflammatory activity [77].

Antimicrobial photodynamic therapy eradicates bacteria by generating toxic singlet oxygen via the photodynamic pathway, exhibiting nonresistance, noninvasiveness, and rapid sterilization [205]. Methylene blue (MB), a phenothiazinium derivative, is noted for its high quantum yield ($\Phi T \approx 0.52$), long excitation wavelength, excellent solubility, and cost-effectiveness. MB also demonstrates potent bactericidal properties, effective even with minimal light exposure or in the dark [206]. CEF dressings with MB-loaded core exhibit significant antimicrobial efficacy against *S. aureus* and *E. coli* when exposed to light ranging from 525 to 800 nm at a power density of 250 or 500 W m^{-2} for

10 min [140].

Furthermore, S-nitrosoglutathione releases carbon monoxide in the body. Loading it into the nanofibers to act as an antibacterial agent and promote angiogenesis and collagen deposition [207]. Hydrocortisone and ascorbic-2-phosphoric acid are used in CEF wound dressings to promote keratinocyte proliferation [158]. Vitamin A promotes epithelial differentiation of stem cells [56]. Tocopheryl acetate, a synthetic form of vitamin E, has the practical ability of anti-oxidation, anti-aging, and elimination of free radicals [104]. Statins, such as simvastatin [3,94], possess antioxidant, anti-inflammatory, and immunomodulatory properties that contribute to improved wound healing. CEF dressings that incorporate GBP [147], ibuprofen [77], and lidocaine hydrochloride [124] not only facilitate wound healing but also provide pain relief. Additionally, metformin hydrochloride is known to accelerate wound healing [66]. CEF dressings featuring an AlgMOD core and an acrylate-end-capped urethane-based precursor shell, loaded with activated carbon, can adsorb malodor-causing compounds, offering a potential solution for treating malodorous wounds [53]. Black soldier fly (BSF) larvae are rich in polyunsaturated fatty acids and proteins, which make CEFs with protein from BSF larvae suitable for wound treatment [106].

5.5. Composite dressings

Although CEFs loaded with various drugs in both the core and shell offer more comprehensive therapeutic effects than uniaxial electrospinning, they are not fully suitable in complex environments. Composite dressings combining CEFs with uniaxial electrospinning [166], hydrogels [208], and microneedles [194] are satisfactory strategies to address these challenges.

The composite dressing on carbohydrate polymers, as reported by Li et al., comprised two electrospun membranes with distinct functionalities [166]. The outer layer comprises random PCL nanofibers embedded in ZnO, providing antibacterial properties. The inner layer features coaxially aligned fibers with the CS shell and PCL core, offering a "contact-guided" effect and anti-inflammatory properties. This dressing facilitated rat wound healing and prevented bacterial infections [166]. Gao et al. prepared a multifunctional Janus electrospinning nanofiber dressing with antibacterial and antiinflammatory properties, controlled release of drugs, and unidirectional water transport by depositing CEF mats on a hydrophilic PCL@polydopamine (PDA)-ε-PL nanofiber membrane [179]. The dual-layer wound dressing with PLA layer as a support and bovine collagen hydrolysate/PVP CEFs as the functional layer is a by product [137].

Yilmaz et al. used gold (Au) NPs-loaded gelatin methacrylate (GelMA) and PLLA (shell) along with EGF-encapsulated collagen (core) nanofiber dressings to fabricate a bilayer nanofiber membrane featuring a central gel layer, effectively mimicking the epidermal and dermal layers owing to the intermediary hydrogel [208].

Biofilms can be disrupted by physical mechanisms and enzyme-catalyzed hydrolysis reactions [44]. Microneedles can eradicate biofilms, creating a conducive environment for antibacterial agents to combat bacterial populations (Fig. 8) [194]. Xie et al. developed a composite dressing comprising Pluronic F-127-PCL shell fibers embedded with Ag NPs, Gallium (Ga) NPs, and Van in the fiber core, along with PVP microneedles. The antibacterial efficacy of the dressings against MRSA and *P. aeruginosa* has been validated *in vitro* [194].

5.6. Portable electrospinning equipment

Given that wounds exhibit asymmetrical and irregular shapes, it is important to develop customizable personalized dressings at the patient's bedside [180]. However, most current electrospinning equipment cannot meet the requirements for bedside spinning owing to low deposition rates, high voltage demands, the need for conductive collectors, and large setups [131,180]. Airbrushing or solution-blow spinning offers a simple alternative [131]. A handheld solution-blow-spinning setup comprising a compressed gas, concentric nozzle, and concentrated polymer solution has been developed to produce CEF dressings beside patients (Fig. 9A). Bioactive factors and drugs can be loaded into the CEFs [180]. Burn is caused by excessive skin-localized heat leading to loss of protective function, increased susceptibility to bacterial infections, inhibition of enzyme and GFs production, and delayed wound healing. The direct deposition of cool nanofibers onto wounds outdoors promptly using a handheld electrospinning equipment is an effective way to delay the progression of burns (Fig. 9B) [183]. In addition, multifunctional handheld CES equipment should be developed to fit different conditions.

6. Summary and perspectives

Wound healing is a multifaceted process of paramount global significance, with the utilization of wound dressings playing a pivotal role. Wound healing is influenced by high inflammation levels and microbial infections, which guide the design of dressings. Notably, CEF dressings stand out due to their ability to mimic the ECM structure of healthy skin tissues and facilitate drug delivery. Different polymers and constructed forms of CEFs are designed to fit different wound microenvironments.

While various forms of CEF dressings show significant application potential, they have some shortcomings. For example, hollow fibers

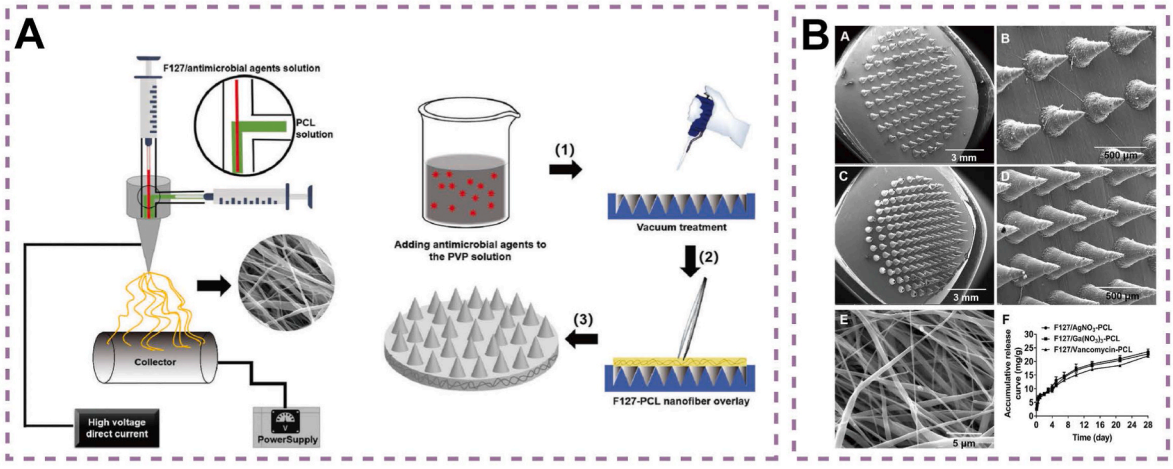

Fig. 8. Composite dressing comprising coaxial electrospun nanofibers (CEFs) and microneedles. (A) Diagram of the composite dressing fabrication process. (B) Scanning electron microscopy images of microneedles and CEFs. Reproduced with permission [194]. Copyright 2021, Wiley.

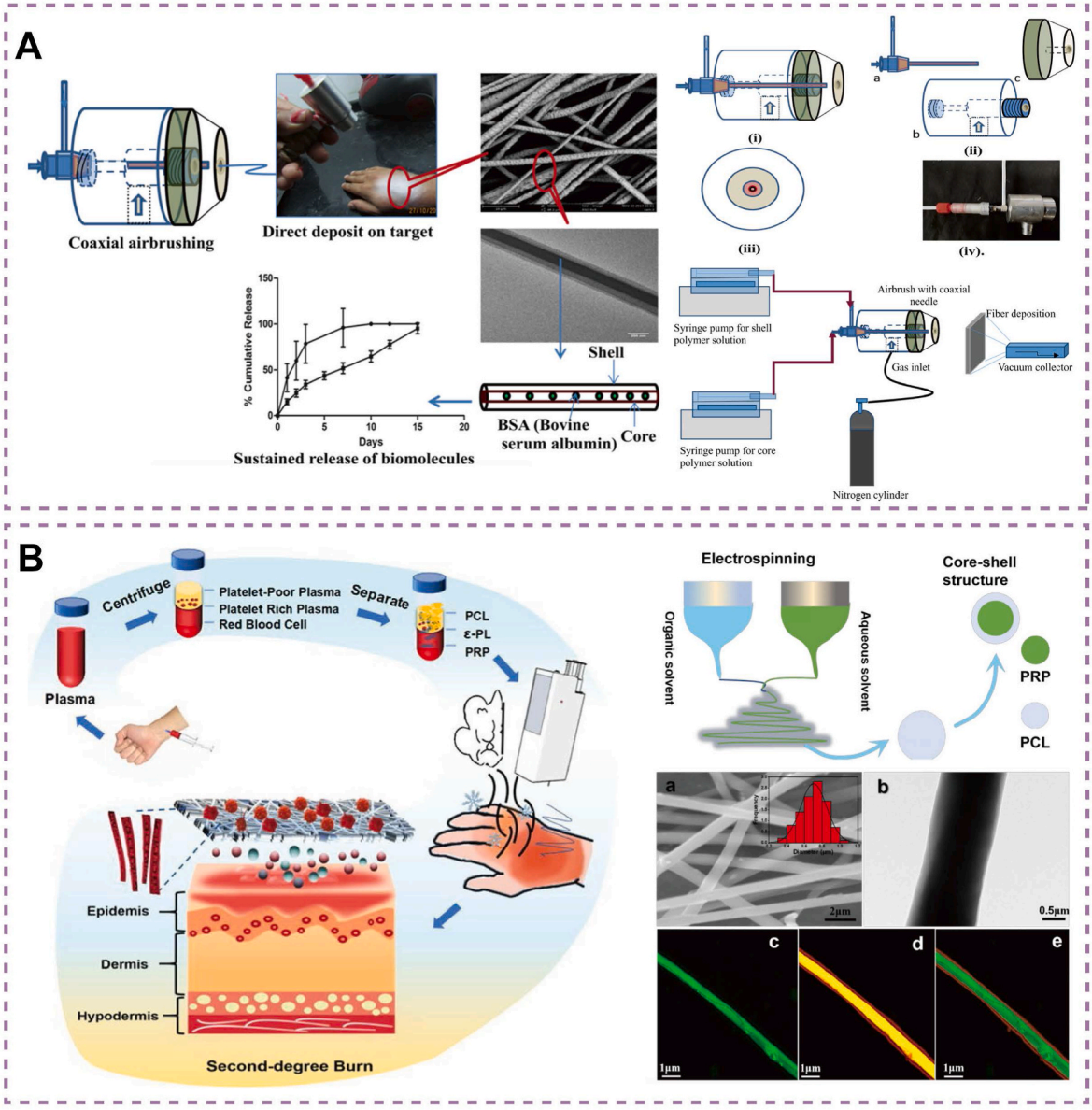

Fig. 9. Handheld coaxial electrospinning (CES) device. (A) Diagram of a solution-blow-spinning handheld electrospinning device. Reprinted with permission from Ref. [180]. Copyright 2018, American Chemical Society. (B) Handheld CES device for producing ice coaxial electrospun nanofibers. Reproduced with permission [183]. Copyright 2023, Elsevier.

offer a large surface area but fail to sustain effective drug release [61]. Multi-layer coaxial fibers demonstrate characteristics conducive to multi-stage drug release. However, they require more stringent solvent conditions, imposing limitations on the selection of CEF polymers [82]. Furthermore, electrospinning solvents are typically toxic and environmentally unfriendly [209]. Developing more environmentally friendly solvents (green electrospinning solvents) may advance CEF production toward environmentally sustainable practices.

Compared with transdermal patches and hydrogels, the adhesion of ECF dressings is unsatisfactory. Producing CEFs with polymers that form physical and chemical bonds with tissue and post-processing CEFs, such as grafting with self-adhesive material, including dopamine [112], increases the adhesion of CEF dressings. Furthermore, coating CEFs with highly adhesive hydrogel or combining CEF dressing with microneedles, which are minimally invasive anchor points for CEF dressing to fix the wound area, can address the problem.

For wounds in areas with high mobility, such as the elbow, high elasticity, flexibility, and good mechanical properties are equally important in addition to high adhesion. 3D printing hydrogels with high elasticity and flexibility, combined with short CEFs with nice mechanical properties, may be effective. Composite dressings of CEFs and 3D printing scaffolds with biomimetic topography can enhance the availability for large full-thickness wounds with or without deep tissue defects.

From an industrial perspective, challenges, such as insufficient production and a lengthy preparation duration, have hindered the large-scale commercialization of CEF dressings. Although researchers have developed advanced electrospinning technologies, such as needle-free, multi-needle, and pulsed gas-assisted electrospinning, to improve the fiber yield of electrospinning [60], significant improvements are required to produce spinning with stable properties and increase industrial production for the application of these technologies to CEF production.

Wound healing is a dynamic process with distinct phases that require specific biological cues. Smart dressings are expected to intelligently assess wound conditions by detecting metabolite release or specific

biomarkers, such as pH, and accordingly modulate the release of tailored drugs or bioactive agents. Electrospun dressings integrated with non-invasive sensors are employed as bionic intelligent skins in intelligent wearable systems [210]. The integration of sensors into wound dressings can facilitate the collection and analysis of metabolic data from the wound microenvironment, further enabling precise control over the release of encapsulated drugs. However, the sensitivity of the electrospun nanofibers decreases post-processing, and specific protocols for adjusting the drug release levels based on the wound environment are lacking. Future research needs to improve the performance of nanofibers in biosensors by modifying their surface chemistry, and the in-suit liquefaction-solidification transition of the polymers at low temperatures is expected to be used in the production of CEFs for controlled drug releases.

CRediT authorship contribution statement

Jing Zhao: Writing – original draft, Visualization, Conceptualization. **Liyun Chen:** Project administration. **Aiwei Ma:** Writing – review & editing. **Xujue Bai:** Visualization. **Yating Zeng:** Writing – review & editing. **Daojun Liu:** Writing – review & editing. **Bo Liu:** Writing – review & editing, Funding acquisition. **Wancong Zhang:** Supervision, Project administration, Funding acquisition. **Shijie Tang:** Supervision, Funding acquisition.

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.

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Data availability

No data was used for the research described in the article.

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