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Review article

Active agents loaded extracellular matrix mimetic electrospun membranes for wound healing applications

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ABSTRACT

Achieving the healing of chronic diabetic ulcers, burn wounds and large traumatic wounds is a major clinical challenge. A variety of approaches have been undertaken to generate skin substitutes, wound healing patches or dressings with adequate barrier properties, stability, degradation, exudate uptake capacity, antimicrobial properties, vascularization potential and wound-healing capacity. Recent approaches to support chronic wound healing focus on the development of a natural extracellular matrix (ECM) mimetic microenvironment in the wound bed. Submicron fiber-based membranes have been shown to successfully mimic many features of the ECM such as its architecture, mechanical properties, composition, and function. Electrospinning is one of the most successful methods for producing porous submicron fiber based wound coverage matrices for promoting wound healing and achieving tissue regeneration. The ECM mimetic properties of the membranes have also been improved with the use of recently developed methods such as coaxial electrospinning with other polymers. Various active components such as therapeutic agents, nanoparticles and biomolecules can be incorporated in electrospun fibers to improve ECM mimetic features and provide additional advantages like antibacterial and angiogenic properties. This article comprehensively overviews the applications of ECM mimetic electrospun membranes as structural and functional components in wound healing and the potential challenges imposed by them in a clinical point of view.

1. Introduction

Skin is the largest organ of human body that functions as a barrier preventing the entry of pathogens into the body, minimizes fluid loss, act as a thermal barrier and protect the body [1,2]. Such a multi-functional organ requires immediate recovery in case of an injury to avoid further complications and pathogenesis. Wound healing is a very complex process involving cellular, molecular, physiological and biochemical activities which help to allow the repairing of damaged skin as well as underlying tissue [3]. This process is orchestrated by the co-ordinated functioning of many cell groups such as blood cells, vascular cells, stem cells, epithelial cells as well as many soluble factors like growth factors and cytokines [4,5]. Thus, wound healing is a dynamic and highly controlled process involving various components from the starting of the injury to the complete closure of the wound and beyond to reestablish the original tissue in a most functional state as possible [6].

Extracellular matrix (ECM) plays important roles in the wound healing process. The ECM not only acts as an architectural support, but also plays a major role in cytokine activity and intracellular signaling helping the regulation and activation of pathways related to cell differentiation and proliferation [7]. By interacting with receptors on the surface of cells, the ECM directly promotes cell adhesion, migration, growth, differentiation and apoptosis [8,9]. To regenerate a fully functional tissue, both the complex function and fibrous form of the native ECM needs to be mimicked by the wound healing matrices or skin substitutes. For this, several material and design characteristics need to be considered. For instance, the base material used for the development of wound dressings or biomaterial scaffolds must not direct any adverse immune reactions. The material must also be biodegradable such that it can be gradually absorbed by the neighboring tissue [10]. Also, the

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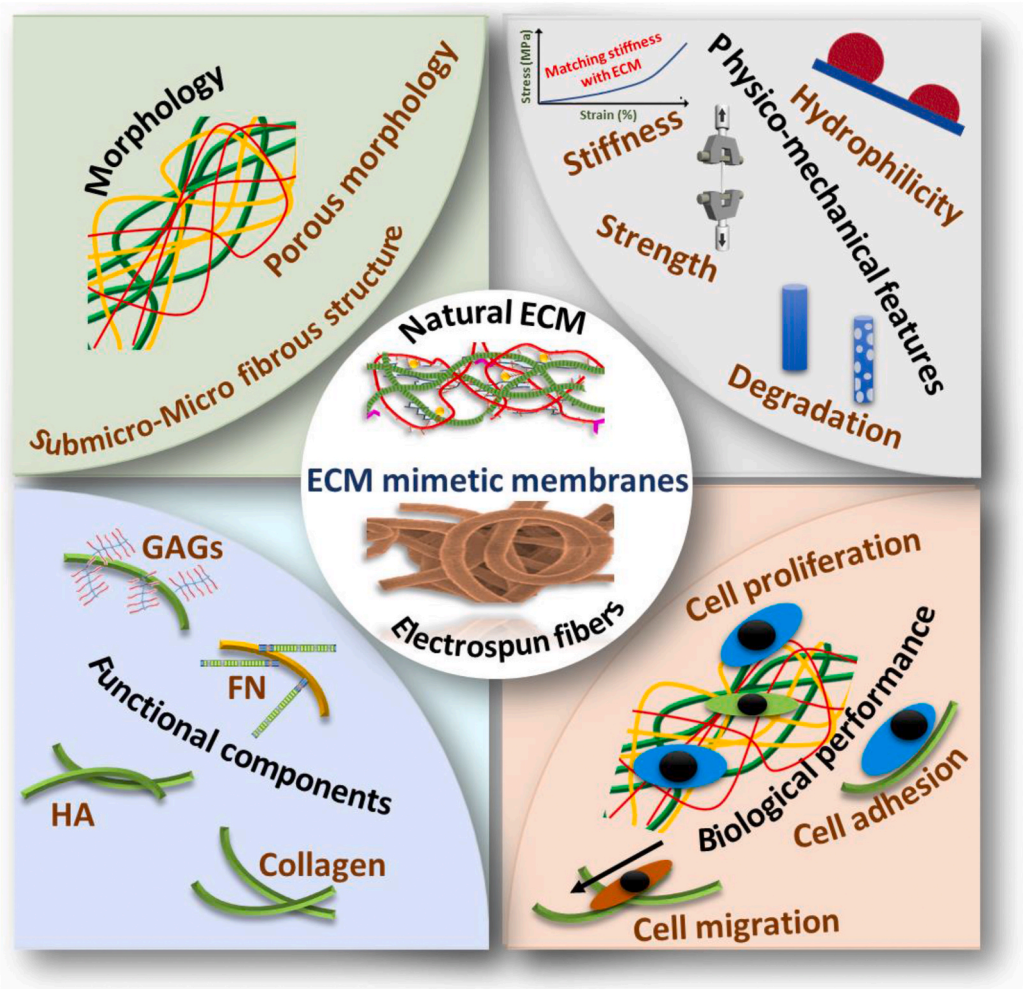

Fig. 1. A scheme showing the major extra-cellular matrix (ECM) mimetic features of electrospun membranes which help in wound healing and tissue regeneration. Abbreviations; GAGs: glycosaminoglycans, FN: fibronectin, HA: Hyaluronic acid.

engineered ECM needs to mimic the geometry and topographical features of native ECM not only at the macro level but also at the submicron level, as each of these influences the cellular response on the engineered biomaterial [11].

Nanofibers have various innate properties that make them promising candidates for the wound healing applications. The topographical characteristics of nanofibers have morphological resemblances to the native ECM of skin which makes them recapitulate the structure and function of ECM (Fig. 1). Nanofibrous membranes show high gas permeation capacity, ability to protect the wound from protein and fluid loss, and aiding in the removal of exudates from the wound site [12,13]. These membranes have shown to improve hemostasis at injury because of the high surface area to volume ratio. Nano-submicron fibers further helps in the absorption of fluids and also allow the incorporation of specific chemical functionalities on the surface of the fibers [14,15]. The fibers can also be loaded with many variety of bioactive molecules which can promote wound healing [16–18]. Such active agents loaded matrices have shown to be as promising candidates for tissue regeneration.

Many methods have been employed to generate porous scaffolds like self-assembly, phase separation, solvent-casting and three-dimensional printing (3D printing). But, many of these methods pose the incapability of creating highly porous scaffolds that can mimic native anisotropic ECM structure [19,20]. An ECM mimetic architecture helps in the precise guiding of cell growth and for the fast regeneration of tissues that recapitulate both the structure and function of lost or damaged ones. For this reason, such fibrous matrices have demonstrated the ability to determine cell morphology and influence their functioning in comparison to bulk-porous scaffolds [21]. Moreover, some studies report that aligned fibers give contact guidance to cultured cells resulting in the alignment of cells along the contact direction [22,23]. Also, morphological features of myoblasts and endothelial cells have been shown to be influenced by the aligned nature of fibrous scaffolds [20].

Electrospinning is a nano/submicron fiber development method which has gained a lot of attention in the past few decades for the preparation of highly porous biomaterials for wound healing applications [24]. Five different methods of loading the fibers with active agents have been reported in the literature. These include blending of active agent with the polymer before electrospinning [25], fabricating core/shell structures through coaxial spinning, attaching the fiber surface with active agents and post-fabrication surface treatment or surface conjugation of active agents [26]. Various biomolecules like enzymes [27], plasmid genes [28], liposomes [29] and proteins [30] have been incorporated into the fibers to achieve controlled release. Various studies have focused on the approaches to better mimic the features of native ECM in electrospun matrices and elicit optimal cellular responses to drive rapid wound healing or tissue regeneration.

Herein this review article, we try to gather all the available information about the latest advances in the development of ECM mimetic electrospun membranes for wound healing applications. We also discuss the structural as well as functional breakthroughs that the researchers have achieved in the field of wound healing and skin tissue engineering

using such matrices.

2. ECM structure and function

ECM is a highly porous biological macromolecular scaffold composed of fibers with varying diameters that give structural and biochemical support for the cells it holds. Tissue source, its structural and functional molecules define the composition of ECM [31,32]. The cells and the ECM in a tissue interact dynamically and have a reciprocal relationship [33]. The cells synthesize the ECM to have specific characteristics and compositions, and the ECM in turn has significant influence on the differentiation, growth and migration of the cells through chemical and biophysical signals. Some signaling molecules are stored within the ECM and are released gradually to act as soluble ligands [9]. Other molecules attach to the surface and interact with the cell receptors to cause haptotaxis induction and activate signaling cascades [7].

Primary constituents of ECM are water, proteins and polysaccharides. Each of these constituents assemble to form a unique niche, tailor-made for the cells of that particular tissue type and helps it to sustain, differentiate and carry out its specific functions [8]. ECM gets remodeled enzymatically and non-enzymatically and by dynamic post translational modifications which occur in the ECM at the molecular level. These biochemical and physical attributes exhibited by the ECM generates specific characteristics of each organs. These properties include extracellular homeostasis, compressive and tensile strength, elasticity and water retention along with other major functions like gene regulation by signal transduction on the binding of growth factors and morphological organization. The ECM consists of two major types of macromolecules: hydrogel like proteoglycans that fill most of the extracellular interstitial areas within the tissue [34] and fibrous proteins like collagens, fibronectins, elastin and laminins.

Proteoglycans are formed by glycosaminoglycan (GAG) chains covalently linked to a particular protein core. The three major classifications of proteoglycans are SLRPS (Small leucine rich proteoglycans) which are involved in signaling pathways, modular proteoglycans which modulate cell adhesion and proliferation, and cell surface proteoglycan that behave as co-receptors assisting ligand encounters with signaling receptors. Additionally, GAG can be split into sulfated and non-sulfated GAGs. Chondroitin sulphate (contributes to cartilage tensile strength and neuroplasticity), heparan sulphate (involved in angiogenesis, blood coagulation, developmental process and tumor metastasis) and keratan sulphate (contributes to cartilage tensile strength, tendons, aorta walls and ligaments) are the sulfated GAGs. Non-sulfated GAG consists of hyaluronic acid which, by counteracting turgor force through water absorption, helps to resist compression. The hydrophilicity of these molecules contributes to the ability to withstand high compressive force by extending to various conformations that are necessary for the formation of hydrogel and that allow the formation of molecular matrices that give it the power to resist excessively higher stress.

Elastin, collagen, laminin and fibronectin are the key fibrous ECM proteins. Within the interstitial ECM, collagen constitutes up to 30% of the total protein mass of an animal [35]. The architecture of the collagen fiber greatly influences the natural scaffold's biomechanical features [36,37]. Regulating cell adhesion, promoting chemotaxis, providing tensile strength and migration, and direct tissue growths are influenced by collagen type and amount [38]. Collagen fibers composed of a heterogeneous mixture of different types of collagens [39]. Elastin is required for tissues that experience repetitive rebound stretches. Importantly, the stretch of elastin is typically restricted by a close connection with collagen fibrils. Elastin fibers are protected by microfibrils of glycoprotein, primarily fibrillin, which are also important for their integrity [40]. Elastin is a protein found mainly associated with collagen in the ECM of connective tissues helping tissues to return to their original shape after a temporary deformation [41]. Another fibrous protein, fibronectin (FN), is closely involved in directing the interstitial ECM organization and plays a crucial role in mediating the attachment and function of cells. Cellular traction forces will extend FN several times over its resting length [42]. Such force-dependent FN unfolding makes FN as an extracellular mechano-regulator. During wound repair, FN is also important for cell migration [43]. After all, Laminins are large heterotrimers constituting the main component of the basal lamina, i.e., one of the basal membrane layers. Laminin plays important role of enhancing cell adhesion, migration, differentiation and proliferation within ECM [44].

To create a suitable microenvironment for the regulation of differentiation, growth and migration of cells, the developed skin substitutes or scaffolds must have analogous structural, chemical and functional properties like the native ECM. As a substrate for the adhesion and proliferation of cells, some other properties of scaffolds like signal reception capacity, growth factor binding, growth factor storage and serving of growth factors are also critical to function as a biologically active ECM mimetic material [45]. As it was impossible to completely mimic such a highly complex structures of ECM, researchers initially focused to develop properties that mimicked the tissue at the microscopic level without giving much focus on functional aspects. As of late, scientists are combining biopolymers with these structures to provide signaling and bio-functionality which are necessary for cell attachment and migration. Even the ultrastructural features of the scaffold influence the ability of cells to migrate into the scaffold or control tissue-specific cell phenotypes. For example, an irregular loosely arranged fibrous surface can facilitate the infiltration of cells into the scaffold whereas scaffolds composed of closely packed fibers prevent cell penetration deep into the scaffold forming confluent cell populations on the surface [46]. Thus, it is very much necessary to create the structural and functional analogy while developing biomaterials to better mimic the native ECM.

3. Role of ECM in wound healing

In every phase of the wound healing process, the whole ECM as well as its constituents play several influential roles. Primarily, it influences the structural biomechanical aspects because the natural scaffold provided by the ECM is necessary for the cell adhesion, migration and proliferation which are key steps in repairing process. Also, the ECM components play the role of linking the functional characteristics of the healing processes like the signal transduction, growth factor delivery, mediation of cell and matrix interactions, and many other major functions [47,48].

Cytokines, growth factors and interactions between ECM components control the functions of cells involved in the wound healing process. For example, the metalloproteinase matrix helps in the migration of cells, while components like the macrophage proteases break down the damaged components of the matrix [49]. In various wound healing studies, ECM components like collagen, glycosaminoglycans, *etc*. have been found to be very effective in promoting healing [50]. An interesting study found that the use of active agents expedites the repair process by promoting the deposition of glycosaminoglycan necessary for granulation and the closure of the wound [51]. It is evident from the above examples that proteoglycans and glycosaminoglycans play a key role in wound healing. New therapeutic strategies aiming at creating a favorable biochemical environment to promote the wound healing process are of great importance for achieving further advances in the management of chronic wounds. Therefore, it is very evident that providing an ECM mimetic microenvironment through rationally designed biomaterials with bioactivity and functionality in wound bed is very important to achieve rapid wound healing and desirable therapeutic outcome.

4. Methods for the development of ECM mimetic materials

The selection of fabrication technique along with the choice of material determine the properties of the resulting scaffolds. Many

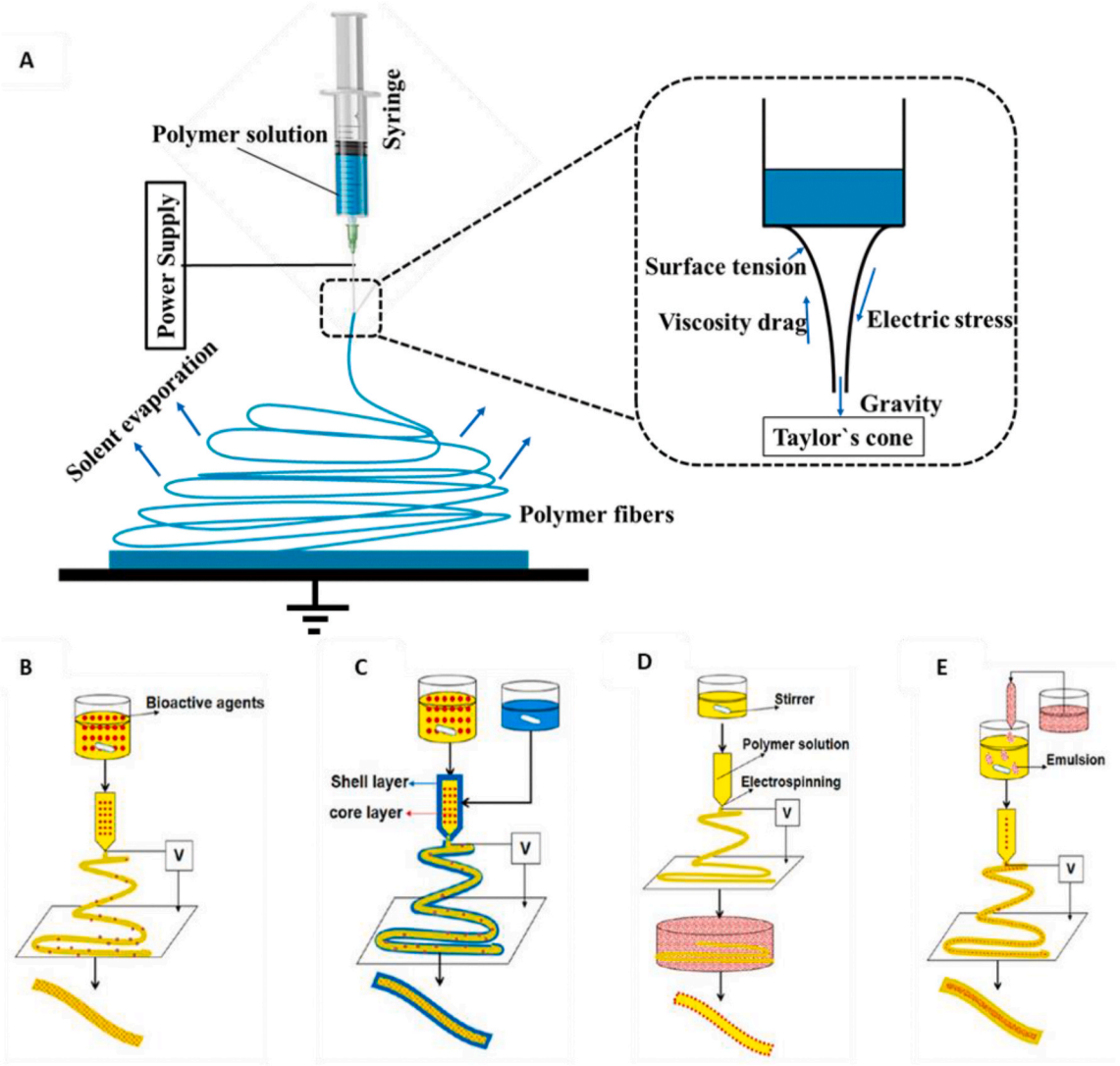

Fig. 2. Electrospinning setup and various active-agent incorporation methods. A. The basic setup of the electrospinning method depicting the necessary components. B. Blended electrospinning setup C. Core-shell electrospinning setup D. Surface functionalization electrospinning setup E. Emulsion-based electrospinning setup. Figures B–E are reproduced from Ref. [190] with the permission of American Chemical Society.

approaches have been developed and used for the fabrication of ECM mimetic porous 3D scaffolds to act as a platform for the adhesion, proliferation and ingrowth of cells. The following section briefly describes various conventional as well as modern techniques that are being used for the development of porous matrices or scaffolds for wound healing and tissue regeneration applications.

4.1. Self-assembly

The property of autonomous organization of components into structures and patterns, known as self-assembly, can be utilized for the fabrication of ECM mimetic structures. Various complex, highly specific non-covalent interactions drive the assembly of structures like micelle/bilayer lipids, and α-helix and β-sheet structural motifs of proteins [52,53]. This method produces fibers having diameters in the range of tens of nanometers. The assembling mechanisms are initiated through mixing of components or by an external stimulus like change in pH, temperature, etc. [54,55]. This makes it possible to directly encapsulate cells, which is easier in comparison to other fabrication methods that require sophisticated instruments. But the mechanisms governing the self-assembly are more complicated and therefore require careful and complex experimental design. Scaffolds produced by self-assembly of proteins and peptides which have been shown to mimic the natural ECM [56,57]. Despite the many advantages, matrices fabricated by this approach show poor mechanical strength and the fragmented fibers pose the threat of endocytosis. Along with these drawbacks, the high cost of synthesis restricts their applications in tissue engineering and regenerative medicine [58].

4.2. Thermally induced phase separation

In biological systems, phase separation is a process where the biomacromolecules such as nucleic acids or proteins spontaneously separates a dense and a dilute phase [59–61]. Similarly, the thermal energy difference during a quenching process is utilized to initiate the pahe separation and void formation in a homogenous polymer solution. After exposing the solubilized polymer to high temperatures, the temperature is rapidly decreased to prompt the phase separation [102,103]. By strong fluid de-blending, the solution then forms polymer-free phase and solvent-free phase. In this technique, the scaffolds microstructure can be manipulated by controlling the polymer properties, solvents and the working temperature [62]. The phase separation can be carried out either between solid-liquid or liquid-liquid phase. This technique offers the benefit of compatibility with many of the other manufacturing

techniques and gives superior mechanical properties with controlled porous structure.

4.3. Melt molding

Melt-based fabrication methods are derived from the conventional polymer fabrication methods. However, these methods are then coupled with pore-generating techniques to generate porosity in the material [63]. Generally, water soluble salts are mixed with polymer during molding and the salts are dissolved in water after molding leading to a porous structure. The advantages of this process are that toxic solvents are avoided, and the pore size can also be controlled by using porogens of suitable size. By combining with techniques like particle leaching, gas foaming and use of porogens, this method shows great potential for the generation of ECM-mimetic tissue regeneration studies.

4.4. Gas foaming

This technique uses a foaming agent with the polymer. To initiate the nucleation and development of gas microbubbles in the substance, high pressure gas is applied on the disks of polymer. These are then lyophilized to generate scaffolds having pore sizes in the range of 100 μm and porosity of about 93% after releasing of gases [64]. The formation of gas is due to reaction of foaming agent with the acidic solution producing porous structure. This procedure has great reliability to create solvents-free scaffolds. But the heterogeneity of the structure having irregular porosity is the major disadvantage of this process. Studies using this method with stem cells have been showing promising results for bone tissue engineering [65].

4.5. 3D-printing

3D-printing is an additive manufacturing technique first portrayed in 1986. In this technique, thin layers of materials are deposited in a layered manner intermitted by hardening of the layers by ultraviolet (UV) radiation [66]. This method then developed to photo-polymerization where mixed layers of a monomer gel and a photo-initiator are cured and crosslinked by a laser source according to the computer design [67]. This method offers many advantages like flexibility to use different polymers, fillers and binders to tune various properties like mechanical strength, porosity, biocompatibility, etc. to generate scaffolds which can better mimic the ECM. In a study on bone regenerative scaffolds, pore sizes in the range of 20–50 μm were achieved [68]. An impediment drawback of 3D printing is the high temperatures used during the extrusion of polymer which would limit the use of proteins and cells because of their temperature-sensitivity [69]. Recent approaches using water soluble polymers and photo crosslinking could solve this issue.

4.6. Decellularization

Decellularization is a method which removes cells and debris from tissues and organs while preserving the biological activity, the biochemical composition and the 3D organization and integrity of the native ECM. As the decellularized constructs are devoid of foreign cells, there is no significant chances of immune rejection [70]. Other than the use in tissue regeneration, it has also gained popularity in other fields like drug screening and stem cell differentiation studies. Different methods for decellularization include physical, chemical and enzymatic treatments. After decellularization, the matrices can further be processed to generate injectable hydrogels, which can then be used as method for localized delivery with minimally invasive intervention [71]. Another simple but effective technique to enhance scaffold bioactivity is the deposition of solubilized ECM on the prefabricated scaffold surface. This allows the cells to interact directly with the ECM proteins which improves bioactivity along with achieving high mechanical properties [72].

4.7. Electrospinning

This technique utilizes electric voltage to generate a 3D structure having fibers in the range of nanometers to micrometers with higher surface area. Many natural and synthetic polymers have been used in this process like chitosan [73], gelatin [74], collagen [75], polyvinyl alcohol (PVA) [17], polycaprolactone (PCL) [76], etc. A high DC voltage in the range of 10–40 kV is used to produce the fibers. Upon the application of such a high voltage, the polymer solution taken in the syringe becomes charged and the polymer droplet at the tip of syringe needle tend to move towards negatively charged/grounded collector as submicron fibers (Fig. 2). Typical electrospun scaffolds show pore sizes in the range of 5–150 μm. To mimic native ECM, these scaffolds provide nano-scale fibrous structures having interconnected pores, and thereby showing great potential to fabricate functional tissues [77]. In addition to ECM mimetic structural features, the ability to impart bioactivity has led to the use of electrospun membranes as biomimetic scaffolds for wound healing and tissue regeneration applications.

Some other techniques like surface functionalization, emulsion-based electrospinning, etc. have also been reported for generating ECM mimetic scaffolds. Keeping in mind the various pros and cons of the various fabricating techniques discussed above, better techniques need to be developed which will help us fabricate biomaterials showing improved mimicry of the native ECM.

5. Nano-fibrous materials as ECM mimetics

Most of the ECM proteins have a fiber like architecture with diameters in the sub-micrometer range. For instance, collagens possess a fibrous structure in which the diameter varies from 50 to 500 nm. There have been many recent advances in the methods to develop ECM-mimetic nanofibrous materials. Nanofibrous materials have high surface-to-volume ratio with large porosity and offer the flexibility to be made into a wide variety of sizes and shapes [78]. These unique features make the nanofibrous scaffolds promising for many biomedical and tissue engineering applications [79,80].

Electrospinning and other related technologies like electro-spraying and air-jet spinning are some of the nanofabrication techniques that are used to generate nanofibrous microporous materials. The use of different polymers, their blends, or nanocomposites paves way for producing membranes of varied chemical compositions. These membranes are known for their great extent of processing flexibility which is helpful in optimizing their physical parameters such as fiber diameter, porosity, and pattern formation on fiber surface increasing the potential for wound healing applications. Electrospinning is one of the proven techniques to generate nanofibrous material that have a soldering-like attachment of the nanofibers at their intersections due to polymer chain entanglements and interpenetration after annealing [78].

Nano-fibrous membranes have been found to adsorb higher serum proteins than less-porous macro -fibrous membranes [81]. Furthermore, studies have revealed that the nano-fibrous scaffolds adsorbed larger amounts of fibronectin from serum in comparison to macro-porous scaffolds. These data indicate that the nano-fibrous scaffolds have better prospects of mimicking the natural ECM with enhanced tissue regeneration and which can also circumvent the potentially adverse immune reaction and possible chances of pathogen transmission when using naturally derived ECM based constructs. The promising ECM mimicry of nanofibrous biomaterials has led to their increased utilization in the management of chronic wounds.

6. Electrospinning for ECM mimetic membranes

Both natural and synthetic polymers can be used to generate fibers using electrospinning either individually or in combination. The natural

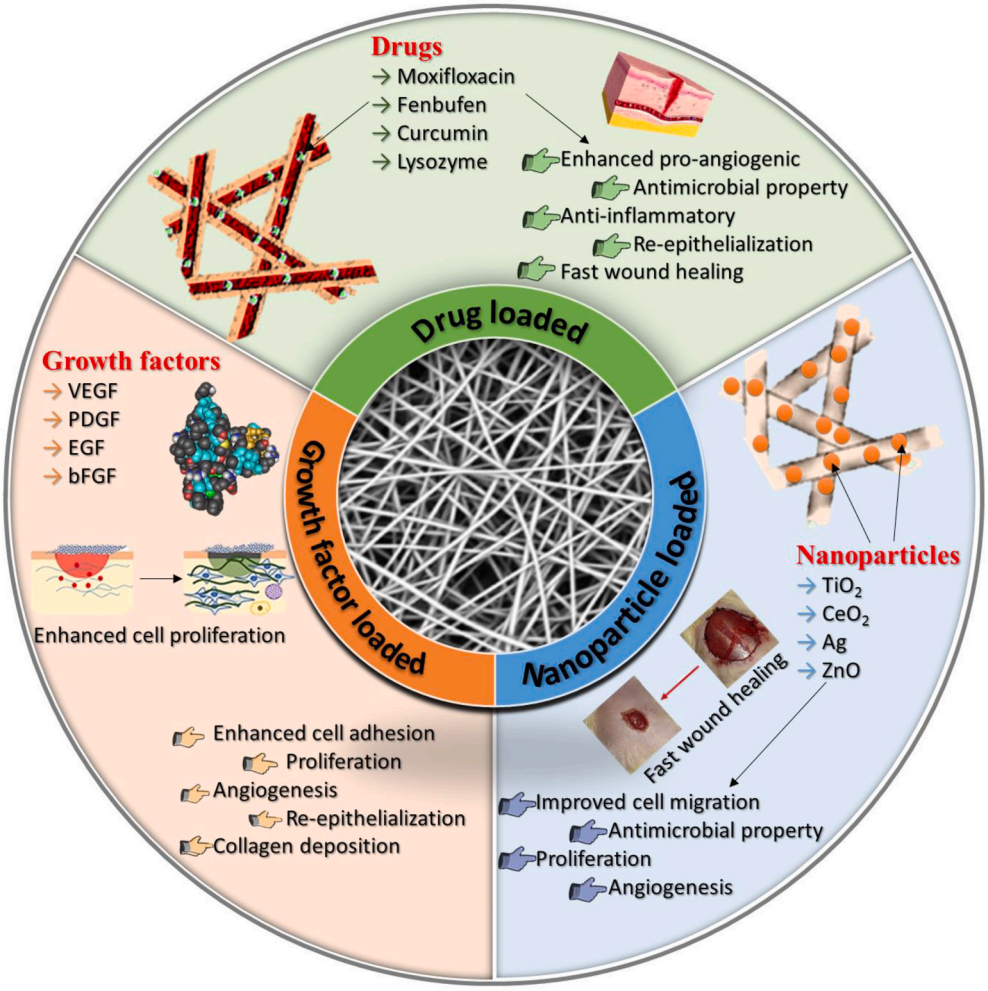

Fig. 3. A scheme showing the incorporation of various active agents in ECM mimetic electrospun fibers and their salient features that help in wound protection and healing.

polymers are more favorable for ECM production because of their physiological similarity to the native ECM, great biocompatibility, lower toxicity and high biodegradability. Synthetic materials, on the other hand, can be easily produced, provide better physical properties along with moderate biodegradability. Most of the synthetic materials lack functional groups on their surface which makes them unrecognizable by the immune system as a foreign material and thus preventing an inflammatory response [82].

Recent advances have made it possible to produce 3D nanofibrous scaffolds with the desired microstructure. In bioengineering, 3D scaffolds should bridge the gap between the nanofibrous technology and clinical applications [83]. There is also a great possibility of integrating bioactive molecules such as drugs, nanostructures and growth factors into nanofibers developed using various techniques (Fig. 2B–E). The high-loading capacity of electrospun nanofibers make them promising materials for gene and drug delivery applications [84,85]. Encapsulation efficiency and the retained bioactivity of the therapeutic agents can be optimized by careful selection of materials and processing conditions [86]. Coaxial electrospinning is an advanced technique in which the fibers are in a core-shell form with complex microstructures produced using multiple pump system through coaxial nozzles. Many parameters influence the characteristics of the fibers such as the type of polymer, surface tension and viscosity of the solution, the polymer solution feed rate, needle-collector distance, needle tip size, *etc*. By precisely controlling these parameters it is possible to adjust the fiber diameter, porosity, and the nanofiber architecture [87].

Electrospun fibers offer several applications in tissue engineering such as vascular grafts, nerve regeneration and bone regeneration. They have been shown to enhance homeostasis, offer flexibility and mechanical strength, functionality when used as wound dressings [88]. A biologically inspired ocular repair dressing composed of hydrogel and electrospun fibers have been designed to treat corneal abrasions and ulcers on eye surfaces [89,90]. In other studies, collagen fibrils are mixed with other polymers as a traditional wound dressing so that the ECM mimetic structure would allow wound exudate absorption and moisture preservation which improves wound healing [91,92]. Sun et al. attempted to imitate the collagen's basketweave pattern to generate ECM-mimetic microenvironment. Interestingly, the developed scaffolds provided higher fibroblast cell response during wound healing compared to random/aligned nanofibers [93].

Overall, electrospinning technology has immense potential in the field of wound healing and tissue regeneration. It offers the advantage of flexibility to use a variety of suitable polymers, polymer composites and polymer/inorganic composites. It also provides the flexibility to tune the microstructural properties as well as the capability to load bioactive molecules to combine therapeutic activity and tissue regeneration capacity at the implantation site. ECM-inspired surface modification or coating techniques provide additional biological attributes to facilitate rapid tissue regeneration [94].

In nutshell, there are many advantages for electrospun nanofibers, such as polymer-dependent biodegradability and biocompatibility, relatively ECM-like mechanical properties, capability to load surface

Table 1
Electrospun drug-loaded membranes for wound healing applications.

S. No	Polymer	Drug	Other Active Agents	Features	Ref.
1	PCL	L-Arginine	–	Supported healing by releasing NO	[163]
2	Chitosan/PEO	Teicoplanin	–	To treat acute and chronic wounds through local antibiotic delivery	[164]
3	PCL	Silver Sulfadiazene	–	Topical drug delivery to prevent infection	[165]
4	Cellulose acetate/Gelatin	Zataria multiflora essential oil nanoemulsion	–	Profound antioxidant and antibacterial activity	[108]
5	Alginate	Dexpanthenol	–	Enhanced cell attachment and cell proliferation	[166]
6	Gelatin/PCL	Chrysin	–	Immunomodulatory action and anti-inflammatory activity	[167]
7	PCL/Methyl-cellulose	Manuka honey	Bioactive glass	Enhanced wound healing ability and dual therapeutic effect	[120]
8	PLA/PVP	Levofloxacin	Naproxen-sodium	Antibacterial and anti-inflammatory activity	[168]
9	Gelatin/Polydopamine	Chondroitin sulphate	Magnesium	Promoted wound healing process by providing anti-inflammatory activity	[169]
10	Gelatin/PVP and Cellulose acetate	Gentamicin	–	Antimicrobial properties to prevent colonization by microorganisms	[170]
11	PLGA/Gelatin	Liraglutide	–	Promoted angiogenic ability	[171]
12	Chitosan/PEO	Moxifloxacin	–	Protected from infection	[172]
13	PLGA	Propolis	–	A promising natural agent to treat burn wounds	[173]
14	PCL-chitosan/PVA/PCL-chitosan	Metformin-Hydrochloride	–	Expedites wound healing by minimizing fibrosis	[174]
15	PCL/PLA	Nigella sativa (Black seed)	–	Natural anti-inflammatory and anti-bacterial agent	[175]
16	PVA	Cephalexin	–	Effective in inhibiting infections	[176]

Table 2
Electrospun membranes loaded with growth factors for wound healing applications.

S. No	Polymer	Growth Factor	Other Active Agents	Properties	Ref.
1	Collagen-HA	VEGF-PDGF-EGF-bFGF	Gelatin NP	Supports re-epithelialization, dermal reconstruction and the formation of mature vasculature	[177]
2	PCL-Collagen	bFGF	–	Significant granulation tissue formation, collagen deposition and re-epithelialization	[178]
3	PCL-PEG	bFGF-EGF	–	High cellular proliferation and keratin 14, 5, 1 expression levels	[179]
4	Chitosan-PEO	VEGF	PLGA NPs	Increased angiogenesis, re-epithelialization and granulation tissue formation.	[180]
5	PELA (Poly (ethylene glycol)-poly (DL-lactide))	bFGF	chloroform	Enhanced cell adhesion, proliferation, and secretion of ECM	[181]
6	PCL-HA	EGF	–	Enhanced cell proliferation and infiltration, upregulation of collagen I, collagen III and TGF-β	[182]

functional moieties and growth factors make it the most practical approach for the development of ECM mimetic membranes/scaffolds. Also, the high flexibility in choice of materials opens doors for delivering a wide variety of bioactive agents including proteins, antibiotics and anticancer drugs. The loading of drugs can be carried out by embedding, coating or encapsulation. A plethora of polymers, drugs and signaling molecules can be chosen to mimic the native tissues' structure and function [95]. The electrospun nanofibers have showed excellent capability for cell proliferation and differentiation both *in vitro* and *in vivo*. Hence, the multitude of advantages and the relative simplicity of technique offered by the electrospinning process has made it the most promising fabrication method to develop nanofibrous biomaterials for wound healing applications.

7. Active agent incorporated ECM function mimetic membranes

Under the wound dressings, infection impedes re-epithelialization and synthesis of collagen which slowdowns the process of healing. In order to prevent bacterial infection, wounds must also be treated with wound dressings containing bioactive agents. In this sense, it is desirable to incorporate antibiotics such as penicillin and methicillin in wound healing patches and dressings [96]. Sustained release of bioactive molecules with anti-inflammatory and anti-bacterial properties from electrospun fibers can be achieved for days to months, which is useful for wound healing. Complex cellular activities which require growth factors, proteins and so on also have a major role in tissue repair and wound treatment [97]. Major classes of active agents integrated into ECM mimetic fibers are drugs, biological molecules and nanoparticles (Fig. 3).

7.1. Drug-loaded nanofibers

High drug loading potential of electrospun nanofibers are exciting for drug delivery applications in wounds [98]. Despite the microbial barrier properties [18,99], nanofibers alone are rarely able to adequately satisfy both wound healing and disinfection requirements. For this reason, they need to be loaded with functional agents which can promote the rate of healing and have anti-bacterial properties. VC-2-p (L-ascorbic acid 2-phosphate) loaded silk fibroin (SF) imparts L929 cell adhesion and proliferation [100,101]. Traditionally, antibiotics are introduced into nanofibers by combining them into the polymer, accompanied by blend electrospinning or core-shell electrospinning in which the bioactive drug is contained within the polymeric outer shell. Various reports of drug loaded electrospun ECM mimetic membranes and their features are provided in Table 1. Metronidazole-loaded chitosan/polyethylene oxide (PEO) nanofibers provided promising outcomes in the management of wound infections [102]. Sadri et al. developed a PEO/Chitosan (CS) electrospun nanofibers with cefazolin and observed that 1% of cefazolin loaded fibers exerted sufficient anti-microbial activity against *Staphylococcus aureus* and *Escherichia coli* [103]. Charernsriwilaiwat et al. showed that electrospun chitosan and PVA membranes loaded with ethylenediaminetetraacetic acid (EDTA)

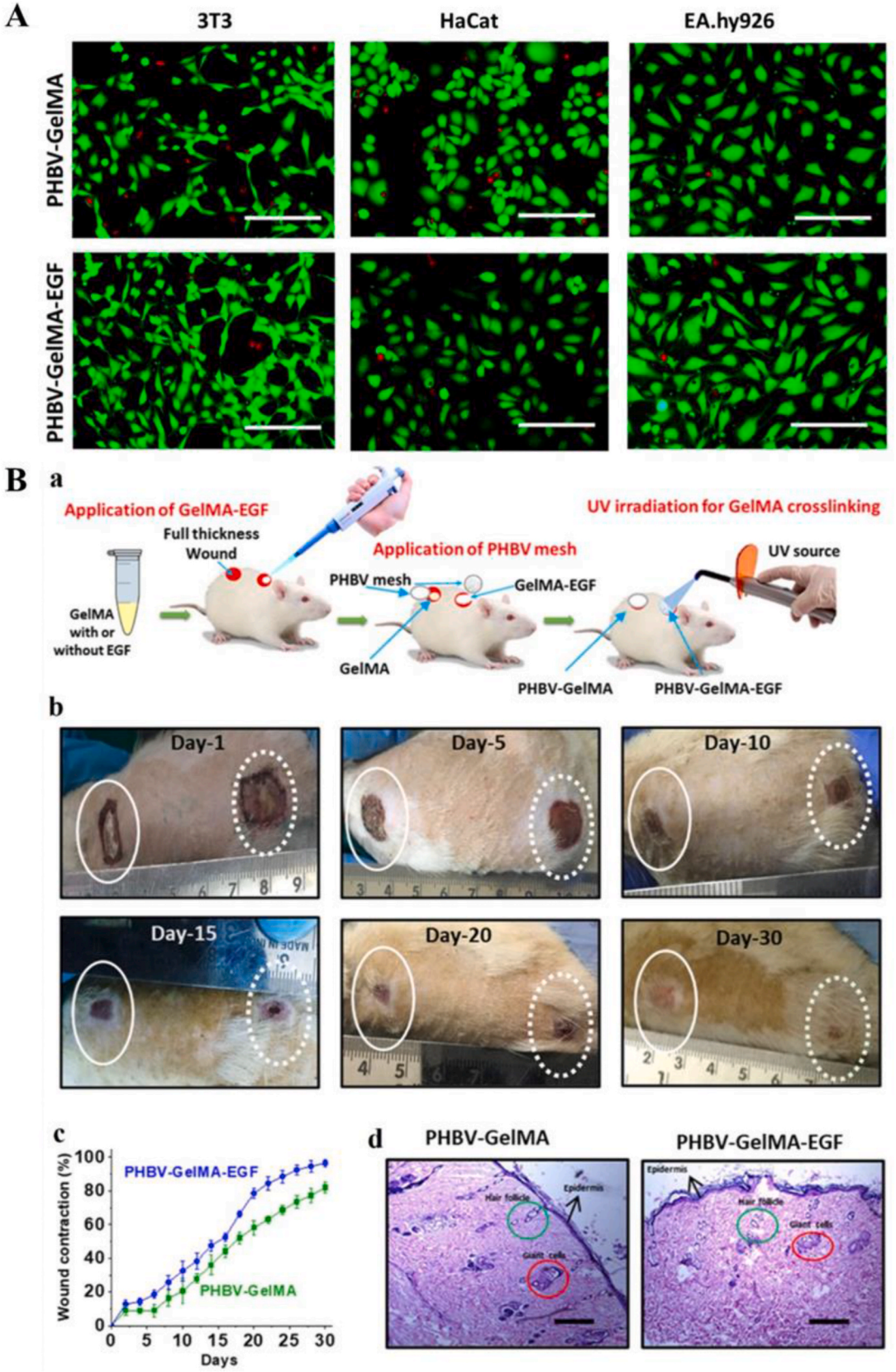

Fig. 4. A. Results of the Live/Dead assay indicating the changes in the morphology of keratinocytes and endothelial cells when cultured with EGF loaded patches (PHBV-GelMA-EGF). **B.** (a) Schematic depiction of the steps for the in-situ crosslinking of patches in wounds and evaluating wound healing ability of the patches. (b) Photographs showing the healing wounds, circles indicate wounds treated with PHBV-GelMA, and doted circles indicate wounds treated with PHBV-GelMA-EGF hybrid patches. (c) Rate of wound contraction plot and (d) the histological analysis of healed wounds. Scale bars in histology images: 200 μm. Reproduced from Ref. [18] with Creative Commons Attribution License (CC-BY-0.4).

Table 3
Electrospun membranes loaded with nanoparticles for wound healing applications.

S. No	Polymer	Nanoparticles	Other Active Agents	Properties	Ref.
1	PCL-Collagen	Chitosan	–	Enhanced hydrophilicity, water-uptake, and blood compatibility, and better wound healing	[75]
2	PCL	TiO_2	–	Improved cell migration, proliferation, angiogenesis, and wound healing	[183]
3	Collagen	Ag	–	Improved antimicrobial efficacy	[184]
4	PCL	CeO_2	Gelatin	Enhanced cell proliferation and viability by three folds	[185]
5	Polyurethane	Ag	lavender oil	Improved hydrophilicity, proliferation of chicken embryo fibroblasts, antibacterial efficiency.	[186]
6	CS-PVA	Ag	–	Improved antibacterial and wound healing properties	[187]
7	PVA-CS	Carboxymethyl chitosan	–	Enhanced antibacterial properties and wound healing	[188]
8	PCL-PEG	Fe_3O_4	–	Improved cell adhesion	[189]

and hydroxy benzotriazole (HOBt) could effectively inhibit both gram-positive and gram-negative bacteria [104]. It has also been reported that tetracycline hydrochloride (TCH) loaded PLLA core/shell nanofibers could provide a sustained drug delivery for up to 30 days [105]. Ampicillin loaded core/shell nanofibers were also reported as ECM mimetic antimicrobial membranes with potential for wound healing applications [106]. Functionalizing the surface of nanofibers with antimicrobial peptides and amino acids is another way to generate ECM mimetic antibacterial wound dressings [107].

Owing to the drawbacks of side-effects of synthetic substances in the human body, plant-derived compounds like essential oils are incorporated in ECM mimetic wound dressings [108–110]. They could provide antioxidant, and anti-inflammatory properties when mixed with nanofibers and promote wound healing. Most common essential oils that have been used widely for their antibacterial effects in wound healing matrices are cinnamaldehyde [111,112], thymol analogues [113–115], menthol [116] and carvacrol [117,118]. Honey is another bio-derived product that is used in electrospun membranes which help in skin repair by promoting cytokine release and tackle infection by stimulating the reaction of the immune system [119,120]. The dressings based on co-axial electrospun membranes provide a slow release of loaded drugs to ensure long term therapeutic efficacy. Ketoprofen (KET)-loaded cellulose acetate (CA) co-axial nanofibers provided a better zero-order drug release profile [121]. Mineral oil/CA/PCL tri-axial nanofibers have shown to improve the proliferation of endothelial cells because of their controlled drug release profile [122].

There is more scope for research in the development of drug-loaded wound dressing materials where the drug release profile can be controlled so as to take into consideration the dynamicity of the native ECM in wounds.

7.2. Growth factor-loaded nanofibers

Growth factors are bioactive macromolecules that are capable of regulating cell division, proliferation, differentiation, and metabolism during wound healing [43,123,124]. A broad range of growth factors and cytokines, especially epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), etc. influence the different phases of the wound healing like granulation tissue formation, regulation of inflammatory response, and the promotion of angiogenesis [7,125–127]. In addition, growth factors are also necessary for ECM formation, remodeling and the re-epithelialization processes [128–130]. The topical administration of growth factors, however, has many drawbacks, such as poor *in vivo* stability, decreased absorption through the skin, removal by exudation before reaching the wounded location, and many other unwanted side effects due to high local concentrations. Table 2 provides the details of reports that used growth factor loaded electrospun membranes for wound healing applications. For instance, Lee et al. demonstrated the development of recombinant human platelet-derived growth factor (rhPDGF) -loaded PLGA-collagen ECM mimetic scaffold where they observed a continuous release of growth factors from the patches which promoted chronic wound healing [131]. Core-shell fibers based on polylactic acid (PLA) and PVA could facilitate sustained release of connective tissue growth factor (CTGF) and promoted cell proliferation, cell migration and angiogenesis [132]. Nanopores present on the surface of ECM mimetic PLA shell ensured the slow and long-term release of CTGF from PVA core. Approaches like co-spinning of hydrophilic polymers (E.g. PVA) loaded with growth factors (E.g. stromal derived factor, SDF1) and a mechanically stable polymer like PCL would also form a robust approach to generate ECM mimetic functional fibrous membranes [133]. Studies also have shown that incorporating EGF in a suitable hydrogel and infiltration of this hydrogel-EGF solution in electrospun membranes can generate hybrid patches that provide slow EGF release, higher cell proliferation and rapid wound healing (Fig. 4) [18]. Such a thin coating of GelMA can provide an ECM mimetic microenvironment for the cell proliferation. EGF released from the patch could induce epidermal to mesenchymal transition as evident from elongated morphology of cells [18]. In addition, EGF loaded patches showed higher angiogenesis. Finally, the patches applied on the wounds generated in diabetic rats by an *in situ* crosslinking approach healed much faster than EGF free patches. Thus, the incorporation of GFs into ECM mimetic nanofibers is therefore considered as a promising approach for expediting wound healing process.

7.3. Nanoparticle-loaded nanofibers

Due to the large surface area, tunable size with low dispersion sizes, easy functionalization and multifunctional capabilities, various inorganic nanoparticles including gold, silica and quantum dots have been emerged as attractive in wound healing applications as antimicrobial agents and drug carriers [134]. In fact, because of the inherent strong antimicrobial property, nanoparticles based on metals and metal oxides have been used as the possible solution for the treatment of drug-resistant bacterial infections [135–137]. By using electrospinning and related techniques, many nanostructures have been integrated into electrospun polymeric wound dressings to promote overall wound healing (Table 3) [138,139]. Use of metallic (silver and gold) and metal oxide (primarily oxides of zinc, titanium, copper and iron) nanoparticles had been the focus of majority of these reports [140–142]. In order to improve the wound healing and simultaneously avoid infection, Rath et al. synthesized gelatin nanofibers containing ZnO nanoparticles and cefazolin [143]. Zn, as a metalloprotein cofactor, is essential for ECM regeneration. In another study, effect of zinc oxide (ZnO) nanoparticles

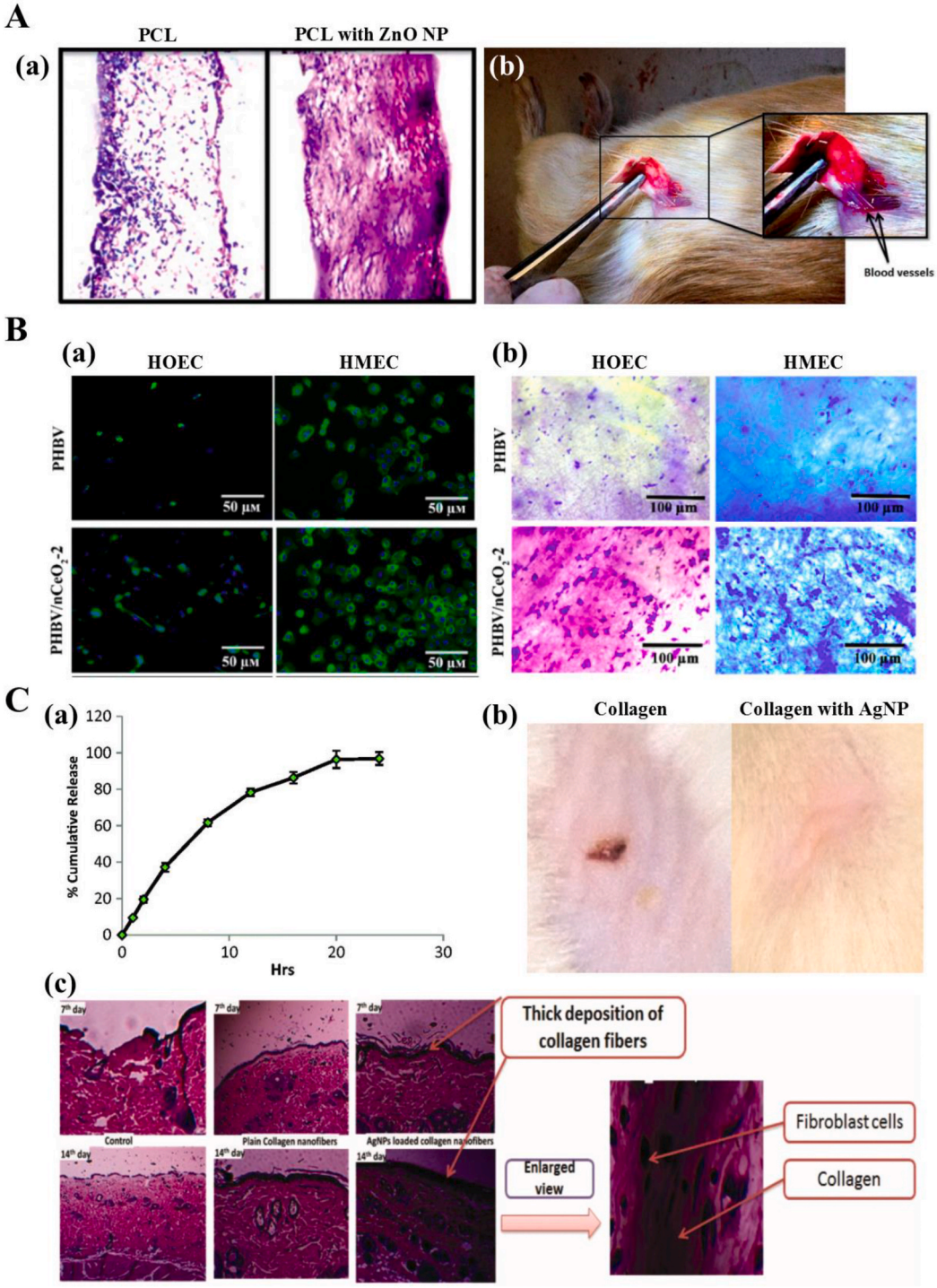

Fig. 5. A. Effect of zinc oxide (ZnO) nanoparticles on wound healing when loaded in electrospun PCL membranes. A(a) Histology cross sections showing the migration and proliferation of cells through PCL and ZnO loaded PCL membranes after 20 days of implantation in guinea pig, A(b) The implanted PCL scaffolds containing 1 wt% ZnO NPs after 20 days of the subcutaneous implantation indicating the development of matured blood vessel. B. Effect of cerium oxide nanoparticles ($nCeO_2$) on cell adhesion and proliferation when loaded in electrospun PHBV membranes. Adhesion and proliferation of human oral epithelial cells (HOEC) and human mammary epithelial cells (HMEC) on PHBV membranes imaged after B(a) DAPI- Phalloidin staining and B(b) crystal violet staining. C. Wound healing potential of silver nanoparticles (AgNP) loaded collagen fibers in rat models. C(a) Release of Ag ions from the nanofibers (Collagen with AgNP), C(b) Wound healing in rats after 15 days of treatment with collagen and AgNP loaded collagen membranes, and C(c) Histology of healed skin tissue after treatment with blank collagen nanofibers and AgNP-loaded collagen nanofibers (7th and 14th days). The thick deposition of the collagen matrix, which is connected to the dense population of fibroblast cells, is represented by Arrow. Figure A(a) is reproduced/Adapted from Ref. [191] with permission of The Royal Society of Chemistry. Figure A(b) is reproduced/Adapted from Ref. [192] with the permission of The Royal Society of Chemistry. Figure B is reproduced from Ref. [144] with the permission of American Chemical Society. Figure C is reproduced from Ref. [184] with the permission of Taylor and Francis online. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

on wound healing was studied when loaded in electrospun PCL membranes. Fig. 5-A(a) shows histology cross sections showing the migration and proliferation of cells through PCL and ZnO loaded PCL membranes after 20 days of implantation in guinea pig. Subcutaneous implantation of ZnO nanoparticles loaded PCL led to the development of matured blood vessels (Fig. 5A(b)). The incorporation of cerium oxide nanoparticles ($nCeO_2$) in electrospun poly(3-hydroxybutyrate-co-3-hydro xyvalerate) (PHBV) membranes resulted in increased adhesion and proliferation of human cells as well as higher wound healing in diabetic rat models (Fig. 5B) [144].

For infections that occur in burns, open wounds, and chronic ulcers, silver is considered as a major antibacterial agent. Ag nanoparticles were also used antimicrobial agents in polymeric nanofibers developed for wound healing applications and offered good promise for resolving the main problems posed by microbial infections [145,146]. The wound healing potential of silver nanoparticles (AgNP) loaded collagen fibers was studied in rat models where a thick deposition of collagen fibers was observed for AgNP-loaded mats (Fig. 5C). However, the agglomeration of the nanoparticles in the nanofibers is an obstruction which could, in particular, compromise the antibacterial effectiveness of these nanoparticle systems [147,148]. Metal oxide nanoparticles such as TiO_2 [149–151], MgO [152,153], and ZnO [154–156] have also been examined for their antimicrobial properties. Zirconium oxide (ZrO_2) nanoparticles have also been incorporated in ECM mimetic electrospun membranes due to satisfactory antibacterial and antifungal efficacy [157,158]. Bioactive glass nanoparticles loaded collagen/PCL ECM mimetic nanofibrous membranes was shown to improve endothelial cell proliferation and thus can be considered as a promising candidate for wound healing applications [159].

Therefore, nanoparticles offer various native ECM mimetic antibacterial properties along with the possibility to attach drugs or other active agents on them which can be released at the wound site in a controlled manner.

8. Challenges and prospects

Having low mechanical strength, especially for natural polymer-based membranes, prevents the widespread use of the otherwise beneficial functions of electrospun nanofibers. Incorporation of various nanofillers in polymer matrix and blending with mechanically robust polymers are tried as the potential strategies to improve the mechanical properties of electrospun membranes. However, exactly mimicking the mechanical properties of electrospun membranes with that of ECM of various tissues is still challenging. Future research may focus on this direction where tissue specific ECM mimetic scaffolds with matching tensile strength, modulus and elasticity will be developed. In addition, biofouling is another major challenge that limit the widespread clinical use of nanofibrous membranes. Loading of antibiotics or antimicrobial nanoparticles in electrospun nanofibers have been reported to address such shortcomings of electrospun membranes. It is desperately important to increase the efficiency of spinning machines and to scale up the infrastructure for commercial manufacturing which are the big challenges at this stage.

Incorporation active agents such as growth factors, peptides and growth factors is very necessary to generate ECM mimetic functional scaffolds that can support cell adhesion, cell proliferation and wound healing [160]. However, loading of such agents in synthetic polymer based electrospun fibers is a challenging task as most of such synthetic polymers can only be dissolved in organic solvents [161] or acids. Most of the biological molecules are damaged or lost the functional attributes when introduced in organic solvents or acids [162]. Introduction of co-axial spinning where a core of hydrophilic polymer loaded with the active agent surrounded by a mechanically stable synthetic polymer is a promising approach to solve this challenge [132]. Loading of active agents in hydrophilic polymeric nanoparticles or nanotubes and incorporation of such nanostructures in electrospun membranes could be another approach to protect labile molecules.

In addition to the electrospinning-based methods alone, combination of multiple techniques such as the integration of 3D printing or bioprinting, cell-loaded hydrogel based electrospun membranes, may be another interesting solution. In fact, it can result in structures that have a high degree of resemblance to native ECM and native tissue using a mixture of specifically cell-laden hydrogel along with a regulated distribution of nanofibers. In addition, other beneficial techniques will be to use different methods to promote cell movement to non-woven structures, such as the application of electrical fields, the production of gradient properties (i.e., stiffness, pore diameter, porosity, etc.) within the scaffold. To sum up, there are already many new challenges with the use of electrospun membranes for wound healing applications which need to be meticulously solved in order to direct electrospun membranes towards the realization of ECM mimetics and thereby opening new doors for broader clinical applications in the future.

9. Conclusions

New developments in fabrication techniques and biomaterial sciences catalyze the development of biomaterials that replicate the features of biological structures thereby guiding the realization of intact tissue regeneration. Providing a suitable environment for the regulation of differentiation, growth and migration of cells, the developed biomaterials that are having analogous structural, chemical and functional properties is necessary to mimic the native ECM. To further advance the research in the tissue regeneration, new therapeutic strategies related to creating favorable biochemical environments which can promote wound healing have been developed. The recent studies focused on the development of ECM mimetic scaffolds and wound healing patches that can protect wounds, provide a scaffold for cell proliferation and accelerate wound healing. The integration of bioactive agents, however, is not always easy, with the challenges associated with their limited stability in organic solvents. Loading of relatively stable nanomaterials as active agents in electrospun ECM mimetic membranes is a recent approach with promising outcomes. It is anticipated that the ongoing efforts, clear understanding on existing challenges and insights on possible solutions result in the emergence of novel approaches that help in the realization of electrospun wound healing matrices that closely mimic ECM.

Credit author statement

Conceptualization: R.A. Investigation: S.N.K., R.A. Resources: R.A., S.N.K. Writing—original draft preparation: R.A., S.N.K., N.V. Writing—review and editing: R.A., S.N.K., A.A.M., Y.B.D., A.H. Visualization: S.N.K., R.A., A.A.M. Supervision: R.A., A.H. Project coordination: R.A. Funding acquisition: A.H. All authors have read and agreed to the published version of the manuscript.

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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