Polymeric wound dressings, an insight into polysaccharide-based electrospun membranes

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ARTICLE INFO

Article history:
Accepted 1 August 2021

Keywords:
Wound dressing
Electrospinning
Polysaccharides
Bioactivity
Crosslinking

ABSTRACT

Chronic wounds deeply invalidate patient's quality of life, involving very high costs for the medical system. Numerous wound dressings have been studied over the years, and active wound dressings replaced traditional passive dressings to promote tissue regeneration and wound closure. Aiming at an optimal reproduction of the physiological environment, electrospun wound dressings are emerging since they mimic the architecture of the extracellular matrix and provide a large contact surface area, enabling exudate absorption and permeability as well as good conformability to the wound site. The use of polysaccharides offers an excellent biomimicry, as they ensure good biocompatibility, biodegradability, and non-immunogenicity. Furthermore, they possess bioactive properties, such as antimicrobial, anti-inflammatory, and antioxidant properties, which can promote and enhance the healing process. The aim of this review is to present the morphological, physical, and chemical features of an ideal wound dressing together with the traditional and the current strategies, and the already commercialized wound dressings. Moreover, the review is focused on the preparation of polysaccharide-based electrospun nanofibrous devices and on the strategies for the modulation and improvement of membrane stability and bioactivity. Lastly, a comprehensive consideration on the process and requirements that lead to the commercialization of the wound dressings is reported.

1. Non-healing wounds

Skin constitutes the largest organ of the human body (Fig. 1), acting as an essential preserving barrier against body dehydration and possible environmental insults (such as pathogens), responsible for weakening organism stability [1].

When a cutaneous damage (namely, a wound) occurs on a healthy tissue, a wound healing process starts progressing through four physiological stages: hemostasis, inflammation, proliferation, and remodeling (Fig. 2) [2].

Immediately after injury, (1) hemostasis takes place, thus platelets arrive into the wounded site, promoting coagulation and preventing further blood loss. Then, the (2) inflammatory response is activated by platelet secreted cytokines (like transforming growth factor-β, or TGF-β, and platelet-derived growth factors, or PDGFs) which allow neutrophils incoming. Neutrophils lie on the injured site for 24 h before undergoing apoptosis and play an antimicrobial role, while triggering the wound healing process; indeed, they secrete cytokines (as inteleukin-17, or IL-17) and growth factors (as vascular endothelial growth factor, or VEGF) which recruit inflammatory cells and stimulate fibroblast, keratinocyte, and endothelial cell proliferation. The (3) proliferation phase starts after 2–3 days and is characterized by granulation tissue formation from fibroblasts; the presence of procollagen, elastin, proteoglycans, and hyaluronic acid offers a good substrate for new blood vessel growth, which guarantees oxygen supply and leukocyte migration. On the other hand, the proliferation of keratinocytes reinforces the protection against the external environment. Meanwhile, cytokines released from neutrophils during apoptosis recruit monocytes, which differentiate in macrophages, increasing the resident proliferating population. Macrophages undergo phenotypical changes to ensure wound resolution, switching from the pro-inflammatory phenotype (M1) to the anti-inflammatory one (M2) and secreting chemokines which activate the T cell response. The crosstalk between all these cell types allows extracellular matrix (ECM) deposition, angiogenesis, and the final phase of (4) remodeling of the ECM through the deposition of collagen and the modulation of matrix metalloproteinases (MMPs) activity, whose deregulation is involved in a delayed wound closure [2–5].

The success of the healing process marks the difference between acute or chronic (non-healing) wounds. Acute wounds gen-

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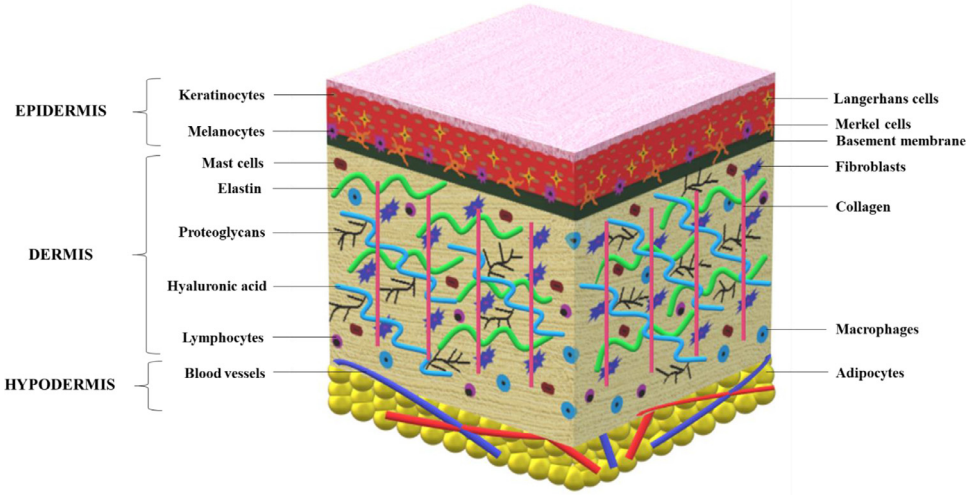

Fig. 1. Skin structure. Schematic representation of skin structure and its main components.

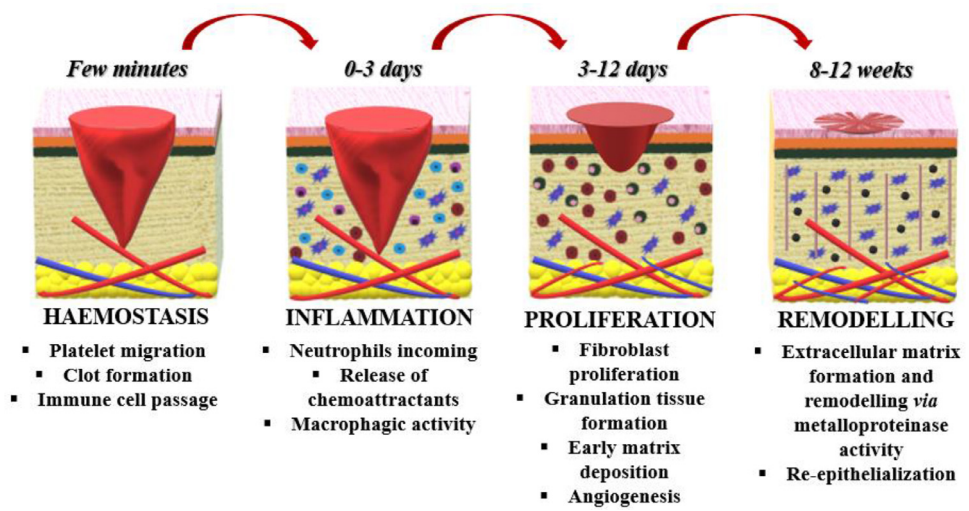

Fig. 2. Wound healing path. Schematization of wound resolution through a normal healing path.

erally refer to abrasions, cuts, skin burns, trauma, surgical injuries, and follow the traditional healing path leading to a complete resolution usually in 8–12 weeks (depending on the extent of the damage across the epidermis and dermis layers) [6–8]. On the other hand, when pre-existing pathological conditions are present (such as diabetes, venous stasis, or autoimmune diseases), the healing process cannot proceed in an orderly and timely manner, causing a persistent laceration of different severity degrees, persisting in the inflammation condition, and paving the way for infections [9–12]. Indeed, with respect to acute wounds, chronic wounds are characterized by lower mitogenic activity and growth factor secretion, suppression of angiogenesis, higher levels of proteases and cytokines, overproduction of MMPs and reactive oxygen species (ROS), resulting in a prolonged inflammatory phase, fibrosis, and destruction of the ECM [13,14].

In a such scenery, chronic wounds constitute a worldwide emergency regarding both patient's quality of life and the national health systems. The prevalence of skin and subcutaneous diseases has been characterized by a notable increase over a 10-years period, ranging from 492 883 in 2005 to 605 036 cases in 2015, as estimated by the Global Burden of Disease (GBD) study, which combines data deriving from seven super-regions, divided into 21 regions (including 195 countries) and implemented with another set of data regarding Brazil, China, India, USA, Japan, Kenya, South Arabia, South Africa, and Sweden; these data have been analyzed for sex, age, and cause of the disease, integrating in a single parameter mortality and years lived with disability [15]. As few representative examples, only in the US chronic wounds require costs of 25 billion dollars per year, with a growth rate of 6 500 patients every year [16]. In the UK, where more than 100 000 ulcers are diagnosed every year, non-healing wounds weigh on the National Health Service for 2.3–3.1 billion dollars per year, which represent about the 3% of the total healthcare expenditure [17]. Further, in Wales the prevalence of wounds reached the 6% between 2012–2013 [18]. Due to the undeniable urgency related to this medical need, numerous efforts have been focused on it during the last years in order to improve patient's life expectancy and contain medical costs.

In this context, this review is focused on the discussion of the current strategies for the treatment of non-healing wounds, in particular wound dressings; presenting the commercialized products, and recent strategies involving bioactive wound dressings and skin substitutes. The review also discusses the use of synthetic polymers and polysaccharides for the preparation of wound dressings, in particular employing the electrospinning techniques, and presents the strategies to improve wound dressings stability and bioactivity. In the end, considerations regarding the clinical application and the commercialization of wound dressings is reported.

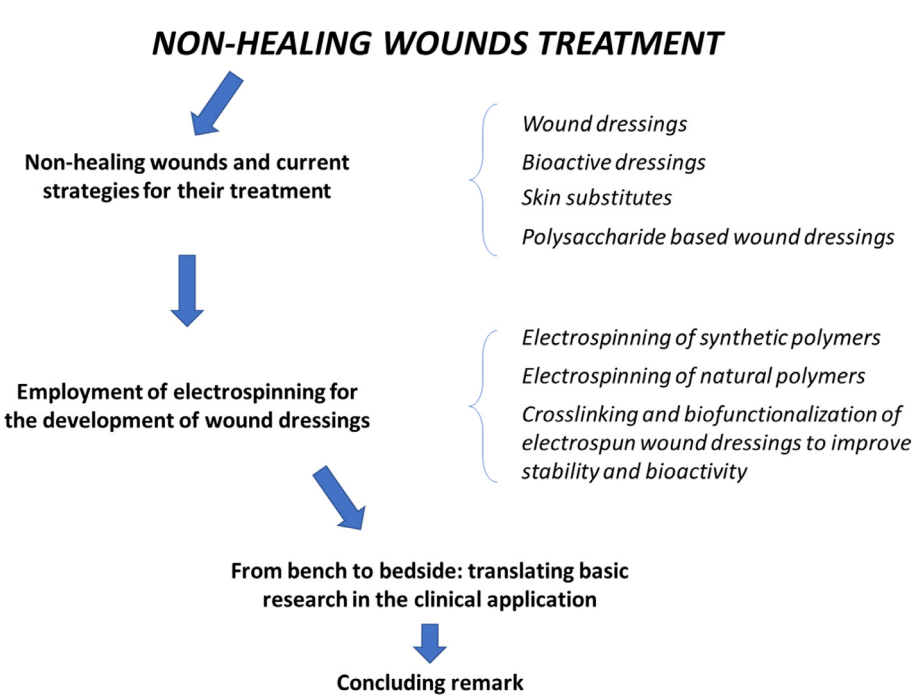

Fig. 3. Schematic representation of the review's content.

A schematic representation of the review's content is reported in Fig. 3.

2. Current strategies

2.1. Wound dressing selection

Wound dressings are devices used to protect the injured site during the healing process, in order to absorb the exudate produced and to improve and accelerate wound closure. An appropriate wound dressing material must be selected considering the pathophysiological process of wound healing and the type of wound to be treated. An exact and univocal definition of an ideal wound dressing is not present, but some characteristics are of paramount importance to allow the regeneration of the damaged tissue (Table 1). For example, a suitable dressing should adapt its shape to the wound site providing at the same time a moist environment; it should also promote cell proliferation and migration (essential for angiogenesis, epidermal migration, and tissue repair), maintain proper tissue temperature, exert an haemostatic action limiting blood loss, prevent bacterial infection while avoiding any immune response to the material itself, and be cost-effective. Furthermore, it should be elastic to support skin mechanical stresses (linear and shear stresses as well as resistance to fragmentation) and designed to minimize the necessity of changes, thus reducing patient's discomfort [19–26]. To this aim, biodegradable devices could be used, if the degradation rate matches the time required for would healing [27,28].

Particular importance must be given to the moist environment, since in 1962 Winter demonstrated that epidermal healing was favored by a moist environment with respect to wounds simply exposed to air and dry conditions [37]. It was observed that a moisturizing context enhances cell regeneration and motility favoring also a suitable enzyme activity, collagen deposition, and epidermal growth factor functionality, thereby promoting tissue recovery. Hence, the maintenance of a moist space where water vapor and gas permeation as well as exudate absorption are allowed are criteria to consider in the production of an effective wound dressing material [38,39].

Traditional wound dressings consist of gauzes, bandages, lint, cotton wool; all these devices protect the wound from infections and allow exudate evaporation, thus preserving a dry environment. However, according to the moist environment principle, these dressings are not the proper ones to obtain complete recovery of the injured site (Fig. 4). For this reason, the attention moved towards a new generation of active wound dressings with the aim to reach the prefixed goal: to prevent the unhealed wound from dehydration and contamination promoting, at the same time, tissue regeneration [40,41].

The main strategies currently in use can be divided in semi-permeable films, semi-permeable foams, hydrogels, hydrocolloids, alginate dressings, bioactive dressings, and tissue engineered skin substitutes (Table 2).

2.1.1. Semi-permeable film dressings

The first semi-permeable film dressings were made up of nylon derivatives implemented with an adhesive polyethylene support. Therefore, they were occlusive dressings unable to retain large amounts of exudates, leading to undesired outcomes, such as liquid accumulation, skin maceration, and bacteria proliferation as well as to the necessity of continuous dressing changes [42]. On the other hand, polyurethane-based semi-permeable films were proven to be more efficient dressings since they are adhesive, well adapt to the wound, and are transparent, thus allowing wound assessment and limiting useless changes with subsequent pain associated. In addition, they retain large amounts of exudates over the wound and promote re-epithelialization since they are occlusive for bacteria and water, but not for air and water vapor; so, in presence of mild exudates, the liquid accumulation is compatible with its evaporation throughout the membrane [43]. Commercial products of this type are Opsite™, Bioclusive™, or Tegaderm™ to name some; they differ for specific characteristics, such as permeability, conformability to the wound, or adhesiveness [44–46].

In the last years, new types of film dressings have been designed, using both natural and synthetic polymers. For example,

Table 1
Schematization of the main features an ideal wound dressing should possess to achieve a faster healing, re-epithelialization, and functional recovery, avoiding scar insurgence [25,29–36].

Wound dressing properties	Relevance
Biocompatibility	It is the first prerequisite of material safeness
Biodegradability	A biodegradable material, which follows tissue regeneration, leaves space to the new healthy tissue also minimizing the need for dressing changes
Non-immunogenicity	No adverse immune response must be directed against the dressing selected
Conformability to the wound	A wound dressing which adapts its shape to the wound site allows an efficient covering and fluid retention. Conformability has not to be confused with sticking to the wound surface, which is not a favorable condition
Moisturizing ability	A moist environment, in which exudate absorption and water vapor/gaseous exchanges are allowed, favors cell viability and migration as well as the deposition of collagen and the functionality of growth factors and enzymes involved in the healing process
Haemostatic activity	Haemostatic wound dressings avoid excessive bleeding, allowing the activation of the coagulation cascade and the healing process
Stimulation of cell migration and proliferation	The simultaneous action of different cell types (as immune cells, endothelial cells, fibroblasts, keratinocytes) allows the regulation of the inflammatory response, the deposition of the extracellular matrix, and the formation of new tissue
Avoidance of pathogen infections	The contamination of the wound compromises the success of the healing process, leading to a chronicization of the inflammation state and to the formation of necrotic tissue
Mimicking of skin architecture and mechanical properties	A wound dressing which recalls native tissue enhances cell colonization, proliferation, and activity leading to re-epithelialization
Maintenance of proper tissue temperature	A decrease in wound bed temperature below normal body values impairs the healing process, due to a reduction in cell activity and consequent slow epithelial regeneration and collagen deposition
Minimization of dressing changes	Dressing changes are painful and, in some cases, could cause secondary tissue damage, lessening the healing process
Cost effectiveness	A manageable and cost-effective material has more chances to encounter the market demand

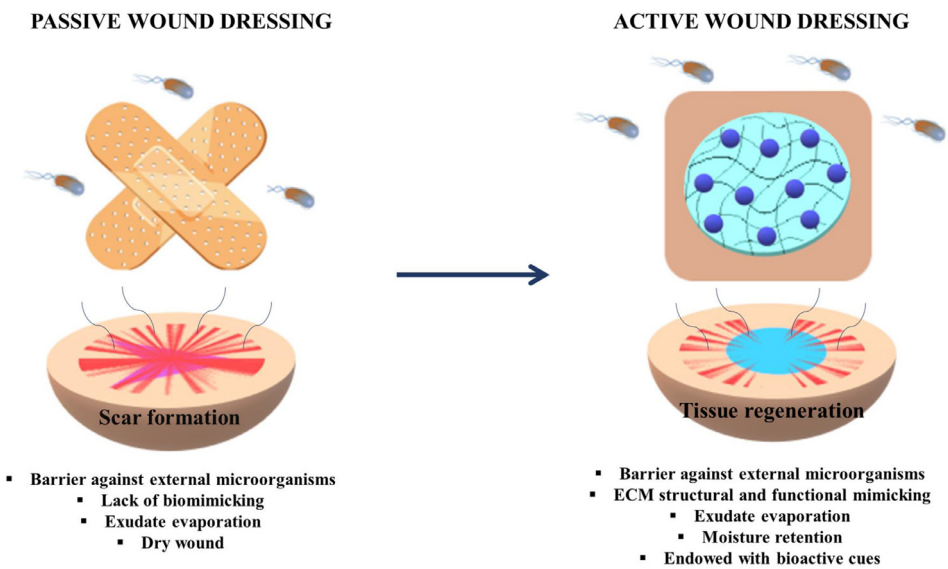

Fig. 4. The evolution of wound dressing employment. Schematic representation of the advantages leading to the choice of active wound dressings as against passive ones.

manageable and insoluble films have been produced from a modified acidic form of carboxymethylcellulose (CMC) implemented with lidocaine hydrochloride, an anesthetic often used in the management of acute wound pain. This matrix showed resiliency in dry state, transparency, adhesiveness, and flexibility after swelling, even if the low swelling degree implies a modest capability to retain exudates. In vitro tests demonstrated a rapid release of the loaded drug, which could be useful in case of local anesthesia [47].

A bi-layered film composed of a polydimethylsiloxane (PDMS) elastomer material has also been characterized and tested on diabetic rats by Wei and coworkers (Fig. 5).

They analyzed dressing biocompatibility and compared it to the commercial product Tegaderm™; similar properties in terms of moisturizing capability, permeability, and adhesion have been detected except for the lower tensile strength and the greater elon-

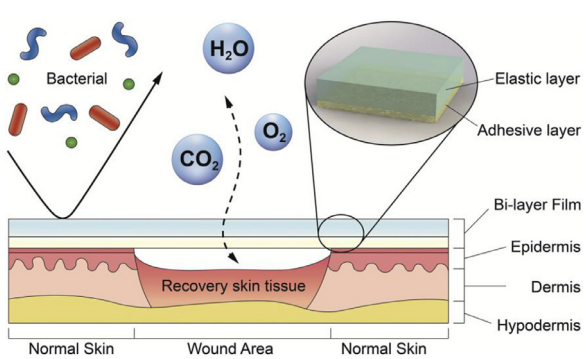

Fig. 5. PDMS bi-layered film. Structure and outcomes of applying the bi-layered PDMS film on a wound. Reprinted from ref [48], Copyright (2019), with permission from Elsevier.

Table 2
Synthesis of the main wound dressings, highlighting their clinical use, advantages and disadvantages.[52–58]

	Semi-permeable films	Semi-permeable foams	Hydrogels	Hydrocolloids	Alginate dressings	Bioactive dressings	Tissue engineered skin substitutes
Clinical use	• Superficial wounds • Infected wounds • Surgical wounds • Burns	• Ulcers • Skin transplants • Mild burns	• Dry wounds • Wounds with medium to moderate exudates • Deep wounds • Fistulas • Surface wounds • Burns	• Venous insufficiency ulcers • Pressure ulcers • Abdominal incisions • Neurosurgical wounds • Burns • Abrasions	• Infected wounds • Blooding wounds • Surgical wounds • Severe burns • Ulcers • Fistulas	• Versatile application depending on the type of wound dressing functionalized	• Severe burns • Deep wounds with loss of tissue
Advantages	• Good gas exchange • Good adhesiveness • Occlusive for bacteria and fluids • High transparency • Low pain	• Flexible • Ability to absorb modest to considerable amounts of exudate • Assisted autolytic debridement • Good water vapor and gas exchanges	• High exudate capacity • Non-adhesiveness • Direct application into the wound • Protective barrier at the wound interface • Necrotic debris removal • Oxygen exchanges • Painless changes • Cost-effective • Easily developed and handled	• Painless removal • Self-adhesiveness • Humidity regulation • Fluid absorption • Assisted autolytic debridement	• No-toxicity • Highly absorbent capability (heavy exudate retention) • Non-adhesiveness • Ability to form gels in presence of exudates • Good bacterial barrier	• Biocompatibility • Biodegradability • Non-toxicity • Low immunogenicity • Accelerated tissue regeneration and functional recovery	• Substitution of the missing tissue • Stimulation of the surrounding tissue to regenerate
Disadvantages	• Adherence to the wound bed • Inability to retain heavy exudates • Impermeable for proteins and drugs	• Poor adhesiveness and stability • Opaque • Not useful for eschars and dry wounds	• Poor mechanical strength • No-effective barrier against bacteria • Possible skin maceration	• Impermeable to gases • Not indicated for infected wounds and diabetic foot ulcers	• Not indicated for dry wounds • Secondary dressings could be needed	• Related to the dressing of choice	• Possibility of rejection

gation at break observed for the PDMS film, which could allow a better contact stability and deformation according to skin movements thereby preserving the moist environment, fundamental in the early stages of healing [48].

Active antibacterial films have been produced too; for example, Hubner and coworkers synthetized a gelatin-based film plasticized with glycerol and enriched with silver-clinoptilolite, a natural zeolite already used in the treatment of skin wounds impregnated with silver ions. The antimicrobial activity was tested on *Escherichia coli* and *Staphylococcus aureus*, showing a glycerol and zeolite concentration dependence with a greater effect on *Staphylococcus aureus* with respect to *Escherichia coli*, although maintaining promising results [49]. Likewise, Jian and coworkers realized a skin-like thermoplastic polyurethane (TPU) bi-layered film functionalized with polyhexamethylene guanidine hydrochloride (PHMG)-grafted graphene oxide (MGO), where PHMG is known for its antibacterial activity against Gram-positive and Gram-negative bacteria and is used for wound disinfection. The addition of graphene oxide increased film porosity and, consequently, the water vapor transmission capability with respect to TPU alone. On the other hand, the long-lasting antibacterial properties were assessed on *Staphylococcus aureus* and *Escherichia coli*; the antibacterial activity increased according to the concentration of MGO examined and it was confirmed over a 30-day period. The MGO-TPU films were then tested in vivo on mice infected wounds, which exhibited wound closure after 9 days and a reduced bacterial viability at the injured site [50].

The semi-permeable films can also be organized in multi-layered systems, intended as more than two layers, with the aim to preserve the biofunctionality of specific molecules incorporated and sustain their controlled release. Tang and coworkers recently used the layer-by-layer assembly technique to develop an eight-layered hyaluronic acid/poly-*L*-lysine film implemented with platelet lysate, since it contains numerous growth factors and proteins, which favor and accelerate the healing process. The films were prepared both in presence or in absence of 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC) as crosslinking agent, showing in any case good hydrophilicity and growth factor absorption capability basing on electrostatic interactions. In vitro studies were carried out on vascular endothelial cells (HUVEC) and fibroblasts validating the biocompatibility of both type of films, while the presence of platelet lysate increased cell adhesion, migration, and angiogenesis with respect to the non-coated systems. The effects of these multi-layered films were also tested in vivo on standard full-thickness wounds, inducing re-epithelialization through granulation tissue formation, collagen deposition, and vascularization after 14 days [51].

Hence, several formulations, obtained varying polymer composition and additive compounds as well as the synthesis procedure, can be thought to produce semi-permeable film dressings; these devices are mostly indicated in case of superficial, frictional, skin-scratching wounds with possible infections. Indeed, they are transparent, flexible, and allow wound assessment and care limiting the pain caused by the contact between the film and the scratch to

be healed; they even maintain an equilibrated moist environment and favor skin regeneration, blocking at the same time the access to external microorganisms and avoiding additional frictions between the new formed skin and the dressing, which could conversely cause illness chronicity. However, their ability to retain exudates is limited and they are not able to maintain the moisture equilibrium over a certain amount of fluid. Furthermore, in some cases they could adhere to the wound bed or seal with wound edges, seriously complicating dressing removal [52,53]. Therefore, in case of high exudate productions, it is necessary to opt for other types of dressings able to retain a large amount of fluid.

2.1.2. Semi-permeable foams dressings

Foam dressings are typically made of polyurethane; they are thick, flexible, and are often used for their ability to absorb modest to considerable amounts of exudate while serving as a cushion over the wound. Furthermore, they promote autolytic debridement and allow water vapor and gas exchanges throughout the wound. Some types of foams do not strictly adhere to skin, so secondary dressings are needed to ensure their stability [59]. This is the case of Cutimed® Siltec, implemented with a silicon layer in order to allow a better contact [60]. On the other hand, multilayered commercial foam dressings have been designed to avoid patient's discomfort, wound adherence, and possible infections, as in the case of Allevyn™, formed by three separate layers (an outer impermeable polyurethane layer, a central absorbent hydrocellular layer, an inner porous layer which avoids epidermal cell migration into the dressing so that it can be easily removed), or Tielle™, another three-layered system made of a polyurethane adhesive and a thin polyurethane foam membrane enriched with a central hydrophilic polyurethane foam layer; the hydrophilic central layer should prevent the dressing from completely drying out, so as to maintain a moist microenvironment, allow non-traumatic removal and gaseous exchanges while acting as a barrier against microorganisms [61,62]. However, careful application on eschars or dry wounds is always recommended, because foams are not generally indicated in these cases; indeed, their high absorption capability could cause wound bed adherence impairing the healing process and causing difficult and painful dressing changes [63].

In the last years, natural polymers have been introduced in the production of foam dressings. As an example, Namviriyachote and coworkers combined polyurethane foam dressings functionalized with silver nanoparticles and asiaticoside with starch, high molecular weight chitosan, and gelatin obtaining an increase in foam stiffness and porosity. Conversely, higher water absorption was achieved by introducing carboxymethylcellulose, alginate, hydroxypropyl methylcellulose, and low molecular weight chitosan. The selected foams were then tested on volunteers having acute dermal wounds showing promising accelerated wound healing without infections or skin reactions [64].

Antibacterial foams have been studied too, as in the case of nanocomposite thermoplastic polyurethane-ZnO foams, which exhibited low cytotoxicity, good biocompatibility, and a significant activity against both Gram-negative (*Pseudomonas aeruginosa, Escherichia coli*) and Gram-positive (*Staphylococcus aureus, Enterococcus fecalis*) bacteria [65].

Xia and coworkers combined antibacterial and haemostatic activity, considering that currently used haemostatic materials does not protect wound against bacterial infections; they synthetized a mesostructured cellular silica foam decorated with silver ions and evaluated its activity towards hemorrhagic *Escherichia coli* infected wounds. Both the in vitro and the in vivo models revealed the ability to inhibit bacterial growth, with a stronger effect in presence of higher silver ion concentrations, while the haemostatic ability was not affected by the introduction of the antibacterial agent [66].

Hence, semi-permeable foams are moisture-retentive dressings useful in case of ulcers, skin transplants, or mild burns associated with mild to heavy exudates, but they are generally contraindicated for eschars or dry wounds. If compared with other types of dressings (as alginates), they require more frequent changes and their poor transparency does not allow proper wound assessment to avoid dressing removal. Furthermore, foams often need secondary dressings to stabilize at the wound site and could be associated to malodorous emissions. So, they must be properly selected considering the localization and the size of the wound to be healed as well as the volume of exudate produced [52,67].

2.1.3. Hydrogel dressings

Hydrogels are crosslinked polymeric three-dimensional matrices, which can contain up to 90% of liquid, usually water. Because of their water-retention ability, they stand out as ideal wound dressings; indeed, they can provide water to dry wounds, absorb exudates, and ensure at the same time a moist environment. Additionally, hydrogels serve as a protective barrier at wound interface, contribute to necrotic debris removal, and favor oxygen exchange through the surface. They also limit the pain associated with dressing substitution and their properties (chemical, mechanical, physical, as well as flexibility) can be modulated in a precise manner [68–70].

Due to their great versatility, a variety of hydrogels has been proposed over the years, ranging from synthetic to natural polymers and possessing the most disparate properties in view of skin regeneration. Poly(vinyl alcohol) (PVA) is one of the oldest synthetic polymers used for wound healing applications, being biocompatible, biodegradable, and showing good mechanical properties [71]. However, its swelling capacity as well as its mechanical properties must be improved to allow skin repair, combining PVA with different types of polymers, such as polyvinylpyrrolidone (PVP) [72], poly(ethylene glycol) (PEG) [73], or poly(ethylene oxide) (PEO) [74]. Jin and coworkers developed a triple polymer hydrogel dressing composed by PVA and two hydrophilic polymers, namely PVP and sodium alginate (SA), where PVP enhanced the adhesiveness and the mechanical properties, while SA improved the swelling capacity. This system was further implemented with sodium fusidate, which acts against *Staphylococci* and other Gram-positive bacteria; in vivo studies carried out in comparison with commercial hydrogel treated wounds revealed a faster recovery with a lower level of severe inflammation in case of the triple polymer hydrogel, confirming the sustained release, permeation, and deposition of the antibacterial compound along with the ability of the hydrophilic polymer to maintain a moist environment and favour cell migration and proliferation [75].

The versatility of hydrogels regards not only their composition, but also their production method or administration way. A 3D-printed biodegradable and thermosensitive chitosan-pectin hydrogel loaded with lidocaine hydrochloride has been studied by Long and coworkers, displaying good printability, dimensional integrity, flexibility, and adhesion properties besides the swelling and water absorption ability [76]. Hydrogels can be even formed in situ to seal the wound site. Konieczynska and coworkers realized an in situ forming dendritic hydrogel-based dressing for second-degree burns. This dressing served as a barrier against bacteria and, thanks to the presence of thioester linkages, it could be dissolved on-demand through the addition of a cysteine methyl ester solution, allowing for dressing removal without painful mechanical debridement [77]. On the other hand, Qu and coworkers developed a conductive and antioxidant injectable hydrogel by combining N-carboxyethyl chitosan (CEC) and oxidized hyaluronic acid-graft-aniline tetramer (OHA-AT) (Fig. 6).

These hydrogels exhibited good rheological properties, swelling aptitude, free radical scavenging capacity, biodegradability, antimi-

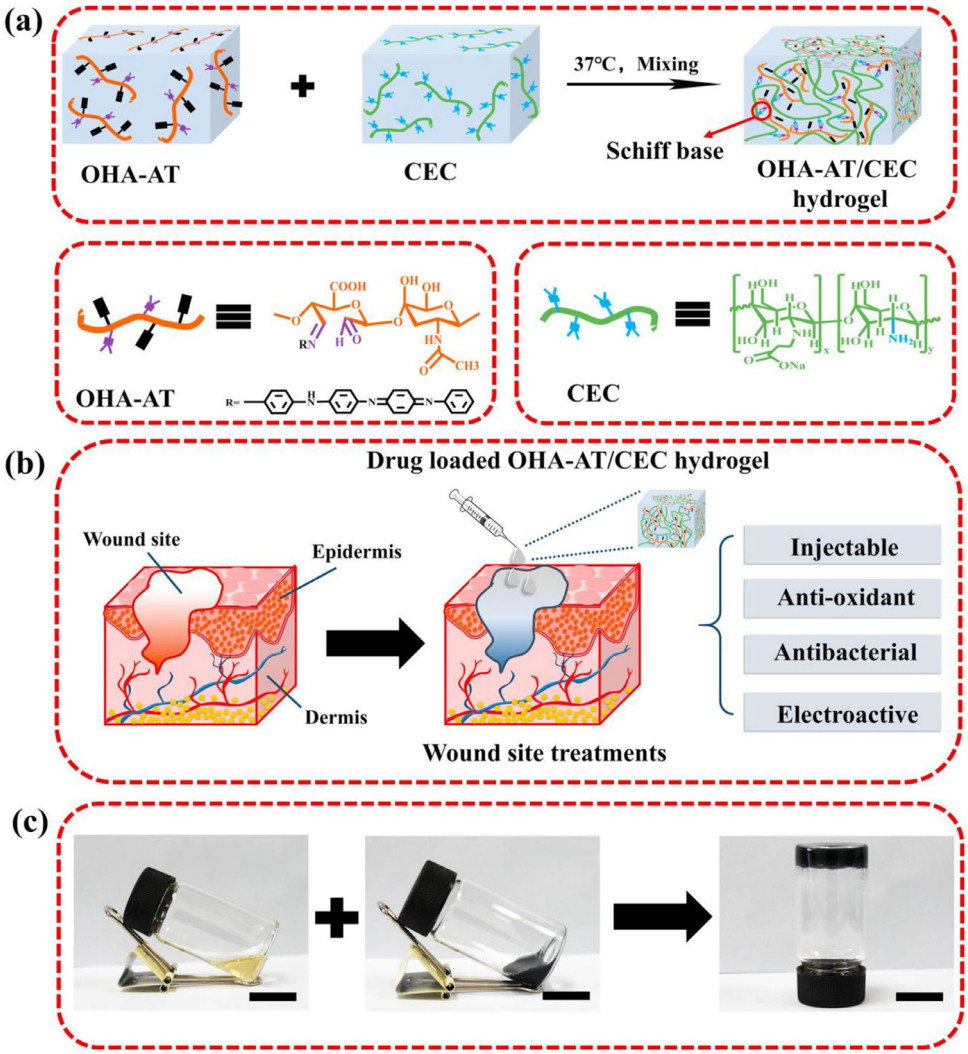

Fig. 6. Hydrogel wound dressing. Schematization of (a) OHA-AT/CEC hydrogel synthesis and (b) application on full-thickness skin injuries. (c) Illustration of the bulk solutions and hydrogels formation. Scale bar: 1 cm. Reprinted from ref [78], Copyright (2019) with permission from Elsevier.

crobial activity (when implemented with amoxicillin), and ability to stimulate a faster regeneration in in vivo models if compared to commercial products [78]. Numerous hydrogel-based products, such as TegaGel®, Nu-Gel®, Carrasyn® Gel are commercially available; their employment varies from chemotherapy peels to ulcers, laser resurfacing, or average thickness wounds. Hence, hydrogels have a wide range of applications, as they stimulate epithelial regeneration by promoting fibroblast and keratinocyte migration and wound debridement. They also possess proper elasticity and flexibility due to the tissue-like water content and are transparent enough to allow wound monitoring. Nevertheless, their employment is hampered by their poor mechanical stability together with their scarce ability to act as bacterial barrier alone, so antimicrobial additives are needed to avoid wound contamination and different polymers must be combined to obtain composite hydrogels with enhanced mechanical properties. In addition, the high-water content present at the injured site can cause, in some cases, skin maceration and dressing immersion in the surrounding tissue. Consequently, the choice of hydrogels must be weighed on the amount of exudate that the wound is able to produce [53,58].

2.1.4. Hydrocolloid dressings

Hydrocolloids wound dressings are interactive absorbing dressings composed by a hydrophobic pressure sensitive adhesion layer (continuous phase) and a hydrophilic filler (dispersed phase). They are designed to allow self-adhesiveness and humidity regulation, while providing the absorption of fluids and autolytic debridement of necrotic tissue [79,80]. The continuous phase is often represented by elastomers or adhesives (such as styrene-isoprene-styrene copolymer and polyisobutylene), while the dispersed one is characterized by gel forming agents (as carboxymethylcellulose, gelatin, or pectin). The hydrophilic phase highly absorbs wound exudates turning into a hydrophilic gel, thus eliminating the excess of liquid while preserving skin from desiccation. Simultaneously, the hydrophobic part protects against infection and maintains proper wound temperature [8,81,82].

Hydrocolloids are one of the most largely employed wound dressings; they are used, for example, in case of venous insufficiency ulcers, pressure ulcers, abdominal incisions, or neurosurgical wounds, but their application is discussed in presence of diabetic foot ulcers; even if they are more expensive than traditional dressings (like gauzes or plasters), the lower number of changes needed make them similarly cost-effective [79,83–86]. Due to their ease and painless removal, hydrocolloids are particularly indicated for pediatric wounds. A clinical trial carried out by Martin and coworkers in 2010, revealed the efficacy of a commercial hydrocolloid dressing (DuoDERM®) with respect to a paraffin-based gauze on a cohort of pediatric patients having dermal burns of differ-

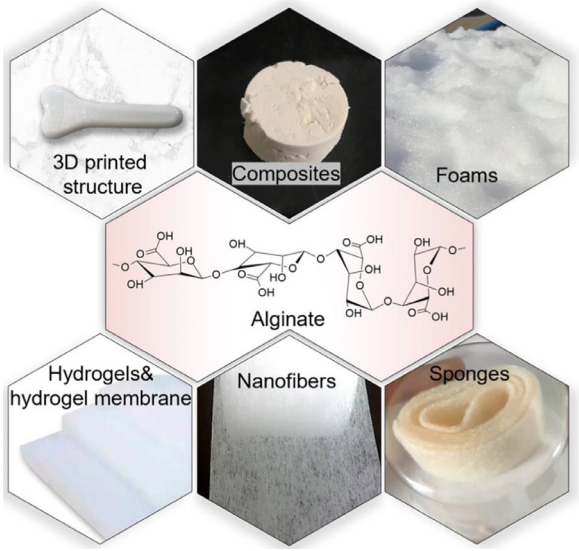

Fig. 7. Alginate applications. Illustration of some possible uses of alginate as bulk material in biomedical products. Reprinted from ref [91], Copyright (2020) with permission of Elsevier.

ent degrees of severity; in presence of DuoDERM® a faster healing process was observed and re-epithelialization was favored reducing the need for surgical intervention and debridement [87]. Other numerous commercial products are available on the market (as Comfeel™, Tegasorb™, Cutinova® Hydro). They favour granulation and epithelialization and easily adapt and adhere to the wound, even when applied on high-friction areas. Nevertheless, like semi-permeable foams, hydrocolloids can produce malodors due to dressing disruption and, above all, their application is not recommended if the wound or the surrounding tissue are infected, since the hypoxic and excessively moist environment created by this type of semi-occlusive dressing could enhance necrotic tissue autolysis and predispose favorable conditions for infections. In these cases, the choice moves towards more appropriate dressings [54,57,88].

2.1.5. Alginate dressings

Alginate is a polysaccharide copolymer mainly obtained from brown algae (*Laminaria hyperborea, Laminaria digitata, Laminaria japonica, Ascophyllum nodosum*, and *Macrocystis prrifere*), characterized by a linear repetition of (1 → 4)-linked β-*D*-mannuronic acid (M) and α-*D*-guluronic acid (G) residues. This repetition can occur in equal (MM or GG) or alternated blocks (MG), conferring peculiar characteristics in terms of physicochemical properties [89]. It is biocompatible, biodegradable, and in presence of divalent cations (especially Ca^{2+}) it undergoes ionotropic gelation, during which G residues reorganize in a specific structure, namely the "egg-box". This ability has been largely exploited for different biomedical purposes [90], such as the production of wound dressings (Fig. 7). Alginate dressings are non-toxic, highly absorbent, non-adherent, and, in presence of wound exudates, they form highly hydrated gels. Alginate dressings are designed in two different formulations: one rich in mannuronic acid (as Sorbsan™ or Tegaderm™ Alginate Ag), which forms more flexible gels after exposure to fluids; the other one rich in guluronic acid (like Kaltostat™ or SeaSorb™), which results in stronger gels when hydrated.

When the dressing is applied on a wound, considerable quantities of calcium ions are replaced over time by sodium ions present in the wound bed, leading to gel formation and producing a moist environment, which stimulates tissue regeneration. This ion exchange is relevant during the hemostasis process, since calcium ions released play an active role in the coagulation cascade; the release of calcium ions even depends on the proportion of G to M residues [92–94]. Moreover, alginate dressings have been proved to interact with the wound environment through macrophages activation and the secretion of tumor necrosis factor-α (TNF-α) and pro-inflammatory cytokines (possibly mediated by the interaction with $CD4^+$ lymphocytes), whose regulation and equilibrium are of pivotal importance in the success of the healing process [95].

Alginate dressings have been produced in different forms, such as films, foams, fibers, hydrogels, and hydrocolloids, in view of skin regeneration [96]. Great importance has been given in the last years to the antibacterial effect of alginate dressings. For example, Chen and coworkers created an oxidized alginate/carboxymethyl chitosan hydrogel implemented with tetracycline hydrochloride encapsulated in gelatin microspheres, noticing a sustained antibiotic release and an antibacterial effect against *Escherichia coli* and *Staphylococcus aureus* [97]. Likewise, alginate antibacterial films have been synthetized through the functionalization with silver sulfadiazine, showing low cytotoxicity on fibroblasts, but inhibiting at the same time bacterial growth (*Salmonella enterica, Escherichia coli* and *Staphylococcus aureus*) [98]. The anti-hemolytic properties of alginate dressings have been also combined with the antimicrobial activity through the synthesis of quaternary ammonium salts of alginate using triethylammonium, tributylammonium and dihexylammonium. Among these, tributylammonium-alginate showed the best anti-hemolytic and antibacterial activity (against *Staphylococcus aureus* and *Escherichia coli*) associated with the lower cytotoxic effect. In vitro and in vivo analysis confirmed the successful healing of full-thickness defects in presence of tributylammonium-alginate mats [99].

Despite of all their advantages, alginate dressings should not be applied on dry wounds, inasmuch their hydrophilicity would attract wound bed fluid leading to a burning sensation for the patient. Indeed, as mentioned above, alginate dressings are high absorbent materials and are able to recall high volumes of water; consequently, in a dry environment, also the little amount of fluid lying in the wound bed is absorbed by the dressing causing skin dryness and a burning sensation. Moreover, in these conditions an increased pressure could be exerted on the wound bed impairing the healing process and causing the formation of necrotic tissue [55]. This implies that monitoring the wound healing state is a key step in wound care management as well as in the selection of the appropriate wound dressing.

2.1.6. Bioactive dressings

Bioactive wound dressings are an extended class of dressing materials including all the biomaterials able to actively stimulate wound healing, by drug delivering mechanisms or thanks to the natural properties of the polymers used for their synthesis [100]. Indeed, many natural polymers (chitosan, hyaluronic acid, collagen, alginate, elastin, to name some) possess bioactive features such as antimicrobial, haemostatic, anti-inflammatory activities, biodegradability, low immunogenicity and toxicity; these properties make natural polymers suitable candidates in the field of regenerative medicine [101–105]. In other cases, materials can be endowed with active compounds, which could enhance tissue regeneration and functional recovery. As an example, mixtures of chitosan and hyaluronic acid have been used to realize wound dressings implemented with chlorhexidine diacetate, an antimicrobial drug, obtaining a modulated release and an antibacterial and antifungal effect towards *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa*, and *Candida albicans* [106]. Similarly, a quaternized chitosan nanocomposite film has been functionalized with silver nanoparticles proving its antifungal activity against *Candida albicans* and its antibacterial action against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* as

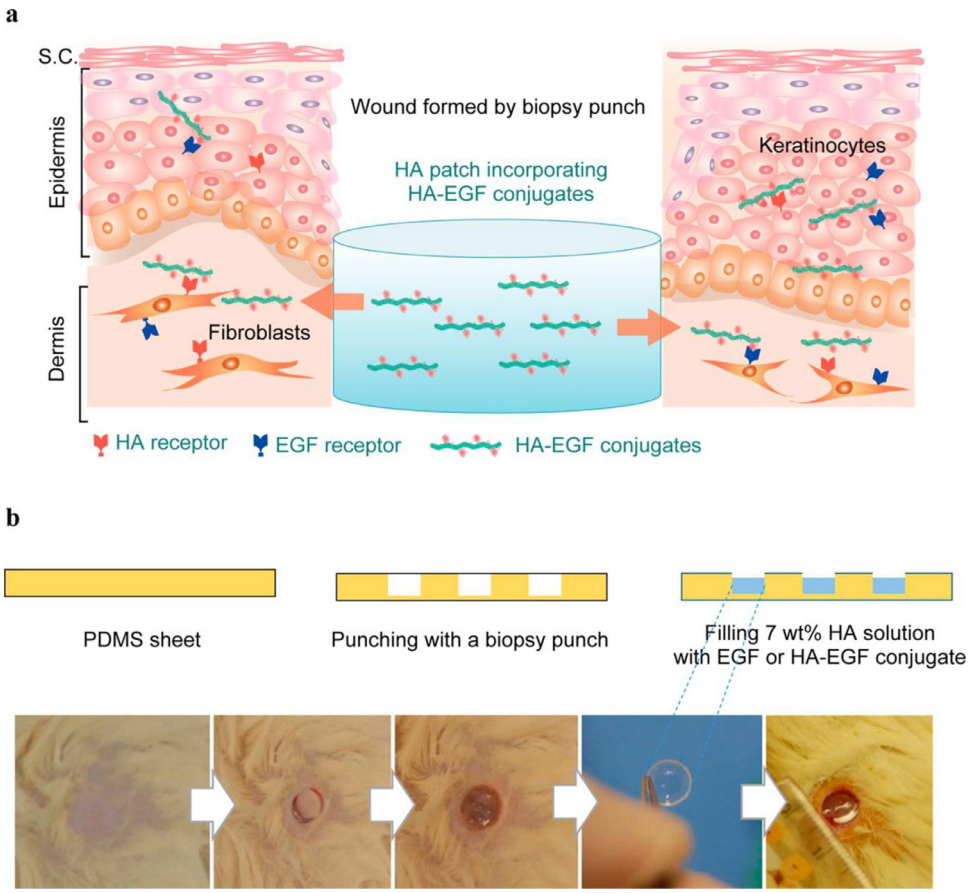

Fig. 8. EGF enriched hyaluronic acid films. Schematic representation of (a) how HA patch films enriched with HA-EGF conjugates deeply interact with the surrounding skin tissue and of (b) their administration on a mouse model wound. Reprinted with permission from ref [108]. Copyright (2016) American Chemical Society.

well as towards a multi-drug resistant strain of *Pseudomonas aeruginosa*, by regulating silver nanoparticle content [107]. The functionalization with growth factors has also been examined as an efficient strategy to ameliorate the healing process. For example, epidermal-growth factor (EGF) promotes tissue regeneration by stimulating cell growth, proliferation, and differentiation. To improve its half-life and prolong its action, with respect to the topical administration, it has been conjugated to a hyaluronic acid film and its biological activity has been tested through in vitro and in vivo studies; controlled release of EGF and a prolonged permanence on the wound site were obtained, since hyaluronic acid protect it from proteases, also allowing also a deeper penetration with a therapeutic effect diffused down to the hypodermis layer (Fig. 8) [108].

Likewise, Maver and coworkers incorporated three different growth factors, EGF, platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF), into alginate/carboxymethylcellulose thin films, leading to promising results in terms of keratinocyte and fibroblast viability and proliferation [109].

Hence, bioactive dressings offer considerable advantages with respect to the non-implemented ones; indeed, the interaction with the injured microenvironment, the local stimulation of cellular activity, and the inhibition of microorganism growth is fundamental in the perspective of faster and total recovery of tissue architecture and functionality.

2.1.7. Tissue engineered skin substitutes

In 1993, Langer and Vacanti defined tissue engineering as “an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function” [110]. Both traditional and modern dressings described above can help tissue regeneration influencing the wound healing process, but they cannot “substitute” the missing tissue. For this reason, since 1990s a lot of tissue engineered skin substitutes, biological or non-biological, have been developed to achieve the so-called “tissue engineering triad”, namely the combination of scaffolds, cells, and bioactive molecules [111,112].

Tissue engineered skin substitutes can be divided, considering their application, in permanent, semi-permanent, or temporary; considering the tissue to be treated, in dermal, epidermal, or composite; and, considering their origin, in biological (autogenous, allogeneic, xenogeneic) or alloplastic (synthetic, composed by biocompatible polymer matrices) [113]. The most common skin substitutes are acellular, synthetic, and act as a barrier against fluid loss and pathogens colonization; among them, the most diffused are Biobrane™ and Integra™. Biobrane™ is a temporary synthetic matrix composed by a silicon impermeable membrane (which avoid water vapor loss) and nylon meshes impregnated with porcine dermal collagen; it is often used for excised skin burns but cannot be applied on contaminated wounds. On the other hand, Integra™ is made up of a silicon epidermal substitute and an artificial dermal layer (a porous matrix composed by crosslinked bovine tendon collagen fibers and chondroitin-6-sulfate); the silicon layer acts as a barrier and is replaced upon vascularization, while the collagen matrix is populated and substituted by resident fibroblasts and cells involved in wound healing. It is particularly indicated for partial or full-thickness defects [56,114,115].

Similar in function, but not in composition is Alloderm™, since it is characterized by cadaveric human tissue screened for the presence of any pathogens and processed to remove epidermal elements and all dermal cells; therefore, the product is acellular and immunologically inert, even if it maintains the dermal matrix and the basement membrane [116].

The other class of tissue engineered skin substitutes is represented by cell-containing scaffolds. In this case, cells, mainly keratinocytes and fibroblasts, are seeded onto the biomaterial and here secrete growth factors, cytokines, and extracellular matrix proteins, which stimulate proliferation and differentiation of the surrounding tissue, leading to skin architecture and function restoration. The cells used can be divided into: (a) autologous, when harvested from the patient itself; (b) syngeneic, if they are genetically identical and immunologically compatible; (b) allogeneic, in case of cells deriving from the same species, but genetically different; (c) xenogeneic, when derived from different species. Even though the ideal condition is the use of autologous cells, their propagation involves long culturing times. On the contrary, the production of allogeneic and xenogeneic skin substitutes has been encouraged over the years, despite the concerns regarding the activation of the immunological response [117,118].

Commercially available allogeneic skin substitutes are, for example, Dermagraft® and Apligraf®. The former is mainly used for full-thickness foot ulcers as well as venous leg ulcers. It is prepared by using human neonatal foreskin fibroblasts, which are cryopreserved to avoid cell alterations or death, while the matrix is made of a bioresorbable polyglactin mesh; in particular, the mesh undergoes hydrolysis, leaving a dermal substitute constituted by fibroblasts, growth factors, matrix proteins, and glycosaminoglycans, which interacts with wound bed favoring re-epithelialization. Low levels of rejection are associated with this dermal substitute [119]. Apligraf® is indicated in different cases, from non-healed ulcers to full-thickness burns or excisional surgery. It introduces a complexity element with respect to Dermagraft®, since it is a bi-layered system of neonatal fibroblasts and keratinocytes; fibroblasts, placed on a bovine collagen matrix, form a thin layer of neodermis then covered by a stratification of keratinocytes. No antigen presenting cells are present, thereby limiting the possibility of an immune response while allowing tissue regeneration through cytokine and growth factor secretion [120]. Likewise, OrCel™ is a bi-layered system in which a co-culture of human dermal fibroblasts and human epidermal keratinocytes from neonatal foreskin coexist. However, in this case, the matrix is represented by a porous type I collagen sponge, to be used for partial-thickness defects repair. In addition, a comparison with Biobrane-L® (a modification of Biobrane™ obtained using a flexible monofilament of nylon) in 82 patients having split-thickness defects revealed shorter healing time in presence of OrCel™ with respect to Biobrane-L® application [121].

Thanks to the abundance of commercial products, tissue engineered skin substitutes and, more specifically, cell-seeded ones, are a good alternative in the treatment of unhealed skin injuries which fail the traditional wound care path. Nonetheless, several limitations are still present in the field of tissue engineered skin substitutes. They often lack mechanical stability, can induce scarring, immune rejection, and fail integration with the surrounding tissue. Furthermore, a rapid blood supply is required after graft application, but most of tissue engineered skin substitutes does not allow correct revascularization leading to cell death and impairing both integration and skin regeneration. The costs in terms of time and price must also be considered; in case of cell-containing substitutes, almost 2-3 weeks are required to obtain the final products with very high production costs. Added to this, there is no commercially available skin engineered substitute able to exactly recreate the anatomy, physiology, biology, and aesthetic of damaged skin. Therefore, new materials able to mimic the architecture of natural skin in a cost-effective and feasible way, while encountering skin mechanical and biological properties are needed to allow functional tissue regeneration without considerably defacing its native aspect [122–125].

2.2. Polysaccharide-based wound dressings

Considering the multitude of wound dressings available on the market or under investigation, it is important to point out the role played by dressing composition. The use of synthetic polymers (as PVA, PLA, PCL) has been largely exploited due to their biocompatibility and advantageous handling properties as well as mechanical stability. However, in the perspective of active dressing materials, synthetic polymers lack intrinsic bioactivity and need to be properly combined with bioactive moieties to reach the healing prefixed goal [126–128]. Hence, the employment of natural polymers, namely proteins and polysaccharides, has a paramount clinical relevance due to the compositional biomimicry offered besides the bioactivity exerted, which could actively stimulate tissue response and regeneration after dressing application [129,130]. Different commercial products (Table 3), starting with alginate dressings and, more generally, hydrogels, hydrocolloids, or bioactive dressings, for example, are yet based on natural polymers, offering numerous advantages in terms of therapeutic outcomes [131,132]. Similarly, the ongoing research is increasingly focusing on the production of wound dressings of natural origin, with the aim to better mimic skin tissue and wound microenvironment and stimulate a whole structural and functional recovery [133,134]. Among natural polymers, polysaccharides (as hyaluronic acid, chitosan, alginate, or cellulose) have shown numerous benefits as natural components of the extracellular matrix, for their antibacterial, anti-inflammatory, moisturizing, or haemostatic properties, to name some, along with their ability to interact with cells present in the injured site guiding the healing response [135–137]. Such promising features direct researchers' efforts towards new types of wound dressings and techniques in addition to those currently in use with the purpose of advancing in the field of wound care with medical devices able to totally re-establish physiological tissue function and morphology.

3. Electrospun mats for advanced wound care

The compelling need for wound dressings able to restore tissue structure, functionality, and aesthetic rather than merely protect wound from external insults, leading to loss of function and scar formation, has led over the years to the production of a huge variety of medical devices (as semi-permeable films and foams, hydrogels, hydrocolloids, alginate dressings until bioactive dressing and tissue engineered skin substitutes) whose employment must be weighted basing on the specific type of wound they have to be applied to [212]. Nonetheless, all these dressings can help wound resolution, but they are not able to mimic skin architecture offering a natural-like environment, where the crosstalk between epidermis and dermis is essential for complete tissue regeneration. Even tissue engineered skin substitutes, which are thought to reproduce skin layers, are not utterly able to exactly mimic its structure and present different issues related, for example, to immune rejection, inadequate vascularization, or high costs [213–215]. For this reason, the attention is slowly moving towards a new type of wound dressings, namely electrospun dressings, whose nanofibrous structure brings considerable advantages with respect to the current strategies; for example, it reminds extracellular matrix (ECM) architecture guiding cellular response, provides a high contact surface for gaseous exchanges and fluid adsorption, and its composition can be adjusted to offer a physiological microenvironment in

Table 3
Summary of the main commercialized wound dressing materials, focusing on their clinical applicability.

Class	Product	Main constituent	Bioactive agents	Application	References
Semi-permeable film dressings	Opsite™	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	Pressure sores, minor burns, cuts, abrasions, post-operative wounds, secondary dressing	[138,139]
	Bioclusive™	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	Minor burns, donor sites, superficial pressure areas, post-operative wounds, leg ulcers, cut. Abrasions, secondary dressing	[140,141]
	Tegaderm™	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	Abrasions, closed surgical wounds, donor sites, friction, lacerations, superficial burns, pressure ulcers, secondary dressing	[142,143]
	Omiderm®	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	Burns, protective layer in daily care, dermabrasion, secondary dressing	[144,145]
	Mefilm®	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	Superficial burns, laceration, abrasions. donor sites, intravenous sites, superficial pressure sores, closed surgical wounds, secondary dressing	[146,147]
	Carrafilm™	Polyurethane coated with a hypoallergenic polyacrylic adhesive	Absent	First-degree burns, minor abrasions, minor split-thickness skin graft donor sites, occlusions for topical medications, prevention of skin breakdown, secondary dressings	[146,148]
Semi-permeable foams dressings	Cutimed® Siltec	Polyurethane supported by a silicon wound contact layer	Absent	Ulcers (venous, diabetic, arterials), pressure sores, skin grafts	[149]
	Allevyn® Ag	Polyurethane (three-layered structure)	Silver sulfadiazine	Ulcers (venous, diabetic, arterials), pressure sores, donor site, surgical incisions, burns	[150,151]
	Tielle	Polyurethane (three-layered structure)	Absent	Ulcers (venous, diabetic, arterials), donor sites, pressure injuries, post-surgical or traumatic wounds	[152,153]
	Biopatch®	Polyurethane	Chlorhexidine gluconate	Catheter-related bloodstream infections, local infections, skin colonization	[154,155]
	Curafoam™ AG Silver	Polyurethane	Ionic silver	Ulcers (venous, diabetic), first- and second-degree burns, surgical wound sites, donor sites	[156,157]
	Lyofoam® Max	Polyurethane (two-layered structure)	Absent	Ulcers (pressure, leg), post-surgical and traumatic wounds, burns, skin grafts	[158,159]
Hydrogel dressings	Tegagel™	Calcium alginate	Absent	Leg ulcers, pressure sores, ischemic wounds, diabetic wounds	[160]
	Nu-Gel®	Polyvinyl pyrrolidone Polyethylene Sodium alginate	Absent	First- and second-degree burns, sever sunburns, superficial injuries, surgical wounds, skin tears	[161,162]
	Intrasite Gel	Carboxymethylcellulose Propylene glycol	Absent	Ulcers (venous, diabetic, pressure), surgical incisions, partial thickness burns, lacerations, grazes	[163,164]
	Carrasyn® Gel	Carbomer 940 Acemannan	Absent	Ulcers (diabetic, pressure, stasis), post-surgical incisions, first- and second-degree burns, cut, abrasions, radiation dermatitis, sunburns	[165]
	Purilon® Gel	Carboxymethylcellulose Calcium alginate	Absent	Non-infected ulcers (leg, pressure, diabetic), first- and second-degree burns	[166,167]
	Solugel™	Propylene glycol	Absent	Minor burns, scalds, sunburns, chickenpox. shingles	[168,169]
Hydrocolloid dressings	Comfeel® Plus	Polyurethane Sodium carboxymethylcellulose Calcium alginate	Absent	Ulcers (leg, pressure), superficial/partial-thickness burns, donor sites, post-surgical wounds, abrasions	[170]
	DuoDERM®	Polyurethane Sodium carboxymethylcellulose Gelatin Pectin	Absent	Superficial wounds, donor sites, skin tears, secondary dressing	[171,172]
	Tegasorb™	Polyurethane Polyisobutylene	Absent	Dermal ulcers, superficial wounds, abrasions, burns, donor sites	[173]
	Cutinova® Hydro	Polyurethane	Absent	Ulcers (leg, pressure, diabetic), superficial and partial thickness burns	[174]
	Hydrocoll®	Polyurethane	Absent	Non-infected wounds, ulcers, bedsores, burns	[175,176]
	RepliCare	Polyurethane	Absent	Ulcers (venous, arterial, diabetic), pressure sores, donor sites, surgical incisions, surgical excisions, burns	[177]

(*continued on next page*)

Table 3 (*continued*)

Class	Product	Main constituent	Bioactive agents	Application	References
Alginate dressings	Sorbsan®	Calcium alginate	Absent	Pressure areas, donor sites, leg ulcers, infected wounds, malodorous and painful wounds	[178]
	Tegaderm™ Alginate Ag	Calcium alginate	Silver sodium hydrogen zirconium phosphate	Ulcers (pressure, diabetic, venous), donor sites, superficial wounds, post-surgical incisions, trauma wounds	[179]
	Kaltostat®	Calcium alginate Sodium alginate	Absent	Ulcers (venous stasis, arterial, diabetic), lacerations, pressure injuries, post-surgical wounds, superficial burns, external infected wounds	[180]
	SeaSorb® Ag	Calcium alginate Carboxymethylcellulose	Ionic silver	Ulcers (pressure, leg, diabetic), grafts, donor sites, traumatic wounds, second-degree burns, infected wounds, cavity wounds	[181,182]
	Curasorb	Calcium alginate	Absent	Deep wounds, ulcers (venous, diabetic, arterial, pressure), donor sites, second-degree burns, abrasions, lacerations and skin tears	[183]
	Algisite™ M	Calcium alginate	Absent	Minor burns, abrasions, lacerations and skin tears, ulcers (leg, pressure, diabetic), surgical wounds	[184,185]
	Algosteril®	Calcium alginate	Absent	Bleeding wounds, infected wounds, donor sites, ulcers (leg, diabetic), amputation stumps, pressure sores	[186,187]
Bioactive dressings	Aquacel® Ag	Sodium carboxymethylcellulose	Ionic silver	Infected wounds, burns, frostbites, superficial and partial-thickness wounds	[188,189]
	MediHoney® Calcium alginate	Calcium alginate	Active *Leptospermum* honey	Infected wounds, first- and second-degree partial-thickness burns, donor sites, trauma wounds, surgical wounds, ulcers (diabetic, venous, arterial, pressure)	[190,191]
	DermaCol™ Ag	Collagen Carboxymethylcellulose Alginate	Ethylenediamine-tetraacetic acid (EDTA) Silver chloride	Ulcers (diabetic, venous, pressure), donor and graft sites, traumatic wound heling by secondary intention, dehisced surgical wounds, first- and second-degree burns, infected wounds	[88,192]
	Iodosorb	Polyethylene glycol	Cadexomer iodine	Ulcers (diabetic, venous, pressure), infected wounds	[193]
Tissue engineered skin substitutes	Biobrane™	Silicone membrane Nylon meshes	Porcine type I collagen	Partial thickness to mid-dermal burns, graft reduction in areas of unclear burn depth, temporary allograft for full-thickness burns	[194,195]
	Integra® Dermal regeneration template	Silicone Bovine collagen Chondroitin-6-sulfate	Absent	Second- and third-degree burns, coverage for bone, tendon, cartilage, and joints, partial- to full-thickness injuries, scar contractures, diabetic foot ulcers	[196,197]
	AlloDerm™	Cadaveric human skin	Absent	Dermal substitute in deep partial- to full-thickness burns, repair of soft tissue injuries	[198,199]
	Dermagraft®	Polyglactin mesh scaffold	Cryopreserved neonatal foreskin fibroblasts	Full-thickness diabetic foot ulcers, venous leg ulcers	[200,201]
	Apligraf®	Bovine collagen gel	Neonatal foreskin fibroblasts and keratinocytes	Chronic foot ulcers, venous leg ulcers, full-thickness burns, excisional surgery	[202,203]
	OrCel™	Bovine collagen sponge	Neonatal foreskin fibroblasts and keratinocytes	Split-thickness donor sites in patients with burns, surgical wounds in epidermolysis bullosa, venous leg ulcers	[204,205]
	TransCyte®	Nylon mesh Silastic layer	Neonatal foreskin fibroblasts	Temporary covering for excised deep partial- and full-thickness burns before autografting, mid-dermal to indeterminate depth burns not requiring autografting	[206,207]
	Laserskin™	Lase-microperforated benzyl esterified hyaluronic acid	Autologous keratinocytes	Diabetic foot ulcers and venous leg ulcers, partial thickness burns, vitiligo	[208,209]
	Epicel™	Mouse fibroblasts layer Petrolatum gauze support	Autologous keratinocytes	Permanent wound closure for severe burns	[210,211]

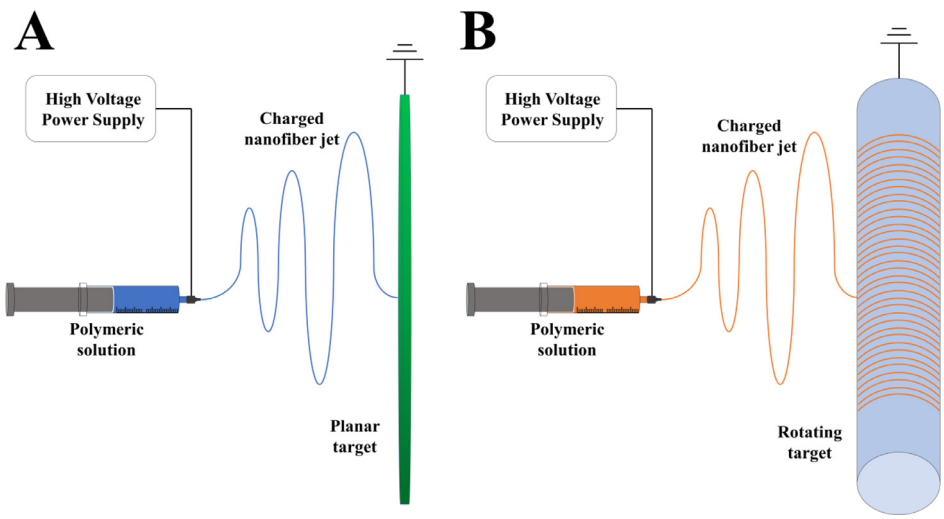

Fig. 9. Electrospinning apparatus schematization. The high voltage supply connected both to the spinneret and the collector enables liquid surface tension overcoming at the tip of the needle and fibre deposition. Two types of setup are represented: A) planar target for the preparation of nanofiber-based membranes; B) rotating target (or mandrel) for the preparation of nanofiber-based tubular scaffolds.

the perspective of complete wound recovery [216,217]. Electrospinning is an electro-hydrodynamic technique used to produce thin polymeric fibers (with a diameter ranging from few microns to few nanometers), which constitute membranes and three-dimensional constructs characterized by large surface area and high porosity. The electrospinning benchtop apparatus (Fig. 9) is composed by a high voltage power supply, a spinneret (usually a needle-equipped syringe) connected to a syringe pump, and a metallic collector. The polymers of choice are dissolved in the proper solvent (or, sometimes, mixtures of solvents); then, the solution is loaded into the syringe and injected through the needle controlled by the syringe pump. In this process, a high voltage (5–30 kV) is applied on the polymeric solution in order to increase its surface charge density, leading to the formation of a cone-like drop, namely "Taylor cone", at the tip of the needle; if the electric field applied overcomes the liquid surface tension, a continuous filament is produced and accelerated towards the collector of opposite polarity. In the space between the needle and the collector, the polymer jet stretches and elongates and the solvents evaporate, so the polymers are deposited on the collector target as non-woven ultra-fine fibers [218–221].

The electrospinnability, intended as the ability to produce mats with a certain fiber diameter and porosity starting from a specific polymer solution, is influenced by a series of parameters: solution (concentration, viscosity, electrical conductivity, surface tension, polymer molecular weight), operational (voltage, injection rate, needle-collector distance, type of collector), and environmental (temperature, relative humidity) parameters [219,222,223].

The electrospinning apparatus can be adapted in order to obtain fibers with tailored properties. Two main additional set-ups are available, depending on the orientation of the apparatus: vertical and horizontal; the orientation influences the strength of the electric field applied, and so fibers thickness and size distribution [224]. Additionally, the spinneret can be modified to realize coaxial electrospinning, where multiple spinnerets are used to obtain core-shell structures (useful for drug incorporation) or multichannel nanotubes (Fig. 10) [225–227].

Coaxial needles consist of a concentric multiple-layer spinneret from which a charged compound jet of miscible or semi-miscible polymers is extruded to produce core-shell aligned polymeric nanofibers with enhanced mechanical strength; moreover, the dissolution of the core sheet using adequate solvents offers the possibility to synthetize hollow fibers. One of the chief advantages of producing core-shell nanofibers lies in the incorporation of bioactive moieties into the nanofibrous scaffolds; basing on the allocation of the drug and on the composition and thickness of the coaxial nanofibers, a tuned release of the therapeutic agents can be achieved with respect to the burst release generally observed in case of conventional uniaxial spinnerets; on the other hand, multiple drugs can be loaded into the structure and distributed between the core and shell layers [228–231]. Multichannel tubes can also be synthetized by modifying the spinneret set-up. As an example, Zhao and coworkers realized multichannel microtubes using a multifluidic compound jet. Three metallic capillaries were arranged as the vertexes of an equilateral triangle in a syringe, serving both as conductive electrodes and inner fluids vessels; two immiscible fluids where then separately introduced in the outer syringe and inner vessels and the resulting films were treated by calcination to obtain the multichannel structures [232]. To increase the productivity of the electrospinning process, multiple-jet nozzle electrospinning can be performed too by means of a single nozzle with multiple jets, multiple nozzles with single jets, or multiple nozzles with multiple jets, where nozzles are intended as needle, holes, channels, or tips. In this case, the quality and stability of the resultant fibers as well as the ability to control the whole process must be carefully considered [233].

Looking at the complexity of an electrospinning apparatus, even the collector can be changed; for example rotating collectors of different geometries can be used (disks, mandrels) for the preparation of membranes and tubular scaffolds with specific fiber alignment [234,235].

Membranes composed by electrospun nanofibers, acting, for example, as photocatalysts, electrodes, filters, or matrices, may apply in a wide variety of fields, from energy conversion and storage to water treatment and tissue regeneration. Indeed, they show a high surface-to-volume ratio, porosity, and three-dimensional organization, which explain the growing interest in electrospun products for large-scale applicability [236]. Considering their use as tissue engineering scaffolds, they can be prepared from a varied choice of polymers in order to set a good microenvironment for cell adhesion and proliferation, whereas their structure mimic the architecture of the extracellular matrix (ECM) [237]. With a diameter falling in the range of collagen fibers (50–500 nm), electrospun nanofibers provide not only structural, but also mechanical and

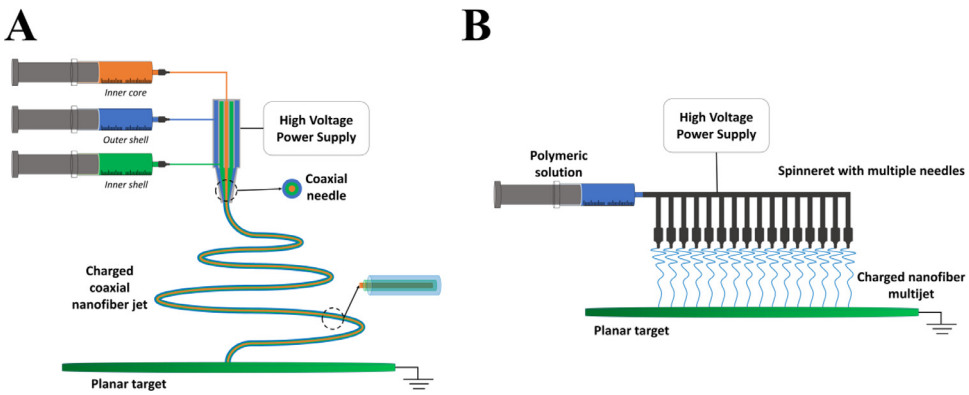

Fig. 10. Schematization of advanced electrospinning apparatus. Electrospinning devices can be modified in order to produce tailored membranes; in A) coaxial needles can be used to produce core-shell structured nanofibers using different polymeric solutions for the core and for the shells of the nanofiber. In B) a spinneret with multiple needles is used to speed up the deposition of nanofibers and the production of electrospun membranes.

biochemical support and can be engineered with biological cues useful for cell instruction and tissue repair; all these characteristics make them suitable candidates for a wide range of biomedical applications, as nerve, cardiac, musculoskeletal, or skin regeneration [238].

3.1. Electrospinning in wound healing

In the context of tissue engineering approaches, the extracellular matrix (ECM) can be considered a natural scaffold whose topology and geometry influences cell structure and physiology, allowing cell ingrowth, proliferation, and differentiation [239]. Thus, when considering biomaterials which must promote tissue regeneration, as in the case of non-healing wounds, an important parameter to examine is their ability to reproduce the architecture of the ECM, which is composed by fibrous structural proteins (collagen, elastin, laminin among the most abundant) and numerous polysaccharides and proteoglycans (mainly hyaluronan and dermatan sulfate). Electrospinning is emerging as an attractive technique in the field of wound healing, because it produces biomimetic nanoscale/microscale fibrous scaffolds with interconnected pores, which remind the natural ECM. This highly porous structure allows gas permeation throughout the membrane, while the high surface-to-volume ratio favors drainage of exceeding exudates and hemostasis [240–244]. Furthermore, electrospun mats exhibit an anti-scarring potential, since the wet environment guaranteed by gaseous exchanges promotes and accelerates wound closure avoiding, at the same time, scar formation (Fig. 11). In addition, when the tensile strength is high enough to tolerate dressing handling and changes, their high flexibility allows them to easily adapt to the wound shape and no secondary dressings are needed to stabilize them [245–250].

An ideal wound dressing biomaterial should mimic ECM structure and function as well as its mechanical properties. Indeed, the skin is a heterogeneous, anisotropic, viscoelastic multi-layered system (composed by hypodermis, dermis, and epidermis) with a non-linear stress-strain behavior. Therefore, referring to skin, it is important to consider its anisotropic nature and the experimental variability deriving from soft tissue mechanical [252]. To overcome the issues related to anisotropy in a tensile test, Crichton and coworkers characterized skin viscous and elastic behavior by means of atomic force microscope (AFM) indentation. They separately examined the stratum corneum, viable epidermis, and dermis, showing how the presence of collagen and elastin in the dermis layer increases its overall stiffness with higher elastic modulus values with respect to stratum corneum and epidermis: the dermis elastic modulus was in the range of 7.3–13.5 MPa (depending on the probe scale selected), while the stratum corneum and viable epidermis layers revealed elastic moduli of 0.75–1.72 MPa and 0.49–1.51 MPa, respectively [253]. Hence, the mechanical properties of an electrospun wound dressing should be tailored to encounter skin features. Different parameters can condition stiffness and strength of electrospun biomaterials, such as fiber diameter, the presence of defects, fiber alignment, the incorporation of biodegradable polymers or nanofillers (as carbon dots), the addition of plasticizers (for example poly(ethylene glycol) [PEG] or glycerol), or the contemporary use of different polymer solutions during the process [254–258]. The importance of the mechanical properties of electrospun nanofiber-based structures is given by their influence on cell spreading and functions: proliferation, differentiation, contractility, motility, response to growth factors and mitogens, and gene expression, as well as on the ability to incorporate and release drugs [257,259,260].

Several factors must be considered in achieving the best structural, functional, and mechanical mimicking of the natural ECM, such as the polymer chosen, membrane thickness, fiber orientation, fiber diameter, and porosity. Among these factors, the polymer or polymers used for the preparation of the membranes is one of the most important, as on the chemical nature of such polymers depend dressing degradability, resistance, mechanical properties, similarity to ECM components and other characteristics, which influence membrane architecture and conformability to the injured site along with its capability to recreate a suitable environment for tissue regeneration and its bioactivity [261–264].

3.2. From synthetic to natural polymers

The use of synthetic polymers (Table 4) has known a considerable increase in the last 15 years and has been approved by FDA for clinical application. Indeed, many synthetic polymers (polyurethane, poly(lactide-co-glycolide), poly(vinyl alcohol), poly-ε-caprolactone, to cite the most used) possess characteristics, such as mechanical strength and integrity, good degradation profile, possibility of surface modifications, or thermal stability, which make them a favorable basis for the preparation of a wide range of medical devices, as electrospun membranes and scaffolds [265–267]. Polyurethane electrospun membranes have been studied as potential wound dressing materials because of their ability to drain fluids, act as a barrier against exogenous microorganisms, favour oxygen exchanges, and control water vapor transmission; they also uniformly adhere to the wound and accelerate the epithelialization process [268]. Mixtures of synthetic polymers can be used to synergistically combine their properties. As an example, Kim and coworkers achieved the ability to tune the release of lysozyme

Table 4
Overview of synthetic polymer-based electrospun membranes, with particular attention on their leading features. Acronyms are defined at the end of the table.

Polymer	Additive	Application	Main features	Reference
PCL	mPEG Amoxicillin	Highly absorbing antibacterial wound dressing	Biocompatibility and high-water absorption capacity. mPEG must be added to PCL to ensure water absorption.	[272]
	PDMAEMA Ag nanoparticles	Antibacterial wound dressing	Biodegradability, biocompatibility, and suitable mechanical properties. Functionalization with silver nanoparticles can be modulated by varying pH and PCL/PDMEMA ratio. The drawback of this device is the hydrophobicity of the polymers used.	[273]
	PLA Chitosan	Bioactive wound dressing	Biocompatibility and biodegradability. The presence of chitosan provides a suitable environment for cell adhesion and proliferation.	[274]
	PES BTAC PVP	Antibacterial wound dressing	Biocompatibility and biodegradability. The degradation is favored in presence of bacteria creating a bacteria-responsive wound dressing.	[275]
	PVA Curcumin	Highly absorbing antibacterial wound dressing	Biodegradability, flexibility, and high absorbing capacity thanks to the PVA layer. Curcumin concentration must be regulated to avoid any cytotoxic effect.	[276]
	PEO Chloramphenicol	Antibacterial wound dressing	Biocompatibility, biodegradability, and cost-effectiveness. The use of PEO accelerates chloramphenicol release.	[277]
	Gelatin 6-aminopenicillanic acid-coated Au nanoparticles	Antibacterial wound dressing	Hydrophilicity, biocompatibility, and antibacterial activity even against multidrug-resistant bacteria, both in in vitro and in vivo tests.	[278]
	PVP Ag nanoparticles ZnO nanoparticles	Antibacterial wound dressing	Biocompatibility, good gaseous exchange ability and swelling capacity.	[279]
PLA	γ-PGA	Tissue engineered skin scaffold	Biocompatibility, biodegradability, and plasticity. PLA alone is slowly degradable; in addition, it constitutes the shell of the structure, so material surface owns a hydrophobic nature.	[280]
	HPG Curcumin	Wound dressing for chronic diabetic wound	Biocompatibility, biodegradability, hydrophilicity, and swelling capacity. Bioactive properties are endowed by curcumin supplementation.	[281]
	PCL *Nigella sativa* herbal extract	Antibacterial wound dressing	Biocompatibility, biodegradability, and drug delivery capacity.	[282]
	PEO Enzymatic cellulose nanofibrils	Tissue engineering skin scaffold	Biocompatibility, biodegradability, and suitable mechanical properties. Liquid uptake ability displays a solvent dependent behavior.	[283]
	PVA Sodium alginate	Bioactive wound dressing	Biocompatibility, biodegradability, ensuring of an advantageous moist environment.	[284]
	PEG Tetracycline hydrochloride	Dressings for malignant wounds and ulcers	Biocompatibility, biodegradability, and drug delivery properties. Degradation in vivo is dependent on proteinase K activity.	[285]
PVA	PHBH	Tissue engineered skin substitute	Biocompatibility, biodegradability, and flexibility. If PVA content is more than 30% the high-water absorption capacity discourages cell adhesion.	[286]
	PCL Gum tragacanth	Scaffolds for diabetic ulcers	Biocompatibility, biodegradability, stability in aqueous environment, and good mechanical properties. Gum tragacanth stimulates collagen production and cell activity.	[287]
	PSSA-MA Neomycin	Bioactive antibacterial wound dressing	Biocompatibility, biodegradability, suitable tensile strength. The ion-exchange capacity, favours the release of the antibacterial drug.	[288]
	Sulfopropylbetaine Quaternary ammonium salt	Bactericidal antifouling wound dressing	Biocompatibility, biodegradability, with a uniform and smooth morphology along with bactericidal and antifouling activity.	[289]
	Chitosan Silk sericin Tetracycline	Antibacterial wound dressing	Biocompatibility, biodegradability, and good mechanical properties associated to an antibacterial effect and bioactivity.	[290]
PEG	PLLA Tetracycline hydrochloride Rhodamine-BSA FITC-BSA	Antibacterial wound dressing	Biocompatibility, biodegradability, avoidance of non-specific protein absorption, and sustained release of the antibacterial drug.	[291]
	PCL Tetrahydro curcumin	Transdermal patch	Biocompatibility, biodegradability, non-immunogenicity, bioactivity, and hydrophilicity. PCL is used to control the membrane degradation rate.	[292]
	PHB Methylene blue	Antimicrobial photodynamic therapy template	Biocompatibility, biodegradability, hydrophilicity, flexibility, antimicrobial properties, and suitable release profile.	[293]
	PMMA Kynurenic acid	Antifibrotic wound dressing	Biocompatibility, biodegradability, and antifibrotic effect. By varying PEG amount, a modulation of the release kinetic is achieved.	[294]
	PLA 5N8Q	Antibacterial wound dressing	Biocompatibility, biodegradability, and antibacterial properties. Membrane plasticity can be modulated by the grafting and mixing strategies.	[295]

(*continued on next page*)

Table 4 (*continued*)

Polymer	Additive	Application	Main features	Reference
PLGA	Polydopamine bFGF Ponericin G1	Antibacterial full-thickness wound dressing	Biocompatibility, biodegradability, hydrophilicity, and good mechanical properties. The device is easily functionalized with growth factors and antimicrobial peptides.	[296]
	Collagen	Tissue engineered skin substitute	Biocompatibility, biodegradability, and favorable cell adhesion. The mechanical properties are not indicated to mimic skin, while the degradation rate is not suitable to support long-term keratinocyte proliferation.	[297]
	CNC Neurotensin	Diabetic foot ulcer wound dressing	Biocompatibility and ability to favour fibroblast adhesion, spreading, and proliferation. Neurotensin functionalization promotes anti-inflammatory activity and dermal and epidermal regeneration.	[298]
	HACC	Antibacterial wound dressing	Biocompatibility, biodegradability, and good mechanical properties. The modified chitosan introduces antibacterial properties.	[299]
	PEO rhEGF rhbFGF	Tissue engineered skin substitute	Biocompatibility, mechanical properties similar to human skin, and good encapsulation efficiency. The addition of growth factors promotes the healing process.	[300]
PVP	PVA Tetracycline hydrochloride monohydrate	Antibacterial wound dressing	Biocompatibility and biodegradability, hydrophilicity, antibacterial properties, and suitable mechanical features. Membranes can be used for drug encapsulation.	[301]
	Indomethacin	Adhesive analgesic/anti-inflammatory patches	Biocompatible and easily functionalized with bioactive properties. The drug release profile is easily tunable.	[302]
	EC Naproxen	Analgesic/anti-inflammatory wound dressing	Biocompatibility and biodegradability. The device allows a sustained drug release, which is tunable by varying PVP:EC mass ratio.	[303]
	Graphene oxide PCL Vancomycin hydrochloride	Antibacterial wound dressing	Biocompatibility, biodegradability, and sustained controlled biphasic release of antibiotic drug.	[304]
	Dextran Acetylsalicylic acid Ibuprofen	Bioactive wound dressing	Biocompatibility, biodegradability, flexibility, and hydrophilicity together with antibacterial properties.	[305]

PCL: Polycaprolactone; mPEG: Methoxy poly(ethylene glycol); PDMAEMA: Poly[(2-dimethylamino)ethyl methacrylate]; Ag: silver; PLA: Polylactic acid; PES: Poly (ethylene succinate); BTAC: Benzyl dimethyl tetradecyl ammonium chloride; PVP: Polyvinylpyrrolidone; PVA: Poly(vinyl alcohol); PEO: Poly(ethylene oxide); ZnO: zinc oxide; γ-PGA: Poly(γ-glutamic acid); HPG: Hyperbranched polyglycerol; PHBH: Poly [(*R*)-3-hydroxybutyrate-co-(*R*)-3-hydroxyhexanoate]; PSSA-MA: Poly(styrene sulfonic acid-co-maleic acid); PEG: Polyethylene glycol; PLLA: poly (*L*-lactic acid); BSA: Bovine serum albumin; PHB: Polyhydrohybutyrate; PMMA: Polymethyl methacrylate; 5N8Q: 5-nitro-8-hydroxyquinoline; PLGA: Poly Lactic-co-Glycolic Acid; bFGF: basic fibroblast growth factor; CNC: Cellulose nanocrystals; HAAC: Hydroxypropyltrimethyl ammonium chloride chitosan; rhEGF: recombinant human epidermal growth factor; rhbFGF: recombinant human basic fibroblast growth factor; EC: Ethyl cellulose.

embedded in electrospun membranes, by blending hydrophobic polymers (poly-ε-caprolactone [PCL], poly-*L*-lactic acid [PLLA], and poly(lactic-co-glycolic acid) [PLGA]) with hydrophilic poly(ethylene oxide) [PEO]; the PCL/PEO blend showed the best morphological stability in aqueous environment and a homogenous and sustained release of lysozyme over time. Moreover, as the release depended on PEO degradation profile, it could be modulated by varying polymer ratio [240]. Poly(vinyl pyrrolidone)–iodine [PVPI] and PCL have been combined too in a core-shell structure and coated with poly-*L*-lysine, obtaining a material with enhanced properties

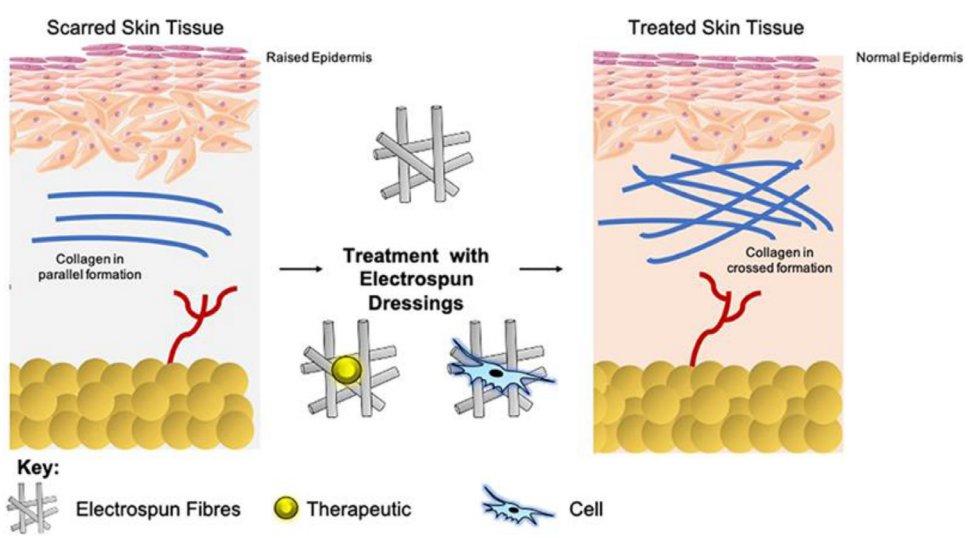

Fig. 11. Electrospun mats for advanced wound treatment. Schematization of the beneficial use of biomimetic electrospun scaffolds, eventually associated with therapeutic molecules or pre-seeded with cells, to avoid scar formation during the healing process. Reprinted from ref [251] Copyright © 2020 Mulholland.

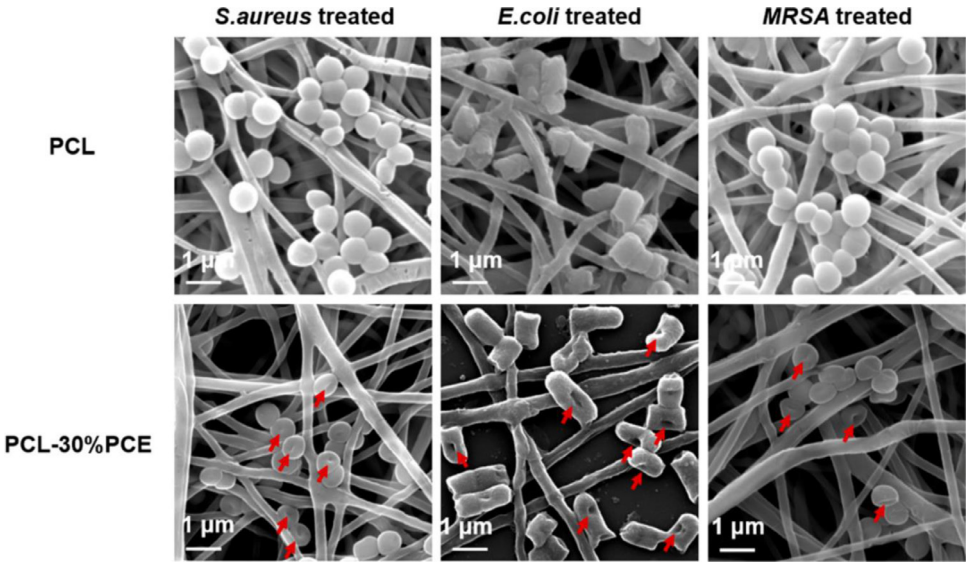

Fig. 12. Antimicrobial electrospun wound dressing. SEM micrographs representing the morphological changes induced on different bacteria strains by PCL-PCE nanofibrous mats with respect to PCL alone. Reprinted with permission from ref [270]. Copyright (2018) American Chemical Society.

Table 5
Summary of the main differences between synthetic and natural polymers basing on peculiar features in the field of wound healing [309–315].

	Synthetic polymers	*Natural polymers*
Biocompatibility	Good	Excellent
Biodegradability	Low	Fast
Immunogenicity	Low	Absent
Hydrophilicity	Low	High
Thermal stability	High	Low
Mechanical strength	High	Low
Molecular interaction with cells	Absent	Present
Bioactive properties	Absent	Present

with respect to PCL alone: better cytocompatibility, cell adhesion and proliferation, antimicrobial activity against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria, and lower expression of pro-inflammatory cytokines (TNF-α and IL-1β) [269].

The employment of synthetic polymers is clearly advantageous in the electrospinning of otherwise non-spinnable polymers. Xi and coworkers combined PCL with poly (citric acid), an elastomer unable to form nanofibrous structures when used alone; such elastomer was functionalized with the antimicrobial peptide, ε-polylysine, creating a biomimetic elastomeric antimicrobial wound dressing (PCL-PCE) active against multidrug-resistant bacteria (MRSA), which resembles skin viscoelasticity (Fig. 12) [270].

Notwithstanding the benefits offered by synthetic polymers in the synthesis of electrospun membranes, the basically hydrophobic surface of the majority of these polymers and the lack of biological signals which could favour cell attachment, growth, and differentiation often limit their employment [271].

For this reason, the attention moved towards natural polymers, both proteins and polysaccharides: collagen, fibrinogen, silk fibroin, cellulose, hyaluronic acid, alginate, chitosan, to name a few. Some of these natural polymers used to manufacture electrospun membranes are natural components of the ECM, thus they are able to closely mimic ECM architecture and wound microenvironment; moreover, natural polymers are biocompatible, hydrophilic, and able to interact with cells thanks to recognition signals and moieties, being particularly useful as tissue regeneration matrices (Table 5) [306–308].

Regardless of all their advantages, natural polymer-based biomaterials exhibit weak mechanical properties and their use in the electrospinning field is hampered by their solubility and by the characteristics of the aqueous solutions of these polymers: viscosity, conductivity, and surface tension. Consequently, blending natural and synthetic polymers has been adopted as an efficient strategy to combine the bioactive properties of the natural polymers with the mechanical strength and stability of synthetic ones [316,317]. Nevertheless, a successful blending entails the knowledge of polymer chemical properties, since specific interactions between polymers chains determine their miscibility. Moreover, once assessed the compatibility of such polymers, particular attention must be paid on the choice of the solvent to be used, given that its evaporation rate influences fiber deposition and morphology as well as the porosity of the resulting mat. Not all synthetic and natural polymers are water-soluble, hence organic solvents must be employed, such as acetic acid, trifluoroacetic acid, dimethylformamide, chloroform, formic acid or solutions based on fluoroalcohols. These organic solvents are easily manageable due to their high solubility and volatility, and are used alone, or, by considering their intrinsic properties, they can be properly combined in mixtures of solvents to improve polymer solubility [267,318–326].

Chitosan/PCL nanofibers have been studied by Levengood and coworkers in a biomimetic/tissue engineering approach showing how the association of chitosan biological features and PCL mechanical properties increases the wound-healing rate, re-epithelialization, and collagen deposition with respect to the commercial product Tegaderm^{TM} [327].

PCL-gelatin nanofibrous mats have been manufactured to combine the hydrophilicity of gelatin with the mechanical resistance of PCL, obtaining a membrane with the biological features of gelatin and the mechanical stability of PCL. Moreover, biocompatibility studies on keratinocytes and dermal fibroblasts revealed enhanced cell adhesion, spreading, and proliferation [328]. Bi-layered systems have been developed to mimic the double structure of skin: an asymmetric electrospun wound dressing has been realized by combining a silk fibroin-PCL layer and a silk fibroin-hyaluronic acid layer to reproduce the epidermis and the dermis layer, respectively. Wettability, porosity, and mechanical properties suitable for wound healing applications have been achieved, as well as biocompatibility and bioactivity in terms of human fibroblast attachment, spreading, and proliferation. Moreover, swelling studies demon-

strated the higher swelling capacity of the bottom hyaluronic layer with respect to the top layer, which is an important feature considering the role of physical barrier played by epidermis [329]. Sealant nanofibrous scaffolds have been engineered by combining PCL-silk fibroin mats with fibrinogen for the regeneration of large-area wounds; these scaffolds promoted an in situ interaction between fibrinogen and thrombin, leading to the formation of fibrin sealant on their surface and promoting consistent tissue regeneration due to their high biocompatibility, mechanical strength, ability to interact with cells, to stimulate collagen deposition and angiogenesis, and to act as a protective barrier [330]. Hence, mixing synthetic and natural polymers proved to be a valid approach to reach the proper mimicking of skin both from a structural and functional perspective; indeed, the mechanical stability of the synthetic part joins the biological activity of the natural one, thereby stimulating tissue re-organization while providing a suitable mechanical support for cell growth.

3.2.1. Polysaccharides

Thanks to their unique combination of features, polysaccharides, among natural polymers, stand out in the field of wound care, as active healing promoters (Table 6); they favour the regeneration and restoration of the damaged tissue both from a structural and functional standpoint, providing a physiological wound environment and directing cellular response towards a traditional healing path [331–333]. Indeed, most of them are abundant in nature and offer a series of advantages, beyond their biocompatibility, over other polymers, such as antimicrobial or anti-inflammatory properties and ability to recreate ECM architecture. Moreover, considering their low-immunogenicity, natural polysaccharides do not trigger an adverse immunogenic response, rather they interact with immune system components in order to stimulate the activation of macrophages, which are active players in the wound healing process [334].

Among polysaccharides, alginate, chitosan, and hyaluronic acid are considered the three main useful candidates in the manufacturing of medical devices to be employed in wound management.

3.2.1.1. Alginate. As mentioned above (see section 2.5: “Alginate dressings”), alginate has been widely used to produce wound dressing materials because of its biocompatibility, its ability to maintain a moist environment, its active participation in the hemostasis process and the possibility to introduce antibacterial properties. Moreover, alginate dressings can be removed with low trauma, leading to a decrease of the pain experienced by the patient during dressing changes [335–337]. The electrospinning of alginate alone presents some challenges due to the high viscosity of aqueous solutions, even at low concentrations, but it can be successfully electrospun if blended with synthetic polymers. Dodero and coworkers designed an alginate-PEO electrospun mat crosslinked with divalent cations and embedded with ZnO nanoparticles. Their biocompatibility was proved on keratinocytes and fibroblasts, which were able to adhere and growth on all the membranes synthetized. Furthermore, strontium and barium-crosslinked mats gave similar viability results to those obtained from a commercial collagen membrane (Bio-Gide®). The benefits of strontium crosslinking were also revealed by the mechanical properties, which were comparable to those of human skin, and by the hydrophilicity, water-vapor permeability, and moisture content. On the other hand, the incorporation of ZnO nanoparticles offered an antibacterial effect without altering mat biocompatibility [338].

Alginate has also been used in association with PVA; a recent study examined the influence of honey incorporation in such electrospun mats, because of its antibacterial, anti-inflammatory, and antioxidant properties (Fig. 13). These honey/alginate/PVA nanofibrous membranes were analyzed from a morphological, chemical, and biological point of view, demonstrating the efficacy of honey incorporation into the porous mats and the biocompatibility when tested on murine fibroblasts. In addition, their antioxidant and antibacterial activity has been proved, confirming the potentiality of such product as wound dressing material [339].

3.2.1.2. Chitosan. In terms of intrinsic antibacterial and haemostatic properties, the employment of chitosan as wound-healing promoter is noteworthy. Chitosan is a high molecular weight polysaccharide composed by (β 1 $\rightarrow$ 4)-linked glucosamine and *N*-acetylglucosamine residues, in variable percentage. It is obtained from the deacetylation of chitin, naturally contained in the exoskeleton of crustaceans, cuticles of insects, and cell walls of many fungi. Thanks to its remarkable combination of properties, as biocompatibility, biodegradability, thermal and chemical stability, and cost-effectiveness, this polysaccharide has been widely used for biomedical purposes, from drug delivery to wound care. Indeed, among its peculiar characteristics, it possesses also haemostatic and mucoadhesive properties; it enhances epithelialization and reduces blood loss while promoting and strengthening blood clots, thus accelerating the healing process. On the other hand, its antimicrobial activity serves as protection against a wide range of bacteria. Therefore, chitosan is largely employed as haemostatic wound dressing as well as in the preparation of antiseptic bandages [340–344].

The ability of chitosan to favour the coagulation process relies on its positive charge: the polycationic nature of this polymer makes it able to interact with negatively charged red blood cell membranes, thus promoting platelet adhesion, activation, and aggregation as well as the adsorption of plasmatic fibrinogen, the increase of its local concentration, and complement activation. The ability of chitosan-based materials to activate the healing processes is proportional to the surface available for the interaction with cells and coagulation factors (Fig. 14) [345]. Therefore, chitosan-based electrospun wound dressings, where the surface-to-volume ratio is maximized, have been considered for this purpose. As for the other natural polymers, the scarce mechanical properties of the electrospun chitosan-based materials has led over the years to the investigation of the association with synthetic polymers, always considering the miscibility of the polymers of choice and selecting, when possible, the same solvent for all polymers in order to avoid problematic solvent mixtures. As mentioned above (see section 3.2: “From synthetic to natural polymers”), most of the polymers currently used are solubilized in organic solvents thanks to their easy processing. However, organic solvent residuals on the as-produced material could slightly affect its biocompatibility and should be carefully and completely removed after the electrospinning process; for this reason, despite all the challenges related to the preparation of an aqueous solution, when water-soluble polymers are present, the use of water is always favored above other solvents [346,347].

Alavarse and coworkers developed a PVA/chitosan electrospun wound dressing and incorporated tetracycline hydrochloride into the nanofibrous mat. Owing to chitosan water insolubility, acetic acid has been used as polysaccharide solvent, requiring an additional step of vacuum drying at room temperature to remove any residual solvent on the membrane. The presence of the antibiotic did not affect morphological and thermal properties of the material. Furthermore, a burst release of tetracycline was observed, determining an increased antibacterial activity against both Gran-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus epidermis* and *Staphylococcus aureus*) bacteria with respect to the unloaded scaffolds. The membranes even revealed good biocompatibility and ability to favour the migration of rabbit aortic smooth muscle cells, which lies in the wall of blood vessels, regulating their motility and the response to an injury allowing wound clo-

Table 6
Overview of polysaccharide-based electrospun nanofibrous scaffolds, highlighting the specific use of solvents aside from the advantages and disadvantages related to polysaccharide choice. Acronyms are defined at the end of the table.

Polymer	Chemical modification/moieties	Additive and solvents	Application	Main features	Reference
Chitosan	Carboxyethyl chitosan	Silk fibroin, PVA in water	Tissue engineered skin substitutes	Biocompatibility and homogeneous nanofiber diameter distribution. PVA incorporation allows avoiding the use of organic solvents.	[400]
	Absent	PEO, ciprofloxacin hydrochloride, ZnO nanoparticles in acetic acid and water	Wound dressing for infected burns	Biocompatibility, thermal stability, and ability to sustain the release of antibacterial agents. Co-polymerization reduces the intrinsic antibacterial activity of chitosan, hence other antibacterial agents are used to enhance dressing performance against infected wounds. Moreover, membranes need a crosslinking procedure due to their water instability.	[401]
	Absent	PVA, Ag nanoparticles, sulfanilamide in water, isopropyl alcohol, acetic acid, and FA	Antibacterial wound dressing	Biocompatibility, good synergistic antibacterial activity, and ability to induce the wound healing process. PVA addition is necessary to favour chitosan electrospinning.	[402]
	Quaternized chitosan	PLA, PDLA In DCM and HFIP	Disinfectant wound dressing	Biocompatibility, mechanical strength, and thermal stability aside from antibacterial and antioxidant properties added to their ability to accelerate wound healing.	[403]
	Carboxymethyl chitosan	PEO, Ag nanoparticles in water	Antibacterial/antifungal wound dressing	Good antimicrobial activity against both bacteria and fungi. The inhibition effect is lower than the tested control antibiotics.	[404]
	Absent	PVA, tranexamic acid in acetic acid	Haemostatic patch	Chitosan and tranexamic acid are combined in order to obtain different release kinetics and regulate hemostasis times. Spinnability of polymer blend and hydrophilicity of the resulting device depend on PVA content.	[405]
Alginate	Sodium alginate	PVA, ZnO nanoparticles in water	Antibacterial wound dressing	Alginate acts as good carrier for antibacterial ZnO nanoparticles, whose concentration must be tuned to avoid cytotoxic effect. PVA is used as a copolymer to electrospun alginate.	[406]
	Sodium alginate	PEO, Pluronic-127, vancomycin hydrochloride in water	Antibacterial wound dressing against methicillin-resistant *Staphylococcus aureus*	Biocompatibility and sustained antibacterial activity, both in vitro and in vivo models. PEO and Pluronic-127 are used as surfactant to modulate solution surface tension and obtain smooth nanofibers.	[407]
	Alginate dialdehyde	PEO, AADin water and ethanol	Biodegradable wound dressing	Biocompatibility, suitable mechanical properties, and adjustable degradability. The addition of PEO or AAD can expand the range of spinnable alginate concentrations.	[408]
	Sodium alginate	PLGA, ciprofloxacin hydrochloride in TFE and chloroform	Absorbing antibacterial wound dressing	Alginate enhances dressing wettability, water absorption capacity, and the ability to incorporate and release the antibiotic drug, but reduces membrane stiffness with respect to pure PLGA membranes. Mechanical properties are similar to human skin.	[409]
	Sodium alginate	PVA, chitosan, asiaticoside in acetic acid	Deep partial-thickness wound dressing	Biocompatibility, sustained drug stimulation of the healing process and down-regulation of the inflammation response.	[410]
	Sodium alginate	PVA, gelatin, collagen in propanol and water	Tissue engineered skin substitute	Biocompatibility, hydrophilicity, water vapor permeability, elongation at break suitable for handling, improved cell adhesion, viability, and proliferation. Young's modulus and ultimate tensile strength are lowered by the presence of collagen, moreover a crosslinking is necessary to stabilize the membranes in biological fluids.	[411]
Hyaluronic acid	Absent	PVA, L-arginine, CNCs in water	Reinforced antibacterial wound dressing	Biocompatibility, swelling capacity, adequate mechanical properties, and antibacterial activity against skin infecting pathogens. Hyaluronic acid nanofibers are characterized by poor mechanical properties.	[412]
	Absent	PCL, chitosan, zein, salicylic acid In ethanol, acetic acid, TFE, and NaOH/DMF	Anti-inflammatory/ antimicrobic skin substitute	Biocompatibility, adequate porosity, mechanical properties, and water loss as well as a good drug release profile. The membranes prevent biofilm formation on nanofibrous matrix surface.	[413]
	Absent	Silk fibroin, ZnO nanoparticles in FA and NH_4OH/DMF	Burn wound dressing	Adequate mechanical and antibacterial properties. Enhancement of the healing process while limiting the inflammatory response. ZnO concentration must be modulated to preserve dressing biocompatibility.	[414]
	Absent	PCL, BSA/EGF in chloroform and FA	Skin tissue engineering scaffolds	Biocompatibility and regeneration ability of full-thickness wounds. Stimulation of cell proliferation, collagen deposition, and TGF-β production.	[415]
	Absent	Collagen in HFIP and FA	Dressing for scarless wound repair	Membranes mimic ECM architecture and chemistry allowing good cell adhesion and viability. The regulation of CD44, MMPs and MMP inhibitors leads to a scarless skin regeneration.	[416]
	Absent	Chitosan, gelatin, PEO in acetic acid and FA	Biomimetic skin tissue engineering scaffold	Similar structure to native ECM, high swelling capacity, and hydrophilicity. Membranes promote cell adhesion and proliferation in vitro and skin regeneration in vivo. Polymeric mixtures must be prepared balancing mechanical properties and swelling rate.	[417]

(*continued on next page*)

Table 6 (*continued*)

Polymer	Chemical modification/moieties	Additive and solvents	Application	Main features	Reference
Cellulose	Cellulose acetate	$MnFe_2O_4$ nanoparticles, collagen, naproxen in chloroform, acetone. water, and NaOH	Anti-inflammatory wound dressing	Biocompatibility and ability to sustain naproxen release, which depend on solution pH. Long operating times are needed to obtain desirable membranes.	[418]
	Carboxymethylcellulose	PVA, ZnO nanoparticles, erythromycin in water	Antibacterial wound dressing	Biocompatibility and good drug release profile. Zinc oxide nanoparticles and erythromycin exert a synergistic antibacterial action against Gram-positive and Gram-negative bacteria. A precise ratio of PVA to carboxymethylcellulose must be selected to encounter proper solution properties and allow its spinnability.	[378]
	Cellulose acetate	Soy protein in HFIP	Tissue engineering skin scaffold	Similar stiffness to natural ECM, good biodegradability, hydrophilicity, and water uptake capacity. They support fibroblast infiltration, growth, and proliferation in vitro and stimulate skin regeneration and wound closure in vivo.	[419]
	Bacterial cellulose	PCL in DMF and chloroform	Tissue engineering skin scaffold	Biocompatibility and tunable hydrophilicity by varying the bacterial cellulose to PCL ratio. Nanofibrous scaffolds are produced with a portable electrospinning apparatus, so that the membrane can be directly deposited on the injured site avoiding some problems related to dressing storage and transportation.	[420]
	Ethyl cellulose	Zein, indomethacin in acetic acid	Tissue engineered skin scaffold	Water stability and sustained drug release.	[421]
	Cellulose acetate	PLA, thymoquinone in DCM and DMF	Antibacterial wound dressing	Biocompatibility and hydrophilicity. Membranes support cell proliferation while preventing bacterial infection thanks to a sustained drug release. They also accelerate wound closure in vivo, controlling granulation tissue deposition. The antibacterial activity of thymoquinone is influenced by the PLA to ethyl cellulose ratio.	[422]
Dextran	Absent	Polyurethane, ciprofloxacin hydrochloride in DMF and THF	Antibacterial wound dressing	Homogeneous morphology and flexibility. Membranes support fibroblast adhesion and proliferation and exert at the same time an antibacterial action against both Gram-negative and Gram-positive bacteria.	[423]
	Acetalated dextran	Resiquimod in ethanol	Tissue engineered skin scaffold	Fibroblasts are integrated into the three-dimensional structure. The controlled degradation rate of dextran allows the release of the bioactive agent which stimulates nitric oxide secretion by macrophages.	[424]
	Methacrylated dextran	PLGA in DMSO and DMF	Tissue engineered skin scaffold	Dermal fibroblasts colonize the entire structure, migrating within the fibrous meshes, where ECM is deposited. The scaffolds support dermal fibroblast contraction, facilitating cytoskeleton rearrangement.	[425]
Pectin	Absent	Chitosan, PVA, tetracycline hydrochloride in acetic acid and water	Tissue engineered skin scaffold	Adequate mechanical properties. Promotion of cell adhesion, proliferation and type I collagen deposition. Mechanical properties and water absorption and release must be ameliorated.	[426]
	Absent	PVA, rectorite in water	Tissue engineered skin scaffolds	Biocompatibility and safety for transdermal application. PVA is used to allow pectin spinnability, which is impaired by high rectorite contents.	[427]
	Oxidized pectin	PEO, gelatin in DMSO	Tissue engineered skin scaffold	Biocompatibility and sustained cell infiltration and proliferation. Degradation can be modulated varying pectin oxidation degree.	[428]
Pullulan	Absent	Sodium alginate, human platelet lysate in water	Tissue engineered skin scaffold	Scaffolds sustain fibroblast proliferation and transition towards a migratory phenotype, promoting skin regeneration and remodeling. Lysate loading affects fiber morphology and mechanical properties.	[429]
	Absent	Chitosan, Ag nanoparticle, Hyaluronic acid or Chondroitin sulphate in water and acetic acid	Antibacterial wound dressing	Good degradation profile in presence of lysozyme. They support fibroblast growth determining cell clustering or spreading. On the other hand, the presence of silver nanoparticle improves scaffold antimicrobial activity. The association of chitosan and chondroitin sulphate impairs nanofibrous mat activity against Gram-negative bacteria because of chitosan positive charges shielding.	[430]
	Absent	Cellulose acetate in DMAc and DMSO	Tissue engineered skin scaffold	Good water uptake capacity and suitable porosity. Good biocompatibility in vitro and promotion of cell adhesion, spreading, and proliferation. Polymer ratio must be set up to achieve the suitable mechanical properties.	[431]

PVA: Poly(vinyl alcohol); PEO: Poly(ethylene oxide); ZnO: zinc oxide; Ag: silver; FA: formic acid; PLA: Polylactic acid; PDLA: poly (*D*-lactic acid); DCM: dichloromethane; HFIP: hexafluoroisopropanol; AAD: adipic acid dihydrazide; PLGA: poly (lactic-co-glycolic acid); TFE: trifluoroethanol; CNCs: cellulose nanocrystals; DMF: dimethylformamide; PCL: Polycaprolactone; BSA: Bovine serum albumin; EGF: epidermal growth factor; TGF-β: Transforming Growth Factor-β; ECM: extracellular matrix; MMPs: matrix metalloproteinases; THF: tetrahydrofuran; DMSO: Dimethyl sulfoxide; DMAc: Dimethyl acetamide.

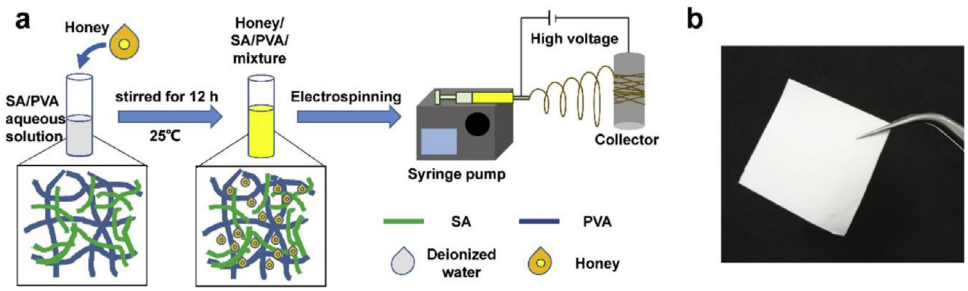

Fig. 13. Alginate electrospun membranes. Schematization of (a) honey/SA/PVA membranes production and (b) illustration of the final product obtained. Reprinted from ref [339], Copyright (2019), with permission from Elsevier.

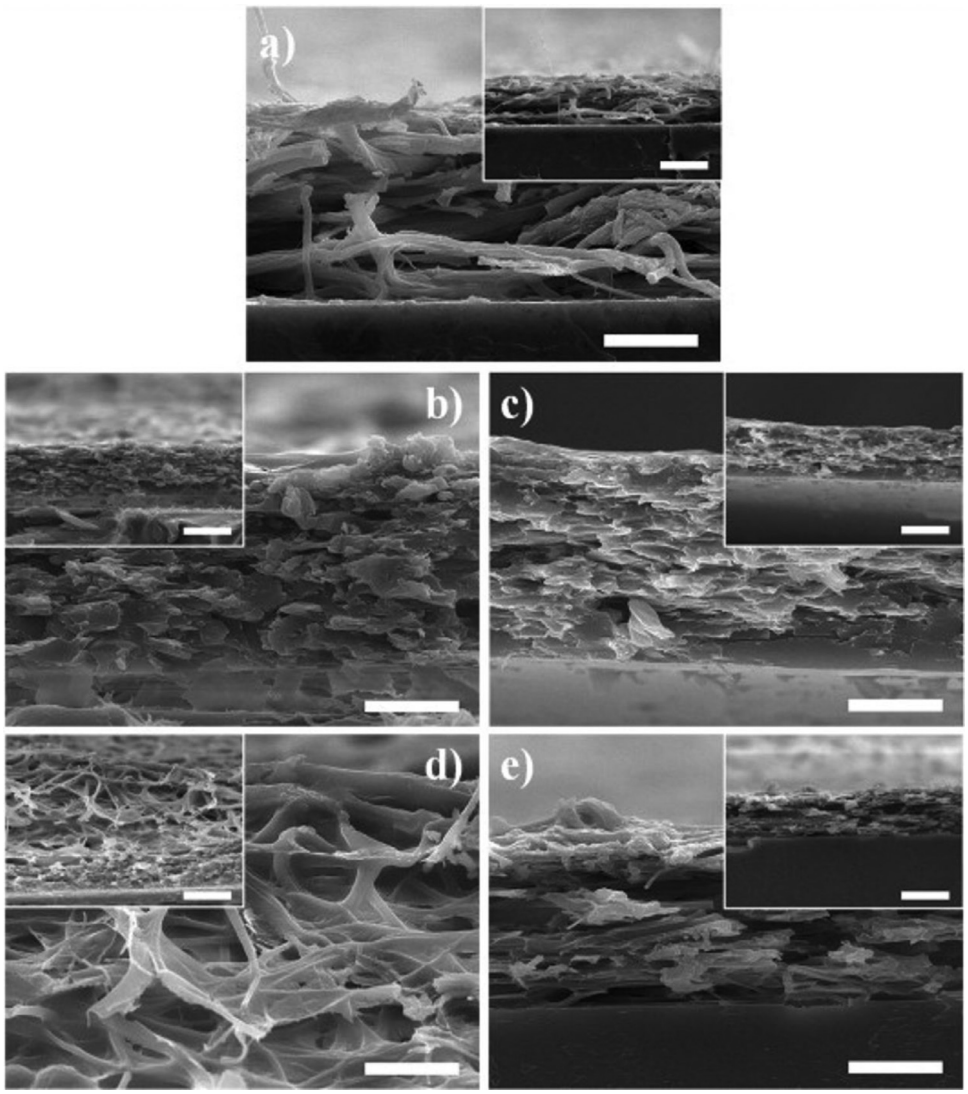

Fig. 14. Chitosan electrospun membranes. Transversal section of platelet adhesion on chitosan membranes after: (a) 10 min of PBS absorption (control, no platelets); (b-c) 10 min of blood absorption on sonicated and non-sonicated mats, respectively; (d-e) 1 min of blood absorption on sonicated and non-sonicated mats, respectively. After sonication, which increases fiber porosity, a higher number of adhered platelets can be seen. At the same time, the lower blood adsorption times determine a reduced platelet adhesion on the nanofibrous structure. Reprinted from ref [348], Copyright (2013), with permission from Elsevier.

sure [242]. The efficacy of chitosan electrospun mats in burns treatment has been analyzed too. Chitosan nanofibers loaded with bromelain, a pineapple extract studied for its role in the debridement of chronic wounds [349], have been realized and, their biocompatibility was assessed in vitro on human dermal fibroblasts; moreover, in vivo studies were performed on induced burns on rats then treated with the electrospun mats. Tissue healing was followed until 21 days and biopsies were analyzed; an effect on re-epithelialization, debridement and reduction of necrotic tissue was observed, revealing good results in view of wound healing applications [350].

Chitosan electrospun membranes have also been implemented with antimicrobial compounds, in order to improve their antibacterial properties. Zou and coworkers designed chitosan/PVA

nanofibers loaded with an antimicrobial peptide encapsulated in carboxymethyl chitosan nanoparticles. The antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* was improved in presence of the antimicrobial peptide. On the other hand, cell adhesion and proliferation proved biomaterial biocompatibility. In vivo studies on full-thickness defects induced on mice revealed faster epithelial regeneration and collagen deposition together with a lower inflammatory response in the case of the medicated group, confirming the effectiveness of chitosan electrospun wound dressings in promoting the healing process and tissue function recovery [351]. Nhi and coworkers investigated the potential wound healing effect of polycaprolactone electrospun membranes coated with chitosan/silver nanoparticles. In order to turn polycaprolactone hydrophobicity into hydrophilicity, the membranes underwent plasma treatment, thus allowing chitosan/silver nanoparticles absorption; an initial silver burst release was detected followed by a sustained release up to 2 weeks. Thus, the antibacterial activity against Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus, Staphylococcus sciuri*) bacteria was evaluated, displaying a good ability to inhibit the growth of all the four types of bacteria. In order to assess mat biocompatibility and possible silver toxic effects, fibroblast attachment and proliferation were evaluated, proving cell viability and the absence of silver toxicity. The as-tested membranes were lastly applied in vivo on mice excisional wounds, hindering the inflammatory response and suggesting the possibility to favour the healing process while preventing bacteria infiltration [352].

3.2.1.3. Hyaluronic acid. Hyaluronic acid is a naturally derived polysaccharide and one of the main ECM components; its unique properties make it one of the best materials in the design of medical devices for skin repair. It is a high molecular weight non-sulfated glycosaminoglycan, its structure is a linear repetition of (β 1 $\rightarrow$ 4)-glucuronic acid and (β 1 $\rightarrow$ 3)-*N*-acetyl-*D*-glucosamine. It is particularly abundant in the extracellular matrix of skin, which contains at least 50% of the total body amount of hyaluronic acid, but it is also found in many connective tissues, such as cartilage, vitreous body, and synovial fluid. Hyaluronic acid plays an important role in many biological processes, such as tissue homeostasis, angiogenesis, tumor biology, and anti-apoptosis activity; these characteristics, together with its intrinsic biocompatibility, biodegradability, viscoelasticity are of paramount importance in view of tissue regeneration and wound healing applications [353,354]. Moreover, its high hydrophilicity, the lubricant and moisturizing properties contribute to skin hydration and reduce the possibility of biofilm formation [355,356]. Hyaluronic acid is recognized by cells through the membrane receptor CD44; the molecular recognition promotes cell adhesion, proliferation, and differentiation [357]. In addition, hyaluronic acid has been studied for its anti-inflammatory and antioxidant abilities; indeed it is involved in all phases of the inflammatory response: it regulates inflammatory cell migration, interacts with inflammatory elements, and executes a scavenging activity towards reactive oxygen species (ROS) and hydroxyl radicals. Therefore, it is largely employed as dermal filler, substrate for dermal regeneration, and in the production of wound dressing materials [358,359]. Among wound dressings, hyaluronic acid-based electrospun mats are particularly attractive, since the biological properties of this natural glycosaminoglycan are combined with the organization in a porous structure, namely the electrospun mat, which nearly reproduce ECM architecture, approaching the natural environment [357].

Hyaluronic acid/PLGA core-shell nanofibrous mats loaded with epigallocatechin-3-O-gallate (EGCG), a polyphenolic compound found in green tea known for its antioxidant and anti-inflammatory properties, have been realized *via* co-axial electrospinning. The EGCG was uniformly incorporated without affecting the thermo-mechanical stability of the membrane and its release in vitro, followed over four weeks, was contemporary to PLGA degradation. Moreover, good fibroblast adhesion and proliferation were observed in presence of EGCG. The healing effects of such electrospun mats have been analyzed on full-thickness wounds in diabetic rats, revealing enhanced skin regeneration, improved re-epithelialization, vascularization, and collagen deposition [360].

The potential of hyaluronic acid as wound healing promoter has been even evaluated in association with chitosan and PCL; a bi-layered scaffold made of chitosan/PCL and hyaluronic acid/PEO electrospun nanofibers has been studied for its morphological, physicochemical, and mechanical characteristics as well as for its biological behaviors. The average fiber diameter (362 $\pm$ 236 nm) was found in the range of collagen fibers (50–500 nm) naturally present in the extracellular matrix. Moreover, improved swelling, hydrophilicity, and water vapor transmission rate were recorded with respect to scaffolds only made of PCL or chitosan/PCL. The bi-layered system was studied for its antibacterial activity too, verifying the inhibition of *Escherichia coli* growth thanks to chitosan antibacterial activity further implemented through the association with hyaluronic acid. Therefore, the ability to provide a suitable environment for an epithelial cell attachment, growth, and differentiation has been assessed showing promising results; cells were able to maintain their morphology, integrate within the nanofibrous mat, and proliferate, suggesting this scaffold as possible candidate for skin tissue engineering use [361].

Hyaluronic acid has also been combined with polyurethane to fabricate electrospun wound dressings. In a recent study, polyurethane/hyaluronic acid nanofibers have been implemented with ethanolic extract of propolis, known for its antifungal, antiviral, antibacterial, and anti-inflammatory properties. The electrospun mats showed good mechanical properties as well as hydrophilicity and water uptake capability due to the presence of hyaluronic acid, even if the hydrophilic behavior and the water intake were lowered when the hydrophobic propolis extract was added. However, the functionalized mats exhibited an increased antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* with respect to non-loaded ones. After confirming the biocompatibility towards fibroblasts in vitro, the polysaccharide-based scaffolds were tested in vivo on dorsal wounds in rats; neither necrotic tissue or infection were observed in the wounded area, and the wound healing progression was improved (Fig. 15) [362].

3.2.1.4. Other polysaccharides. Among the polysaccharides, also cellulose, pectin, dextran, or pullulan stand out as good candidates for the synthesis of electrospun wound dressings.

Cellulose, a linear chain of thousands of glucose molecules linked by β (1–4) glycosidic bond, is the most abundant polysaccharide in nature, which can be extracted from plants. It is known for its biocompatibility and biodegradability aside from its low-cost availability. However, the low solubility in organic solvents and the scarce propensity to form blends due to the strong hydrogen bond network affect the biomedical applicability of this polysaccharide [363]. For this reason, different cellulose derivatives have been investigated. The most studied is cellulose acetate, a biocompatible, biodegradable, non-toxic, and highly hydrophilic derivative widely employed to produce membranes, films, fibers, which can be used in different biomedical fields [364,365]. Among them, its use as wound dressing also in the form of electrospun mats is well documented [366–371]. Nevertheless, because of its poor mechanical properties, the clinical application of cellulose acetate requires the association with other polymers able to compensate for cellulose acetate deficiency [372]. such as polycaprolactone [373]. Zein [374]. Polyurethane [375], or polyvinyl alcohol [376]. Carboxymethyl cellulose is another cellulose derivative largely used for biomedi-

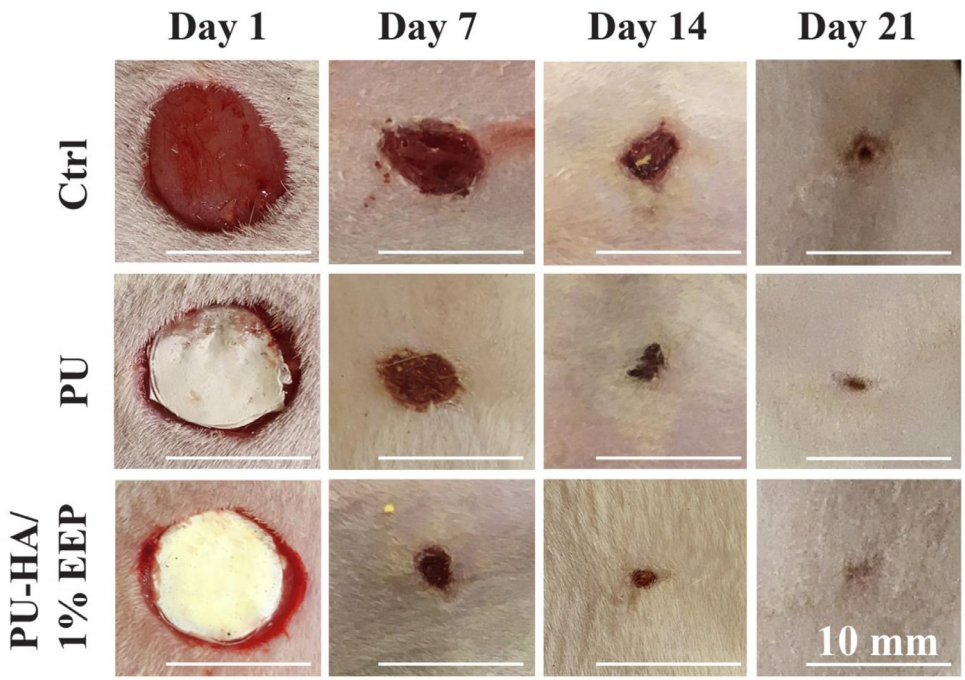

Fig. 15. Polyurethane/hyaluronic acid nanofibers. Photographs of nanofibrous mat application on full-thickness defects and of wound healing progression after 7, 14, 21 days of treatment. Adapted from ref [362], Copyright (2020), with permission from Elsevier.

cal purposes, as wound care management [377]. It is particularly known for its ability to act as drug delivery matrix implementing the bioactive properties of the wound dressing material; carboxymethyl cellulose nanofibers have been loaded with numerous bioactive agents, such as erythromycin [378], tetracycline hydrochloride [379], diclofenac and lidocaine [380], or plant extracts [381].

Plants are not the only source of cellulose, since it can also be produced by some bacteria strains (as *Gluconacetobacter, Alcaligenes, Azotobacter, Achromobacter, Rhizobium, Agrobacterium, Salmonella*) where it is found as a gelatinous layer at the air-liquid interface of the culture medium. Bacterial cellulose possesses similar chemical structure to plant cellulose, but it lacks impurities like lignin or hemicellulose in its high ordered structure besides bringing some advantages in terms of porosity, mechanical strength, permeability, flexibility, or hydrophilicity. It is particularly used in the field of wound healing because its porous three-dimensional network support granulation tissue deposition, exudate absorption, gaseous exchanges while ensuring a moist environment and reducing pain [382–384].

Pectin is the most heterogeneous plant-derived anionic polysaccharide, mainly composed by (1,4)-linked-α-*D*-galacturonic acid (or homogalacturonan (HGA)) linear chains and rhamnogalacturonan (RG) domains, namely rhamnogalacturonan-I (RG-I) and rhamnogalacturonan-II or xylogalacturonan (XGA). The arrangement of these structural components depends on the source of extraction, generating a certain degree of variability in pectin employment [385]. HGA chains allow pectin crosslinking in presence of multivalent cations, while RG domains are responsible for its biological activity. By combining these two features with biocompatibility and mucoadhesiveness, this polysaccharide can be largely used for different biomedical applications, such as anticancer therapy, drug delivery system, bone regeneration, and wound healing [76,386,387]. Even if pectin polyelectrolyte nature could hinder the electrospinning process, different examples in literature report the incorporation of pectin in nanofibrous wound dressings, as it is easily available and inexpensive besides offering skin protection and the possibility to topically deliver drugs which could help the healing process [388–390].

Dextran is a water-soluble polysaccharide readily available from bacteria. It is considered an analogue of extracellular matrix glycosaminoglycans, since it interacts with specific glucan receptors on fibroblasts stimulating growth factor secretion and cell proliferation. For this reason, apart from its biocompatibility, biodegradability, and hydrophilicity, it is applied in numerous biomedical fields, like wound management [391,392]. Due to the hydrophilic nature of this polysaccharide, when synthetizing electrospun wound dressing, the coupling with hydrophobic polymers is always considered an efficient strategy to improve the mechanical strength and the thermal stability of the obtained material [393–395].

Pullulan is a polysaccharide produced from starch by *Aureobasidium pullulans* given by α-1,6-linked maltotriose units. In addition to the common benefits of other polysaccharides (such as biocompatibility, biodegradability, non-toxicity), pullulan, thanks to its particular chemical structure, possesses a high water-absorption capacity, excellent water solubility and adhesive properties as well as the ability to form resilient films and fibers, being an ideal alternative for the production of wound dressing materials [396–399].

Overall, the advantage of employing polysaccharides for wound healing purposes, beyond their ability to recreate a proper structural environment, lies in their bioactive properties, since they act themselves as healing agents; moreover, the bioactivity can be enhanced by the addiction of bioactive compounds, such as antibiotics, anti-inflammatory drugs, or growth factors, which could favour a normal healing process and limit the inflammatory response, thereby promoting re-epithelialization and avoiding the insurgence of possible infections. However, the structural and bioactive properties of such scaffolds are not the only features to consider aiming at the production of a wound dressing material easily adaptable and able to sustain tissue regeneration. Indeed, its stability in an aqueous environment and its degradation rate play an essential role in the formulation of a wound dressing available for the purposes it has been designed for.

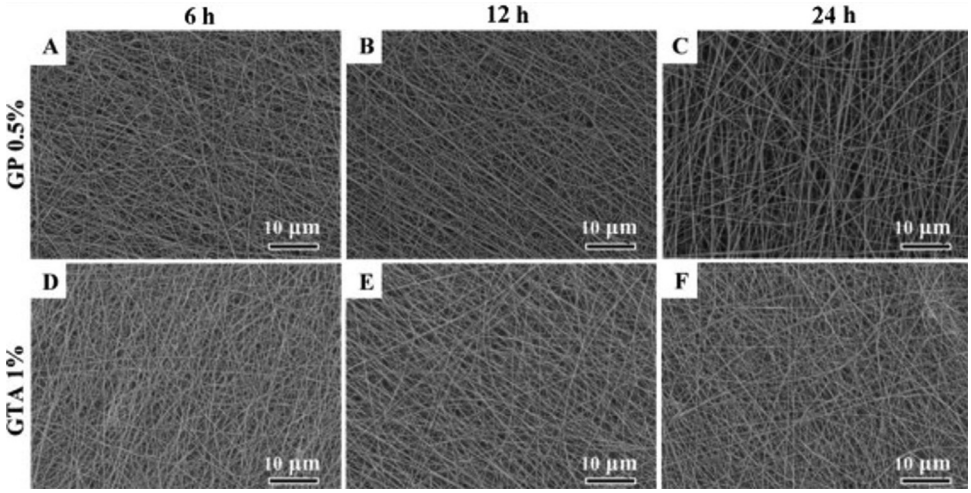

Fig. 16. Crosslinking strategies for chitosan-based membranes. Comparison between chitosan/PEO nanofibrous mats crosslinked with genipin (GP) or glutaraldehyde (GTA) after 6 h, 12 h, 24 h of treatment. Reprinted from ref [447], Copyright (2015), with permission from Elsevier.

3.3. Improvement of electrospun wound dressings features

3.3.1. Stability and crosslinking

One of the drawbacks related to the use of natural polymers and, in particular, polysaccharide-based electrospun mats for biomedical applications is their instability and rapid hydrolysis in an aqueous environment; thus, usually an adequate crosslinking procedure has to be carried out in order to improve their stability as well as the mechanical properties, while preserving their fibrous structure [432,433]. Different strategies have been attempted over the years in order to crosslink natural polymer biomaterials, ranging from chemical to enzymatic to physical methods (Table 7): chemical crosslinking involves the formation of covalent bonds between polymer chains, using coupling and crosslinking agents [434]; physical crosslinking includes strategies such as irradiation (γ-irradiation, UV irradiation, high-energy electron beam irradiation) or heat treatments [435]; enzymatic crosslinking considers the employment of specific enzymes to catalyze precise chemical reactions (transglutaminase, oxidoreductases) [436].

The chemical approach has been widely explored in the last ten years to realize natural polymer crosslinking. Glutaraldehyde is largely employed as chemical crosslinking agent, even if its use is associated in some cases to by-product cytotoxicity and a low crosslinking reactivity. [437–440]. Carbodiimide-based crosslinkers are one of the most used class of chemical crosslinkers, among them the EDC-NHS (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-*N*-hydroxysuccinimide) is the most represented. Carbodiimide-based crosslinkers have the advantage to be less toxic than glutaraldehyde, in addition to a high conversion efficiency and to the ability to act also in mild reaction conditions [441–444]. On the other hand, despite its high cost, genipin has been also studied as crosslinker for biopolymers containing residues with primary amine groups; furthermore, it exhibits lower toxicity after crosslinking if compared with glutaraldehyde (Fig. 16) [445–447]. Physical crosslinking is mainly performed using UV irradiation, which, in presence of a specific photoinitiator, determines radical formation, thus activating chemical groups on polymer chains and leading to the formation of a crosslinked network; despite its efficacy it can cause a partial degradation of the polysaccharide contained into the membrane [448,449]. As an alternative physical method, controlled thermal treatment has been successfully attempted, because it favors polymer chain entanglement together with amide bond formation [450].

Mirzaei and coworkers compared genipin-crosslinked wound dressings of chitosan/PEO to glutaraldehyde-crosslinked ones. In both cases, the fibrous structure was maintained after crosslinking, even in presence of water. On the other hand, the swelling ratio did not significantly decrease using genipin as crosslinking agent, while the presence of glutaraldehyde led to a significant reduction of the swelling ratio when compared with non-crosslinked mats. Moreover, cytotoxicity studies revealed good fibroblast adhesion and proliferation in presence of genipin, while glutaraldehyde crosslinked membranes caused a significant reduction of cell viability with respect to the control, suggesting the use of genipin as an efficient alternative for polymer-based dressing crosslinking [451].

A study by Adeli and coworkers showed that the effects of glutaraldehyde used as a crosslinker depends on the protocol adopted and the material used for membrane design. In this study, PVA/chitosan/starch nanofibrous mats were crosslinked using glutaraldehyde vapor, revealing uniform structure, high porosity, good water absorption and water vapor transmission ability, and an appropriate degradation rate in phosphate buffered saline (PBS). In addition, adequate mechanical strength and flexibility were observed both in dry and wet state. In vitro tests proved the biocompatibility of the crosslinked membranes and their antibacterial action against *Escherichia coli* and *Staphylococcus aureus*. Moreover, the wound healing ability was tested in vitro by means of a scratch assay, demonstrating good cell migration and so the potential application of these electrospun mats, with limited side effects deriving from the use of glutaraldehyde [452].

Another strategy, adopted by Séon-Lutz and coworkers, was used to obtain hyaluronic acid based-nanofibers for wound dressing application (Fig. 17). Hyaluronic acid was dissolved in water, and the electrospinning process was facilitated by the addition of PVA. Moreover hydroxypropyl-β-cyclodextrin was added as a stabilizer and served for the encapsulation and controlled release of naproxen, an anti-inflammatory drug. Membranes were crosslinked by the addition of EDC-NHS, obtaining uniform and stable nanofibers even in presence of high relative humidity levels (90%). As the chemical crosslinking was insufficient to ensure stability after the immersion in water, an additional step of freeze-drying was necessary to avoid fibers dissolution. Mechanical tests revealed the transition from a very rigid scaffold in dry state to a softer one once hydrated, which could allow a better conformation to the wound shape without breaking. Moreover, no cytotoxic behavior was observed, and a burst release of naproxen was detected

Table 7
Schedule of the principal crosslinking strategies and the chemical mechanism underlying the crosslinking process. Acronyms are defined at the end of the table.

Crosslinking method	Crosslinking agent	Polymers	Chemical modification	Reference
Physical	Heat	Chitosan Pullulan Chondroitin sulfate Hyaluronic acid	Citric acid and thermal treatment at 150 °C. Heat activates citric acid, whose carboxylic moieties bind chitosan amino groups. Moreover, heat treatment promotes physical entanglement between fibers.	[454]
		Chitosan PVA	EGDE reacts with chitosan hydroxyl groups. The crosslinking reaction is catalyzed by heating at 60 °C.	[455]
		Keratin PVA	Thermal crosslinking at 140 °C with the aid of citric acid, whose carbonyl groups react with PVA hydroxyl moieties.	[456]
	UV irradiation	MHA MaPVA	The photoinitiator D-2959 is activated upon UV irradiation, which allows the reaction between maleilated hyaluronate acrylic vinyl groups and methacrylated PVA by free radical polymerization.	[457]
		MACSPVA	The UV activation of photoinitiator D-2959 leads to the crosslinking of the vinyl groups of methacrylated chitosan.	[458]
		Alginate PEO GelF-MA	Membranes are soaked in a Ca^{2+} bath and further photocrosslinked by means of UV irradiation thanks to the addition of Irgacure 2959 radical photoinitiator.	[459]
	γ irradiation	Cellulose Gelatin CNCs	γ radiation promotes the formation of hydrogen bonds between gelatin amino acid residues.	[460]
		Chitosan PVA	γ rays induce the radiolysis of water present in the PVA solution, leading to the formation of free radicals along the polymer chains. Chitosan hydroxyl and amino groups are activated allowing PVA-chitosan radical copolymerization.	[461]
		CMHA	The radiolysis of water induced by γ irradiation leads to the formation of radicals at the secondary carbon of the carboxymethyl groups determining hydrogel crosslinking.	[462]
Chemical	Aldehydes	SLA	Hydrogel membrane are crosslinked by coupling calcium ion (for the ionic crosslinking of guluronic residues) with glutaraldehyde (for the chemical crosslinking of alginate hydroxyl moieties).	[463]
		Chitosan Pullulan	After thermal crosslinking, electrospun mats have been immersed in cinnamaldehyde, whose carbonyl groups react with chitosan amino groups through Schiff base reaction	[464]
		Gelatin Chitosan	Cinnamaldehyde and glutaraldehyde have been combined to crosslink gelatin/chitosan membranes. The formation of intermolecular hydrogen bonds between adjacent hydroxyl groups and of new imine (C≡N) linkages leads to matrix crosslinking.	[465]
	Amidic coupling	Pullulan Gelatin	Carbonyldiimidazole activates pullulan hydroxyl moieties leading to the formation of carbonate groups (-OCOO-) between pullulan chains; moreover, it also promotes the formation of carbamate (-OCONH-) and carbonate ester (-OCO-) groups between pullulan and gelatin.	[466]
		Gelatin Hyaluronic acid CNCs	EDC-NHS crosslinking solution has been added to the polymer mixture; EDC activates the carboxylic moieties of gelatin and hyaluronic acid creating an acid anhydride, which can form an amide bond with gelatin amino groups or an ester one with hyaluronic acid hydroxyl moieties.	[467]
		Hyaluronic acid	EDC-NHS crosslinkers have been employed to promote intra-fiber crosslinking exploiting the esterification of hyaluronic acid carboxyl and hydroxyl groups.	[468]
	Genipin	Gelatin Nanocellulose	Genipin crosslinking is performed through nucleophilic attack of gelatin amino group to the olefinic carbon atom (C3) or to the carboxylic group of genipin, leading to genipin carbonyl and dihydropyran ring opening or to amide bond formation, respectively. Nanocellulose has been incorporated into the crosslinked network thanks to physical entanglement.	[469]
		Chitosan PET	Genipin-crosslinked chitosan has been immobilized on polyethylene terephthalate, where the crosslinking reaction is provided by the nucleophilic attack of chitosan primary amine to genipin ester function, forming a secondary amide, or to genipin dihydropyran ring, realizing a nitrogen heterocycle.	[470]
		Chitosan PVA	Genipin reacts with chitosan primary amines to form secondary amides; PVA is incorporated through physical entanglement.	[471]
Enzymatic	Transglutaminase	Collagen CMCS CMCL	Transglutaminase added to the film preparation mixture catalyzes the formation of protease-resistant ε-(γ-glutamyl) lysine covalent linkages through an acyl-transferase reaction, where the γ-carboxamide group of peptide-bond glutamine acts as acyl donor and the ε-amino group of lysin as acyl acceptor.	[472]
		Gelatin PVA	Microbial transglutaminase has been added to the electrospinning solution, since it needs an aqueous environment to operate. The crosslinking reaction is contemporary to the electrospinning process.	[473]
		Gelatin HPC	Gelatin crosslinking has been obtained through the transglutaminase-mediated formation of ε-(γ-glutamyl) lysine covalent bonds, while glutaraldehyde has been used to react with hydroxypropyl cellulose hydroxyl groups. Moreover, additional entanglement has been obtained thanks to the formation of hydrogen bonds between gelatin and free hydroxyl groups of hydroxypropyl cellulose.	[474]
	Oxidoreductase	Chitosan Gelatin	Tyrosinase-CNK catalyzes the oxidation of gelatin tyrosine residues, which allows gelatin covalent grafting on chitosan chains leading to permanently crosslinked gels.	[475]
		Silk fibroin mHA	Laccase catalyzes intermolecular crosslinking of silk fibroin/hyaluronic acid network through the oxidation of *p*-hydroxyphenylacetamide and tyramine phenolic hydroxyl groups leading to the formation of polymerization products.	[476]
		Chitosan PVA	Both chitosan and PVA have been modified with phenolic hydroxyl groups to allow horseradish peroxidase activity, which catalyzes the conjugation of phenol derivates by reducing hydrogen peroxide added to the solution.	[477]

EGDE: Ethyleneglycol diglycidyl ether; PVA: Poly(vinyl alcohol); MHA: Maleilated hyaluronate; MaPVA: methacrylated poly (vinyl alcohol); MACS: Methacrylated chitosan; PEO: Poly(ethylene oxide); GelF-MA: Methacrylated gelatin; CNCs: Cellulose nanocrystals; CMHA: Carboxymethyl hyaluronic acid; SLA: Sulfanilamide-loaded sodium alginate; EDC: *N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide; NHS: *N*-hydroxysuccinimide; PET: Polyethylene terephthalate; CMCS: Carboxymethyl chitosan; CMCL: Carboxymethyl cellulose; HPC: Hydroxypropyl cellulose; mHA: Tyramine-modified hyaluronic acid.

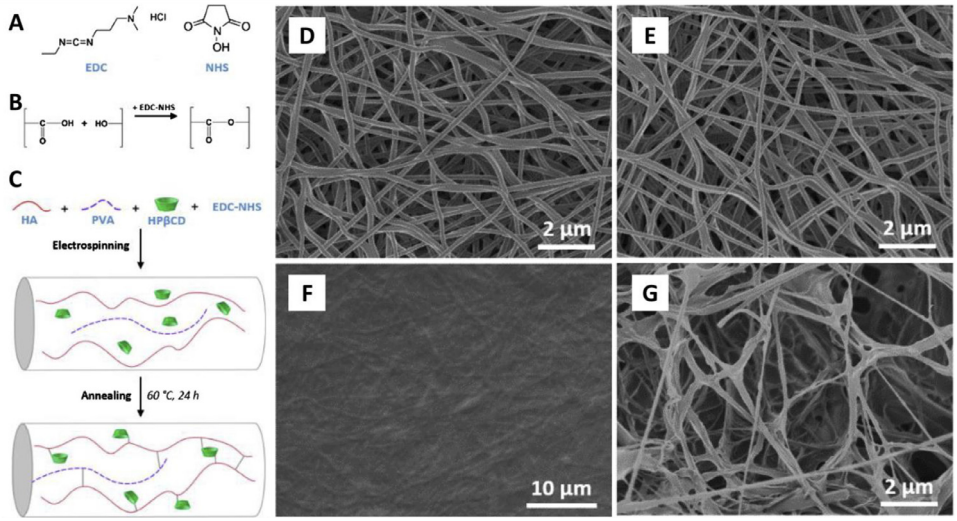

Fig. 17. Crosslinking strategies for hyaluronic acid-based membranes. Schematization of (A) EDC-NHS chemical structure, of (B) the in situ crosslinking reaction, and of (C) the production of crosslinked HA/PVA/HPβCD nanofibres. SEM microgrphs of crosslinked mats (D) before annealing, (E) after annealing, (F) after 48 h soaking in water and ambient drying, (G) after 48 h soaking in water followed by freeze-drying. Adapted from ref [453], Copyright (2019), with permission from Elsevier.

after 24 h followed by a lower and sustained release, which could be advantageous to control wound inflammation and avoid acute pain [453].

The use of crosslinking agents is of pivotal importance to confer electrospun membranes the proper stability and mechanical strength in view of wound treatment. However, there is not absolute concert in the choice of the best crosslinker, since all the agents in use present both advantages and disadvantages, depending on the crosslinking mechanism as well as from the composition of the membrane itself. Undoubtedly, the main concerns are related to the possibility to obtain stable and biocompatible medical devices, where the introduction of any possible crosslinker does not produce side cytotoxic effects preserving at the same time all the favorable features which characterize the material. For this reason, the crosslinking of electrospun membranes is still an open field, with an increasing interest in finding the most appropriate crosslinking strategy which could be effective for a broad spectrum of membrane formulations avoiding any toxic outcome.

3.3.2. Biofunctionalization

Although some polysaccharides own intrinsic biological properties, the functionalization of the final wound dressing material with bioactive moieties, which can be topically released, can be greatly beneficial to further stimulate the progression of a normal healing path and promote total tissue recovery in an aseptic microenvironment. Thus, the implementation with bioactive compounds (also referred as biofunctionalization) which could exert an antimicrobial action as well as accelerate re-epithelialization and limit the pain associated to the wound and the inflammatory process is of assume great importance in the design of an electrospun scaffold for skin tissue engineering applications (Table 8). The aim of the biofunctionalization is to achieve and accelerate complete tissue recovery, in terms of both structural and functional integrity, while reducing the convalescence time. The bioactive compounds that can be added to electrospun membranes and scaffolds can be chosen basing on their natural involvement in the healing process or according to their ability to assist this process.

Growth factors, such as VEGF, PDGF, TGF-β, EGF, are typically secreted after injury, at the beginning of the healing cascade activation, and are involved in angiogenesis, tissue regeneration and remodeling; therefore, their use could favour the desired structural and functional recovery (Fig. 18) [478,479].

The wound site is often susceptible to infections, so measures to prevent the infiltration and growth of bacteria and other microorganisms are needed, paving the way for a variety of antimicrobic biohybrid dressings [480]. Electrospun scaffolds can be enriched with antibiotics, for example ciprofloxacin, metronidazole, and mafenide acetate, or antibacterial wide spectrum agents, such as silver nanoparticles, zinc oxide nanoparticles, antimicrobial peptides. These compounds are already widely employed in case of infected wounds or are adopted to enhance the antimicrobial behavior of wound dressings [321,481–484].

An interesting class of bioactive compounds that can be used for biofunctionalization is represented by vitamins. Vitamin E has an anti-inflammatory activity, helps coagulation and angiogenesis, and reduces scar induction. Vitamin D is involved in the regulation of the immune response, improves re-epithelialization and granulation tissue formation, and mitigates the development of excessive inflammation besides regulating calcium homeostasis. Vitamin C enhances the expression of collagen and acts as antioxidant as it is able to quench and react with different radical oxygen species [485–487].

Anti-inflammatory, analgesics, and anesthetic drugs, for example non-steroidal anti-inflammatory drugs, can be even employed to reduce the patient's pain [488–490].

The porous and nanofibrous nature of electrospun wound dressing along with their high surface-to-volume ratio allow the fine tuning of drug loading and encapsulation and the fine control of drug release. Moreover, alternative electrospinning methods (as coaxial electrospinning) can be used to achieve multiple drug loading within electrospun membranes, or to control the release of loaded drugs [491,492].

As an example, carboxymethylchitosan (CMCS)/PEO nanofibers have been functionalized with vitamin C and phenytoin sodium, for its documented anti-inflammatory activity and its ability to modulate exudate production [493]. The two drugs were separately dispersed in two aliquots of the CMCS/PEO solution and a two-syringe system was used to obtain the dual-functionalized electrospun membrane. Release studies demonstrated a sustained release over time which was translated in an increase of the healing efficiency, resulting in the regeneration of the basal layer of epidermis without the presence of inflammatory cells, observed in an in vivo study carried out for 14 days [494].

Table 8
Examples of electrospun nanofibers functionalized membranes with various types of bioactive compounds. Acronyms are defined at the end of the table.

Therapeutic agent class	Bioactive compound	Polymers	Method for incorporation	Biological effects	References
Vitamins	E	Cellulose acetate	Dissolution into polymer mixture before electrospinning	It possesses antioxidant properties protecting skin from ROS attack.	[497]
	C	Alginate PEO	Addition to polymer solution ahead of electrospinning	It can scavenge free radicals produced by skin, reduce tyrosinase activity, and increase pro-collagen gene activity.	[498]
	D	Collagen PLGA	Dissolution into polymer blend enriched with bovine serum albumin as carrier	It modulates the immune response regulating at the same time the inflammation process and the production of endogenous antimicrobial peptides.	[499]
	B12	Chitosan	Loading onto polymer solution prior to electrospinning	It enhances skin cell proliferation also favoring the angiogenesis process during wound healing.	[500]
	A	Gelatin	Addition to gelatin solution before the electrospinning process	It increases the production of collagen close to the injured site.	[501]
Growth factors	VEGF	Chitosan PEO	Incorporation within nanofibers by blending with polymer solution	It promotes angiogenesis during the early stage of wound healing and the deposition of granulation tissue.	[478]
	PDGF	Hyaluronic acid Collagen Gelatin	Loading on gelatin nanoparticles then blended with hyaluronic acid solution	It plays a pivotal role as initiator and modulator of wound healing besides stabilizing new vessels.	[502]
	EGF	PCL Chitosan PVA	Adsorption and covalent immobilization on scaffold surface	It stimulates cell migration and proliferation thus allowing granulation tissue deposition and skin reconstruction.	[503]
	TGF-β1	PCL	Bioink printing onto electrospun nanofibrous matrices	It supports the deposition of new ECM at the wound site.	[504]
	b-FGF	PLLA Dextran	Addition of b-FGF functionalized dextran glassy nanoparticles to PLLA solution before electrospinning	It promotes angiogenesis, cell proliferation, migration, and differentiation, enhancing wound healing and reducing scar formation.	[505]
Antibiotics	Gentamicin	Ethyl hydroxy ethyl cellulose PVA	Admixture of gentamicin-loaded halloysite nanotubes to polymer blend	It possesses a broad-spectrum activity against both Gram-positive and Gram-negative bacteria, responsible for serious infections.	[506]
	Tetracycline hydrochloride	N-maleoyl-functional chitosan PEO	Incorporation into the electrospinning solution	It is commonly used in the treatment of various types of cutaneous bacterial infections.	[507]
	Ciprofloxacin hydrochloride	Alginate PEO	Blending with polymers prior to electrospinning	It is a bactericide antibiotic active against a broad spectrum of bacteria for the treatment of mild-to-moderate infections.	[508]
	Levofloxacin	Chitosan PVA	Conjugation through cleavable amide bond formation with chitosan, then added to the electrospinning solution	It exerts a broad-spectrum activity, being useful in case of mild-to-moderate bacterial infections.	[509]
	Cephalexin	Gelatin methacryloil PCL	Incorporation into precursor solution prior to electrospinning	It reduces bacterial infections with a broad-spectrum bactericide activity against Gram-negative and Gram-positive bacteria.	[510]
Antimicrobial agents	Sulfonamide	Cellulose acetate PEO PLA	Addition to polymer blend before electrospinning	It possesses antiviral and antimicrobial efficacy, being effective, among others, against a broad spectrum of Gram-positive and Gram-negative bacterial strains.	[511]
	Ag nanoparticles	Pectin PEO	Immersion of crosslinked membranes in an $AgNO_3$ solution, thus allowing Ag^+ entrance and in situ reduction to locally nucleate homogenously dispersed Ag nanoparticles	They display good antimicrobial properties against a broad spectrum of microbes and parasites; additionally, their large surface area favors the contact with microorganisms to be killed.	[512]
	ZnO nanoparticles	Gelatin	Production of ZnO nanoparticles through hydrothermal reaction by using graphene oxide as support and subsequent spraying of the as-formed nanocomposites on gelatin nanofibers	They exert an antimicrobial activity against a wide variety of pathogens, while ensuring safety and biocompatibility.	[513]
	Nisin	Cellulose acetate PCL PVP	Use of triaxial electrospinning to create a three-layered system with PVP-nisin constituting the core of the structure	It is an antimicrobial peptide with a narrow spectrum activity against Gram-positive bacteria or Gram-negative ones when associated to chelating agents.	[514]

(*continued on next page*)

Table 8 (*continued*)

Therapeutic agent class	Bioactive compound	Polymers	Method for incorporation	Biological effects	References
Analgesic/anti-inflammatory drugs	Ibuprofen	HPMCPVP	Dissolution into PVP and hydroxypropyl methyl cellulose solutions and dual spinneret electrospinning to produce a wound dressing which allows, respectively, a faster and lower release of ibuprofen	It belongs to the class of NSAIDs and is extensively used in the treatment of various types of moderate pains.	[515]
	Naproxen	PCL Chitosan nanoparticles	Addition to PCL solution parallel to chitosan nanoparticles to obtain core-sheath nanofibers with naproxen to be released in the sheath layer	It is an analgesic/anti-inflammatory NSAID usually employed in the treatment of pain, fever, or inflammation.	[516]
	Diclofenac	Na-CMC	Adsorption on wound dressing surface	It is a useful local pain killer, favoring wound healing and reducing inflammation and stress-related pain.	[517]
	Flurbiprofen	PEO Silk fibroin Collagen	Mixing with PEO solution as shell constituent of core/shell nanofibers	It is an analgesic, anti-inflammatory, antipyretic NSAID generally used in the treatment of mild-to-moderate pain.	[518]
	Ketoprofen	Ethyl cellulose Poly(N-isopropylacrylamide)	Direct addition to precursor electrospinning solution	As component of NSAIDs, it possesses anti-inflammatory and analgesic activity, being effective in case of acute and chronic pains.	[519]
	Salicylic acid	Collagen PVA	Dissolution into PVA solution followed by blending with collagen	It is often used for local pain relief and inflammation treatment.	[520]
	Paracetamol	HPMCAS PVP	Dissolution in the polymer mixture and sonication before electrospinning	It is an effective analgesic drug in presence of mild-to-moderate pain relief.	[521]
Anesthetics	Lidocaine	Chitosan PCL	Addition to chitosan solution, then separately electrospun with respect to PCL through a dual spinneret electrospinning set-up	It is a local anesthetic drug largely employed for the treatment of wound related pain.	[522]
	Benzocaine	Cellulose acetate	Mixing of benzocaine into cellulose electrospinning solution	It is often used to topically anesthetize the injured site limiting the pain associated to skin disruption.	[523]

PEO: Poly(ethylene oxide); PLGA: poly (lactic-co-glycolic acid); VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; EGF: Epidermal growth factor; PCL: Polycaprolactone; PVA: Poly(vinyl alcohol); TGF-β1: Transforming Growth Factor-β1; ECM: extracellular matrix; bFGF: basic fibroblast growth factor; PLLA: poly (*L*-lactic acid); Ag: silver; ZnO: zinc oxide; PVP: Polyvinylpyrrolidone; HPMC: Hydroxypropyl methyl cellulose; NSAIDs: non-steroidal anti-inflammatory drugs; Na-CMC: Sodium carboxymethyl cellulose; HPMCAS: Hydroxypropyl methyl cellulose succinate.

Saudi and coworkers developed a PCL/chitosan nanonet-nanofiber electrospun mesh implemented with diclofenac sodium anti-inflammatory drug. The incorporation of the drug did not affect fiber chemical structure, but it helped the formation of a new ultrafine nanonet phase on the already present structure and changed nanofiber morphology, crystallinity, and mechanical behavior. A slow release kinetic was observed, both by diffusion of the drug or permeation through the mesh. Furthermore, in vitro studies on mouse fibroblasts revealed good biocompatibility of such structures, presenting them as suitable high payload platforms [495].

In a similar strategy, a chitosan/alginate wound dressing has been formulated for the local release of gentamicin, showing good antibacterial activity in vitro against *Staphylococcus aureus* and *Escherichia coli* as well as biocompatibility towards fibroblasts. The drug release was dependent on gentamicin concentration, and, in case of high concentrations, a burst release was observed within the first 12 h, followed by a lower and sustained release for 10 days. Then, in vivo studies found the better concentration of antibiotic, at which greater re-epithelialization, dense collagen formation, and development of blood vessels, hair follicles, and sebaceous glands were observed (Fig. 19) [496].

Consequently, a tissue engineering approach in which porous nanofibrous polysaccharidic scaffolds are endowed with bioactive factors is a key step in enhancing polysaccharide intrinsic biological properties, thus accelerating skin regeneration. Indeed, numerous compounds can rebalance the healing process, helping cell activity and proliferation, stimulating angiogenesis and re-epithelialization, modulating the inflammatory response and the remodeling process, and avoiding the onset of infections. All these factors can be finely tuned by properly combining polysaccharides and bioactive agents, even considering the type of wound the synthetized material must be applied to.

3.4. From bench to bedside

Notwithstanding all their benefits and the numerous examples in literature supporting their promising application in wound treatment, to the best of the authors' knowledge the only commercialized electrospun polysaccharidic dressing is SurgiCLOT®, a dextran-based fibrin sealant patch specifically thought for bone bleeding. Indeed, the production of polysaccharidic electrospun matrices entails some criticalities which hamper their placing on the market and clinical application [524].

As already discussed, electrospinning is a simple and effective technique to obtain ultra-fine fibers with a wide variety of polymers. However, numerous variables are responsible for the success of the electrospinning process, namely operational, solution and environmental parameters. Among them, solution parameters play a critical role in defining the spinnability and mainly depend on the polymers chosen for membrane synthesis. Considering polysaccharide viscosity, surface tension, electrical conductivity as well as their molecular weight and chain entanglement, numerous concerns are related to the electrospinning of these natural polymers [417,525–527], entailing the association with synthetic polymers to improve solution spinnability as well as the otherwise weak me-

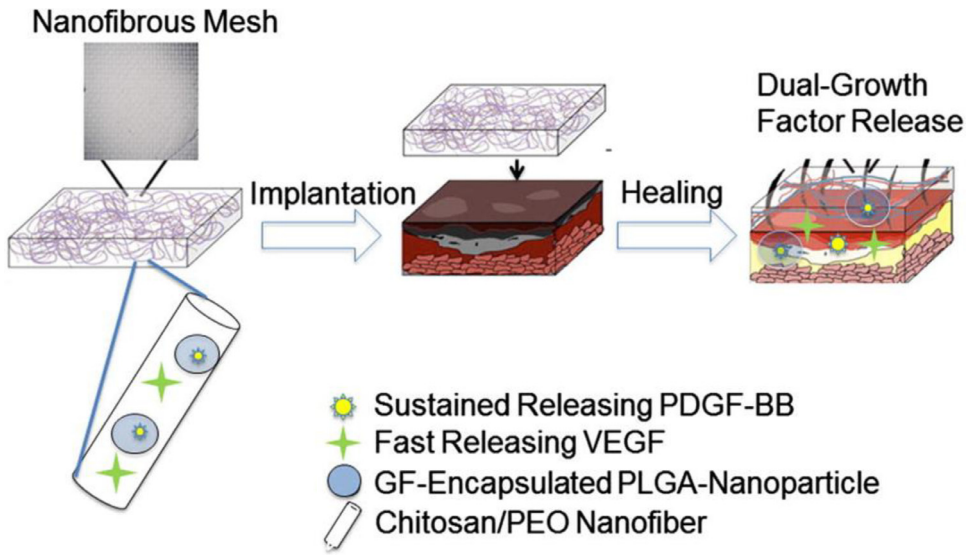

Fig. 18. Biofunctionalized membranes. Schematic representation of growth factor-functionalized nanofibrous mats application on a wound and of the dual release mechanism thought to promote the healing process. Reprinted from ref [478], Copyright (2013), with permission from Elsevier.

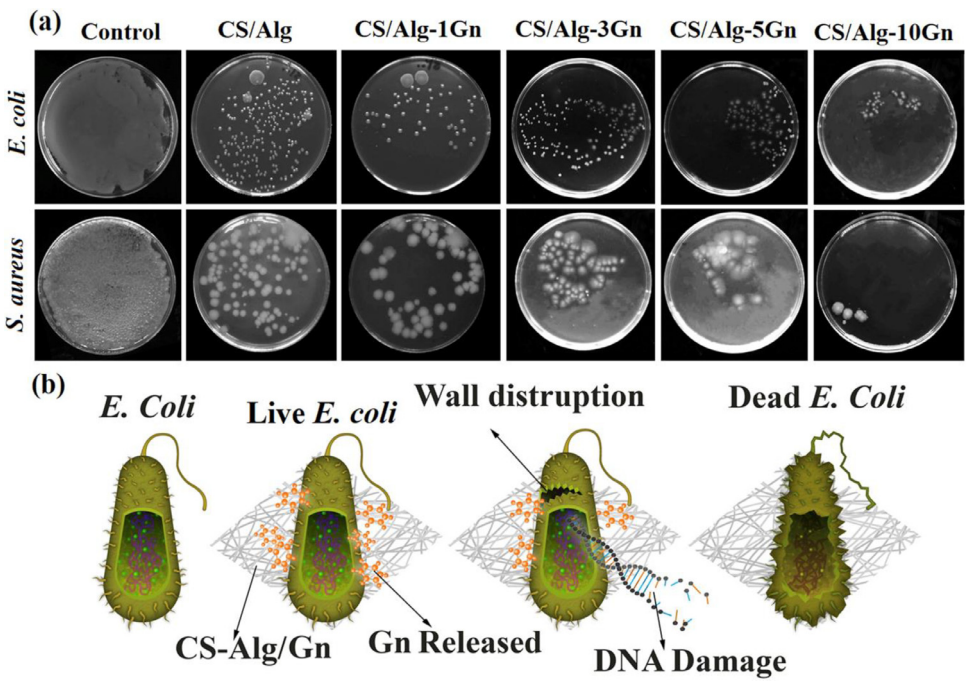

Fig. 19. Biofunctionalized antibacterial membranes Illustration of (a) E. coli and S. aureus CFU on chitosan/alginate membranes implemented with different gentamicin concentrations (1, 3, 5, 10 wt%). Schematization (b) the antibacterial mechanism underlying the functionalized nanofibrous mats. Reprinted from ref [496], Copyright (2020), with permission from Elsevier.

chanical properties of the final product [528–530]. However, when blending natural and synthetic polymers, it is fundamental that the polymers to be mixed are chemically compatible; at the same time, the proper solvent must be chosen to allow adequate miscibility and spinnability. In most cases, organic solvents are selected, since most polymers are not soluble in water, and even mixtures of solvents are often employed to ensure successful blending. Nevertheless, the use of organic solvents affects membrane biocompatibility; so, if water cannot be used, some additional steps are needed to throw residual solvents out [531–534].

Another critical point in polysaccharide-based mat synthesis is constituted by the stability in water of the as-produced membranes; indeed, considering their application as wound dressings, the ability to resist in an aqueous environment as well as the swelling capacity and the possibility to absorb fluids is fundamental. To solve this problem, a post-processing crosslinking procedure must be carried out, thereby stabilizing the nanofibrous structure in water and allowing its application to the wound, paying particular attention on the biocompatibility of the crosslinker to be used [535,536].

In addition, advanced wound dressings often include the controlled release of specific therapeutic agents incorporated, thus requiring the use of tailored encapsulation strategies which do not alter solution parameters or the stability of the membrane; this implies a fine control of the encapsulation efficiency and the degradation rate in order to tune the release profile of

such compounds and leave space to the new forming tissue [537,538].

Nanofibrous wound dressing to be applied on humans also need to be properly sterilized. Different sterilization procedures should be performed, but it is essential to assess how this procedure affects membrane mechanical and physicochemical properties. Indeed, conventional sterilization methods (such as autoclaving, dry heat, steam, gamma radiation, ethylene oxide, peracetic acid, plasma, ozone gas sterilization, or UV disinfection) can be used on nanofiber-based products, but biodegradable polymers could be susceptible to high temperatures as well as to other strong treatments, which determine chain scission with consequent mechanical instability. Hence, the correct treatment must be selected basing on the specific composition of the nanofibrous material, finding the best compromise between sterilization and structural integrity [539,540].

Given the complexity of process and post-process parameters to control, it must be also considered that the commercialization of these medical devices entails large-scale production. The relatively low productivity of a traditional laboratory set-up impedes to scale-up, requiring the exploitation of other set-ups and technologies (such as multiple-needle electrospinning or melt electrospinning) to produce large-scale membranes. The major difficulties are related to the administration of large volumes, to the precise control of all critical production steps ensuring adequate reproducibility in maintaining the desired membrane functionality, and to the environmental impact that such massive production could imply [238,541].

Whilst the numerous complications in satisfying the market demand, the use of polysaccharidic nanofibrous wound dressings could determine considerable advantages in the field of wound care. In fact, different polysaccharide-based wound dressings are already on the market, proving their effectiveness in wound management. This is the case, for example, of TraumaStat™, HemCon®, Algisite, CarraSorb H, Hyalomatrix®, Laserskin® [542–544].

On the other hand, to confer these polysaccharides the form of nanofibers could be an advance in wound management, since they could act as porous, highly absorbing, biomimetic scaffolds, which replicate extracellular matrix structure and functionality, further enhancing tissue regeneration and functional recovery.

To this end, it is essential to step forward into the implementation of industrial electrospinning procedures and strategies to overcome the present limitations and allow a massive and more precise control in the development of polysaccharide-based wound dressing materials.

4. Conclusions

Chronic wounds are a worldwide increasing problem, since they evolve in a persistent inflammation phase which leads to tissue loss, with dramatic consequences for the patient. Thus, numerous studies and efforts are focused on the production of wound dressings which could help wound resolution and epithelial tissue formation. Several classes and types of wound dressing materials have been already synthetized and commercialized, but there is not an absolute criterion to choose the most appropriate one; the wound characteristics (such as size, presence of mild or big exudates, formation of necrotic tissue, level of inflammation) guide the choice of the proper dressing. The characteristics, the advantages and the drawbacks and the clinical uses of these medical devices have been here thoroughly revised.

Electrospinning arises as a promising technique in the treatment of chronic wounds, as electrospun nanofibrous wound dressings offer a good biomimicry; they strictly reproduce the architecture of the extracellular matrix (ECM) conforming their shape to the wound site and efficiently promote hemostasis, absorption of wound exudates, and permeability, while avoiding scar formation.

To this end, the choice of the polymer to be used in the production of these electrospun membranes is of pivotal importance to reach the prefixed goal, which is the tissue regeneration and the complete recovery of tissue function. Synthetic polymers are known for their great mechanical properties, thermal stability, and degradation profile, but they lack intrinsic properties possessed by natural ones, as the ability to stimulate cell adhesion, proliferation, and differentiation thanks to the presence of peptide sequences recognized by cell surface receptors as well as the possibility to reproduce an environment as close as possible to that of native ECM, as most of the natural polymers (collagen and hyaluronic acid above all) are constitutively present in the ECM. Several strategies, here reported, can be used to endow the wound dressings with bioactive and antibacterial properties, using drugs and compounds which can be loaded, embedded or linked to the nanofibers.

However, electrospun mats based solely on natural polymers, as proteins and polysaccharides, possess weak mechanical strength in addition to the complexity of the electrospinning process given the poor spinnability of the obtained solutions. Therefore, blending natural and synthetic polymers has been proved as an efficient approach to combine, respectively, biocompatibility and bioactivity with strength and stability in time.

Among natural polymers, the use of polysaccharides is advantageous for numerous aspects; they are biocompatible, biodegradable, non-immunogenic, non-toxic and offer antimicrobial, anti-inflammatory, or antioxidant properties, as well as the capability to maintain a moist environment, stimulate blood clot formation and the deposition of granulation tissue, or limit patient's pain during dressing changes. Numerous studies are directed on the production of polysaccharide-based electrospun wound dressings considering also their stability in an aqueous environment, as the physiological one is; moreover, several approaches are available to improve the stability of the polymer based nanofibers: physical and chemical crosslinking strategies can be applied and must be chosen and adapted to the specific polymers used, as illustrated through this review.

Considering the skin tissue engineering approach, in which a harmonic combination of scaffolds, cells and bioactive factors is realized, these electrospun scaffolds are tested for cell ingrowth and functionalized with bioactive compounds (for example, drugs, growth factors, vitamins), which could enhance the polysaccharide bioactivity and accelerate re-epithelialization and tissue recovery in a microbe-free environment.

Chronic wounds are a critical issue which has not a unique solution. The materials and the technologies available for the production of wound dressings, and the chemical, pharmacological and biological compounds, which can be used to enhance the bioactivity and the antibacterial properties of these medical devices offer a wide choice of solutions, but more importantly they offer the tools for the development of new solutions in the perspective of a total and faster skin regeneration, restoring its function and avoiding scar formation. To this end, the electrospinning stands out for its versatility and for the possibility to easily tune the composition and the mechanical characteristics of nanofiber-based membranes, which can be post processed with several strategies to improve their biological properties.

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.

Acknowledgments

Financial support was received from University of Trieste fund program: Finanziamento di Ricerca di Ateneo, FRA 2016 to Prof. Gianluca Turco, for the project entitled "Produzione e caratterizzazione di matrici nanostrutturate a base di bio-polimeri naturali ottenute da electrospinning, applicazioni biomediche di medicina rigenerativa" (code U17-FRATURCO-16).

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