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Review

Asymmetric Membranes: A Potential Scaffold for Wound Healing Applications

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Abstract: Currently, due to uprising concerns about wound infections, healing agents have been regarded as one of the major solutions in the treatment of different skin lesions. The usage of temporary barriers can be an effective way to protect wounds or ulcers from dangerous agents and, using these carriers can not only improve the healing process but also they can minimize the scarring and the pain suffered by the human. To cope with this demand, researchers struggled to develop wound dressing agents that could mimic the structural and properties of native skin with the capability to inhibit bacterial growth. Hence, asymmetric membranes that can impair bacterial penetration and avoid exudate accumulation as well as wound dehydration have been introduced. In general, synthetic implants and tissue grafts are expensive, hard to handle (due to their fragile nature and poor mechanical properties) and their production process is very time consuming, while the asymmetric membranes are affordable and their production process is easier than previous epidermal substitutes. Motivated by this, here we will cover different topics, first, the comprehensive research developments of asymmetric membranes are reviewed and second, general properties and different preparation methods of asymmetric membranes are summarized. In the two last parts, the role of chitosan based-asymmetric membranes and electrospun asymmetric membranes in hastening the healing process are mentioned respectively. The aforementioned membranes are inexpensive and possess high antibacterial and satisfactory mechanical properties. It is concluded that, despite the promising current investigations, much effort is still required to be done in asymmetric membranes.

Keywords: wound healing; asymmetric membranes; electrospinning; bacteria

1. Introduction

The largest organ of the body is skin and its functions and structures can be affected by chronic wounds or traumatic events [1–3]. Under normal conditions, skin possesses a complicated multi-layer structure, which can be considered as a self-healing material [4]. Indeed, skin is an essential organ

that can preserve the inner organs of the body from different mechanical, chemical, and pathogen insults. Other functionalities like supporting nerves and blood vessels, preventing dehydration, and regulating the temperature of the body are regarded as skin tasks [5]. Additionally, skin plays a fundamental role in sensory detection and immune surveillance processes [6,7]. Several reasons like chronic wounds, surgical interventions, acute trauma, or even genetic disorders lead to loss of skin integrity [8]. It has been demonstrated that scalds and burns can create deep and broad wounds. These wounds compromise body image and immunity and they lead to scarring, remarkable disability, and even death [9,10]. The annual World Health Organization's reports have verified that more than 300,000 persons (per year) have lost their lives as a result of fire fire-related burn injuries [8]. Emergence and promotion of regenerative medicine during the last few years has led to a descending sequence in the mortality rate caused by burns However, the rate of mortality is not satisfactory (still high) and more efforts are required to minimize this rate [11].

Some of the most complicated and interactive processes in human life are repairing epidermal, superficial partial-thickness, deep partial-thickness, and full-thickness wounds [12–14]. Indeed this process can support intricate interactions between extracellular matrix molecules and other subtypes. Researchers have claimed that soluble mediators, different resident cells, extracellular matrix molecules, and infiltrating leukocyte subtypes can reestablish damaged parts and replace the lost area. For this purpose, five stages that include hemostasis, inflammation, migration, proliferation, and maturation [12] have been introduced for the wound healing process. Figure 1 represents various stages of the wound healing process.

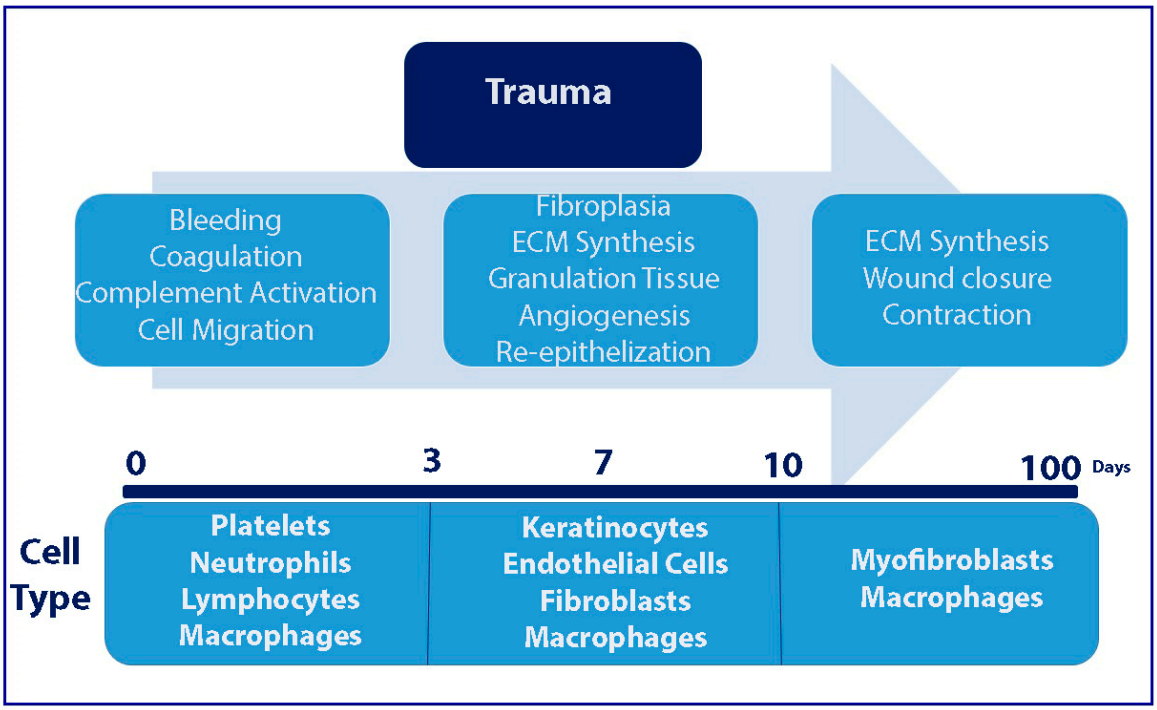

Figure 1. Major stages of the trauma healing process.

As a result of previous explanations, researchers have made an effort to find a promising alternative for native skin that has a similar structure and functionality for wounds and injuries. Since broad skin loss can be considered as a major challenge to clinicians, autologous skin graft has been introduced in injuries treatments. Indeed these allografts are regarded as possible therapeutic alternatives, however, their functionality depends on religious grounds, availability of the skin banks, and standardized sterilization to reduce risks for patients [15]. Hence, researchers tried to find better alternatives for wound care, which are less painful and faster than previous technologies. Meanwhile, several items like

clinical efficiency, low-cost, availability, patient safety, and ability to regenerate the native properties of skin were the most essential issues in the progress of new wound dressings [8,12].

Many different skin substitutes are already applied in clinical applications. The aforementioned cell-containing and cell-free skin substitutes can offer protection from contamination and fluid loss while they are able to deliver extracellular matrix components and cytokines to the wound bed. Moreover, wound dressings are applied as temporary coverings or remain permanently in the wound bed during healing or thereafter [15–17]. It is necessary to mention that in advanced skin regeneration techniques, cell biomaterials and growth factors are combined with modern biomanufacturing strategies, which can enhance the regeneration of healthy and vascularized tissues. Although there are promising advances in the field of cutting-edge skin substitutes and tissue engineering, a myriad of the innate features of native skin like specific cells, which can respond to the perception of pressure, cold, pain, heat, pigmentation, and vibration, have not been regarded. Other factors like strength and elasticity of the native skin have not been attained by the present methods. Researchers have attempted to combine stem cells with gene recombination. They stated that this combination could produce and deliver growth factors to the wound bed to overcome several limitations like physical inhibition and biological degradation of bioactive molecules. Hinrichs and coworkers were the first groups that proposed polyurethane-based asymmetric membranes to mimic the structural organization and properties of epidermis and dermis layers in the wound care process [18]. Asymmetric membranes impair bacterial penetration and avoid exudate accumulation as well as wound dehydration. In general, synthetic implants and tissue grafts are expensive, hard to handle (due to their fragile and thin nature) and their production process is very time consuming, while the asymmetric membranes are affordable and their production process is easier than previous epidermal substitutes. Despite that asymmetric membranes possess suitable wound-healing properties and acceptable biocompatibility, loading of these membranes with other bioactive agents like chitosan can enhance and promote the performance of such membranes.

Asymmetric membranes with extraordinary properties and high similarity with the native skin have gained tremendous attention and they have played a vital role in wound healing applications. In other words, the asymmetric membranes possess a denser outer layer that can imitate the epidermis skin layer, which protects the scarred area from bacterial, chemical, and physical threats and also manages the exchange of gases [19]. Additionally, the complete absorption of exudates and accurate management of cell adhesion and proliferation are performed by the interior layer of these membranes (these layers have porous structures) [20–22].

In addition to wound healing applications, asymmetric membranes are able to be utilized in other applications. These membranes with a small, thin, and pore size upper layer can facilitate a high vapor flux, and also they can manage high liquid entry pressure, which is essential for thermos osmotic energy conversion and membrane distillation processes [23]. It has been accepted that asymmetric membrane structures including porous substrates (effective for the surface exchange) and thinner dense layers are a beneficial choice to enhance the hydrogen separation performance. The obtained results have confirmed higher hydrogen permeability and stability of asymmetric membranes in comparison with symmetric membranes [24,25]. Very recently, a group of researchers fabricated a novel asymmetric membrane based on small intestinal submucosa. They stated that these novel membranes possess a bilayer structure with loose and dense layers, which can provide better mechanical stability and even wettability. The loose layer of the aforementioned membranes is suitable for the 3D proliferation of human bone mesenchymal stem cells, which can create better osteogenic effects in vivo. Since the preparation method is facile and these asymmetric membranes are available, they are expected to be favorable candidates for guided bone regeneration [26]. It is necessary to mention that asymmetric membranes with excellent properties are applied in various applications like filtration and gas separation [27,28].

So far many techniques including bioprinting, wet or dry/wet phase inversion, electrospinning, and $scCO_2$-assisted phase inversion have been proposed for manufacturing asymmetric membranes [19].

It is necessary to mention that this wide range of methodologies for manufacturing asymmetric membranes can pave the route for the utilization of various polymers to promote asymmetric membranes. For example, hyaluronic acid, polyvinyl alcohol, collagen, polycaprolactone, and chitosan are considered as promising candidates for the production of these membranes. It has been accepted that non-degradable polymers used for the preparation of nanofibrous scaffolds included polyurethane (which can also be prepared in a degradable form), polydimethylsiloxane (PDMS) [29], polyethylene terephthalate (PET) [30], polyethersulfone (PES), and even polystyrene (PS) can be applied in wound healing. Non-degradable synthetic polymers also include hydrogels, such as poly(acrylic acid) (PAA), poly(methyl methacrylate) (PMMA), and particularly poly(di(ethylene glycol) methyl ether methacrylate) (PDEGMA). Moreover, degradable synthetic polymers like polylactides (PLLA and PDLLA) and their copolymers with polyglycolides (PLGA) and polycaprolactone (PCL) and its copolymers with polylactides (PLCL) are promising candidates for such applications. In terms of nature-derived polymers, chitosan with antimicrobial effects, hemostatic properties, high biodegradability, and biocompatibility is considered as one of the best candidates. The surface of chitosan is identified by platelets and only in a few seconds, the coagulation process begins with the protonated amine groups of chitosan attracting the negatively charged residues on red blood cell membranes, resulting on a strong agglutination, thrombin generation, and fibrin mesh synthesis within the microenvironment created by this polysaccharide [19,31–33]. Chitosan is an inexpensive and available natural polymer that can simply be loaded on asymmetric membranes and in our suggestion, the detailed and recent information about chitosan can be very useful in the development of chitosan-based asymmetric membranes. Here in this review, we try to explain the properties and preparation methods of asymmetric membranes and highlight the role of chitosan based-asymmetric membranes and electrospun asymmetric membranes in hastening the healing processes. We also suggest areas of future research that will help bring asymmetric membranes towards wound dressing applications.

2. Production Methods and General Properties

In the 1950s, a group of researchers proposed that asymmetric membrane could be achieved by cellulose acetate through the phase inversion approach [34,35]. Since then, the asymmetric membrane has gained tremendous attention and found many applications in various fields like gas separation, wastewater purification, dialysis, and wound healing process [23,36–40]. So far many methodologies have been explored and utilized by researchers in asymmetric membrane production. The major techniques (like bioprinting, $scCO_2$-assisted phase inversion, electrospinning, dry/wet method, and wet-phase inversion technique) are illustrated in Figure 2. The bioprinting technique is one of the newest techniques that is proposed to combine fibroblasts and keratinocytes in asymmetric membranes [41,42]. Indeed, bioprinting cannot only provide acceptable flexibility in planning and production of tissue-engineered constructs but also allows the deposition of different cell types and biomaterials. In this technique, printing of individual layers assimilating the related skin cells is the key factor of asymmetric membrane production. In this condition, fibroblasts and keratinocytes are located in the bottom and top layers respectively (Figure 2d). [43,44]. Another technique that can enhance the deposition of polymeric solution and also produce an asymmetric membrane under the supercritical condition of CO_2 amount is the $scCO_2$-assisted phase inversion technique. It has been verified that membrane production is done when the $scCO_2$ solubilizes in the casting solution, and then the removal of the solvent from the main solution occurs [45,46]. One of the best advantages of this technique is that by changing the conditions of processing like depressurization rate and concentration of the solution, many properties and features of the membrane such as hydrophilicity, porosity, morphology, and mechanical properties can simply be manipulated (Figure 2b).

The electrospinning method is capable to produce fibrous membranes that are equivalent to the native extracellular structure. After loading the main polymeric solution into the syringe and exposing it to the high voltage electric field, the solution is directed to the collector and finally, the nanofibers are

produced. Many researchers have claimed that different factors like environmental conditions [47–49], processing variables (like the voltage, flow rate, and collector size) and characteristics of polymeric solution (e.g., solvent type, conductivity, and viscosity) can immediately influence the aforementioned process. Additionally, it is necessary to mention that by manipulating the material used and optimizing the nanofiber deposition items like orientation, density, and size, the properties of asymmetric membranes can be simply controlled [50–52] (Figure 2c). The last methodology that can be applied in the production of membranes is called the wet-phase inversion technique. This method includes the casting polymer immersion (under non-solvent coagulant bath) that can improve the deposition process and therefore main membranes are formed. One of the major factors that is influenced by the phase separation process's duration is the formation of a porous sub-layer with a dense top layer [53]. However, the obtained membrane often demonstrates a thin top layer and some defects. Additionally, the dry/wet-phase inversion can begin the formation of the membrane under a pre-evaporation process before the polymer absorption into the coagulation bath. Indeed, this process can not only enhance the polymeric solution's density but also a denser top layer is created that can protect the critical area of the wound from various contaminations [54–56] (Figure 2a). Figure 3 has summarized the advantages and disadvantages of all of the techniques.

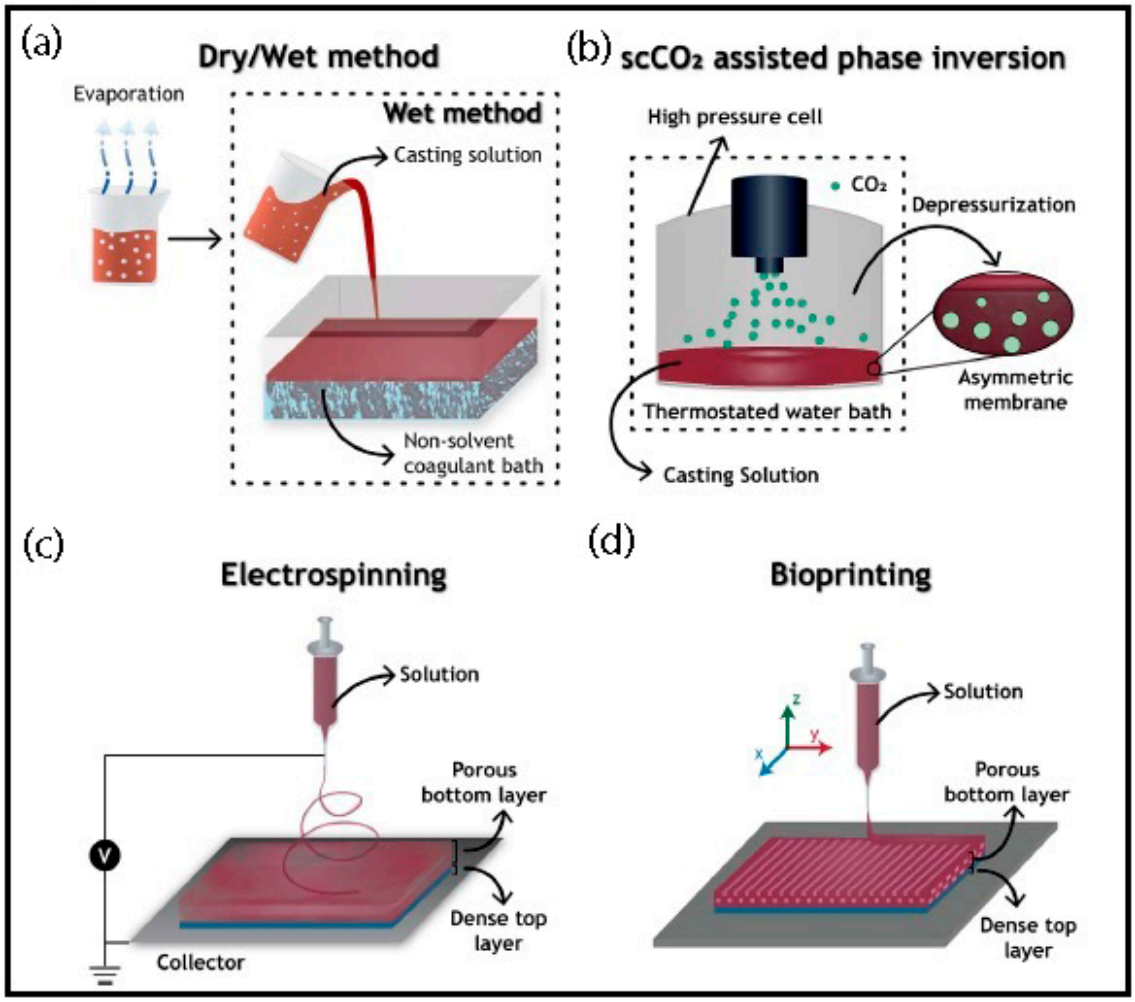

Figure 2. Four main methodologies for the production of asymmetric membranes: (**a**) dry/wet, (**b**) $scCO_2$-assisted phase inversion, (**c**) electrospinning, and (**d**) bioprinting [57].

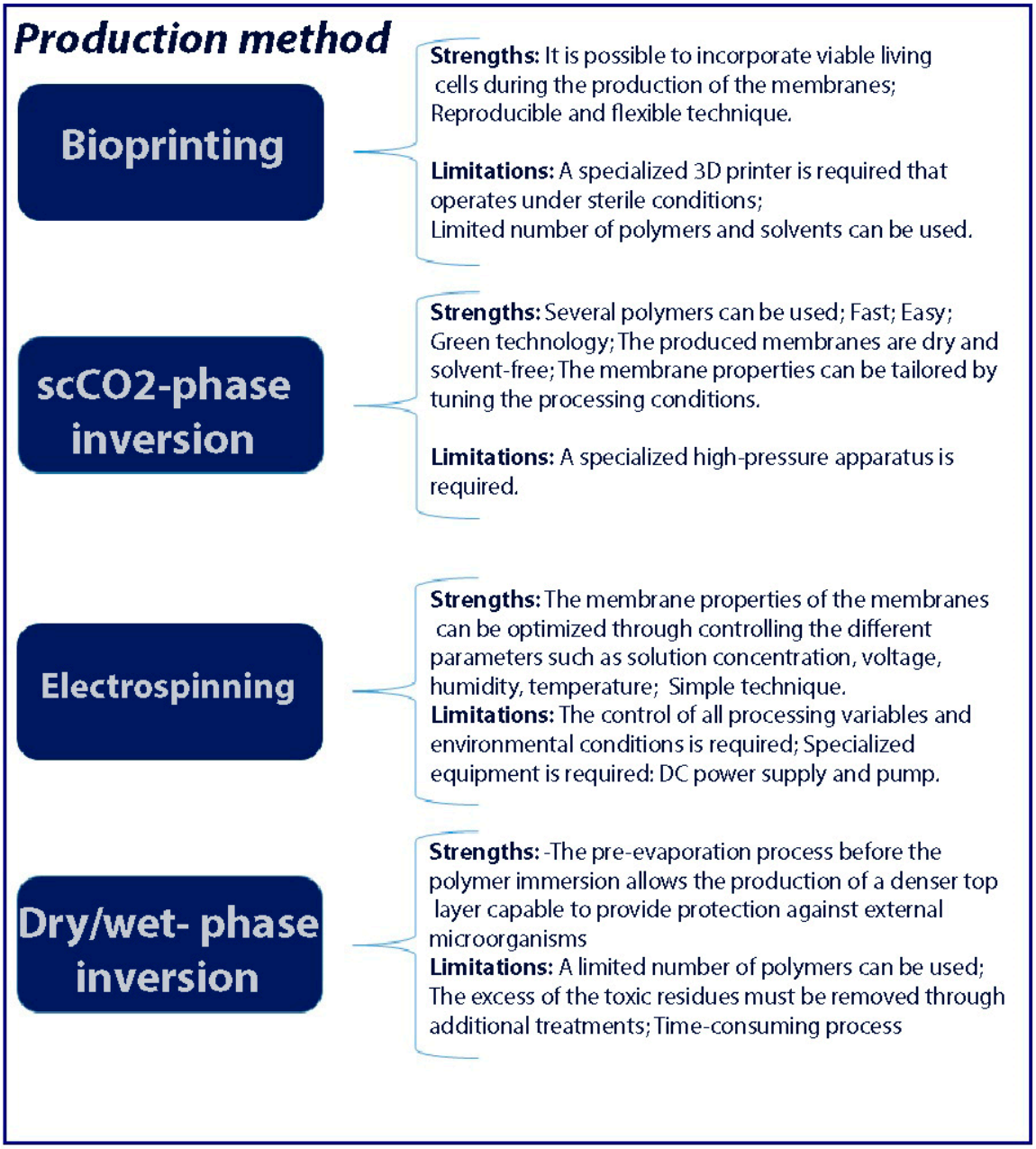

Figure 3. A summary of strengths and limitations of asymmetric membranes production methods.

The researchers have claimed that asymmetric membranes could not only repair different layers of skin but also they should fulfill several properties like antimicrobial activity, porosity, and mechanical properties. As is known, the presence of bacteria around the wound can delay or discontinue the process of wound healing and even this colonization by bacteria may endanger human life [58,59]. Hence, wound dressing or the presence of antibacterial agents [60–65] can control the growth of bacteria and it is the main property of asymmetric membranes. For example, Mousavi et al. in their review about gold nanostars have stated that these multi-branch materials can rupture the external membrane of bacteria and provide extraordinary antibacterial effects [66]. The porosity of wound healing agents can modulate the adhesion of cells and control their migrations. Besides, this property will fulfill the exchange of waste and nutrients around the wound [67]. The porosity values of 60%–90% have been proposed as the optimum values for promoting the wound healing mechanism [68]. Therefore, the upper surface of the membrane must include pores with a certain diameter to avoid wound infection [19]. It is necessary to mention that, these diameters should be sufficient enough for nutrients exchange and facilitate the penetration of the cells [69].

In terms of mechanical properties, stability and flexibility are considered as the main features to protect the wound from external risks. Previous researchers have proposed that the wound dressing agent must provide similar properties of native skin. For example, the wound dressing agent should fulfill a young modulus under extension, torsion and suction of about 4.6–20 MPa, 0.42–0.85 MPa, and 0.05–0.15 MPa respectively [70].

3. Chitosan Based Asymmetric Membranes

So far many polymers like collagen [71], cellulose [72], silk fibroin [73], alginate, and chitosan [74] have been applied to produce wound healing mechanisms due to their acceptable hydrophilicity and non-toxic effects. Other effective factors like drug release abilities, antibacterial, and biodegradable properties can hasten and facilitate the healing process. Among the aforementioned polymers, chitosan as a linear polysaccharide, which is derived from chitin has gained considerable attention in tissue engineering and skin-repairing applications (see Figure 4). Mi and collaborators [31] proposed the first chitosan based asymmetric membranes by a dry/wet-phase inversion technique in 2001. They have prepared the chitosan solution by acetic acid and then the final solution was per-evaporated for about 1 h (10–60 min) in 50 °C. Then the NaOH-Na_2CO_3 bath was used for immersion. The researchers have realized that the physicochemical properties of membranes can be influenced by duration of the per-evaporation process. Miguel et al. in their valuable review have explained all the aspects of chitosan properties as asymmetric membranes [57].

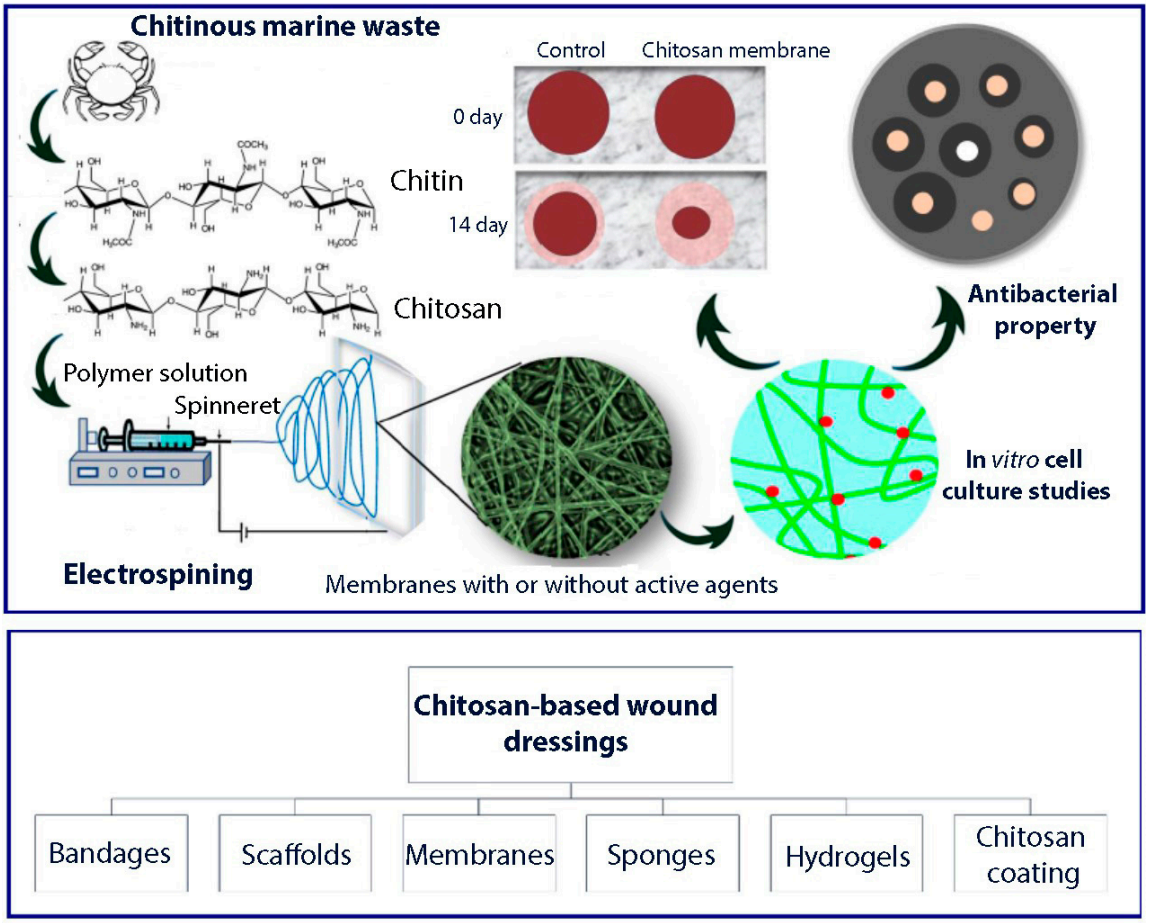

Figure 4. Schematic illustration of chitosan-based asymmetric membranes' preparation [75].

Chitosan sponges are capable to hold water and they possess extraordinary mechanical properties with high porosity. Since there are several amino groups in the structure of chitosan, this valuable material possesses potent bacteriostatic properties. However, it is necessary to mention that the solid-state chitosan sponge has a poor bacteriostatic effect that can limit its performance for chronic wounds. The incorporation of chitosan scaffold with metallic or non-metallic materials could be a promising candidate to enhance and promote the antibacterial effects. As summarized in Table 1, chitosan can be considered as a promising framework for skin repairing applications.

Table 1. Recent chitosan-based asymmetric membrane in the wound healing process.

Membrane Composition	Main Properties	Fabrication Method	Reference Number
Polycaprolactone-hyaluronic acid/chitosan-zein	High anti-inflammatory and antibacterial effect	Electrospinning	[76]
Chitosan/PVP/nanostarch	High re epithelialization and collagen formation rate	Coating by stearic acid and evaporation/casting techniques	[55]
Bromelain-loaded chitosan	Curing of burn wound	Electrospinning	[77]
poly(ε-caprolactone)/chitosan	Treatment of chronic wound caused by the ischemia.	Electrospinning	[78]
Chitosan-collagen nanospheres	High swelling ratio and acceptable porosity	Freeze-drying	[79]
PVA/Chitosan	Extraordinary antibacterial effect and great cytocompatibility	Electrospinning	[80]
CS/Polyhydroxybutyrate/ polyvinylidenefluoride	Treatment of post-surgical ulcer	Electrospinning	[81]
Chitosan/AgNPs	High Re-epithelialization rate with non- toxic effect	Stearic acid coating and freeze-drying	[82]
Chitosan/PVA/zinc oxide	Useful for diabetic wounds	Electrospinning	[83]

Very recently a group of researchers has proposed quaternary ammonium chitosan nanoparticles (TMC NPs/CS) with asymmetric wettability that can be applied in skin repairing applications [84]. These nanoparticles have been prepared by a simple multi-step method. Screening the acceptable concentration of chitosan sponges by considering the physicochemical properties was the first step. Then quaternary ammonium chitosan nanoparticles were incorporated with chitosan sponges and stearic acid was applied to modify one side of the mentioned sponges. These novel wound healing agents are not only available and nontoxic but also promote the antibacterial performance of chitosan sponges. Figure 5 has demonstrated the appearance of wounds in diabetic mice with bacterial infection and the results of an in vivo study of healed wounds. It has been confirmed that chitosan with extraordinary characteristics are potent agents for preventing the bacterial contaminations and they can facilitate the tissue growth process. Although many efforts have been made to promote wound healing agents, the incorporation of patient-derived skin cells or even stem cells can be considered as a suitable candidate for this purpose.

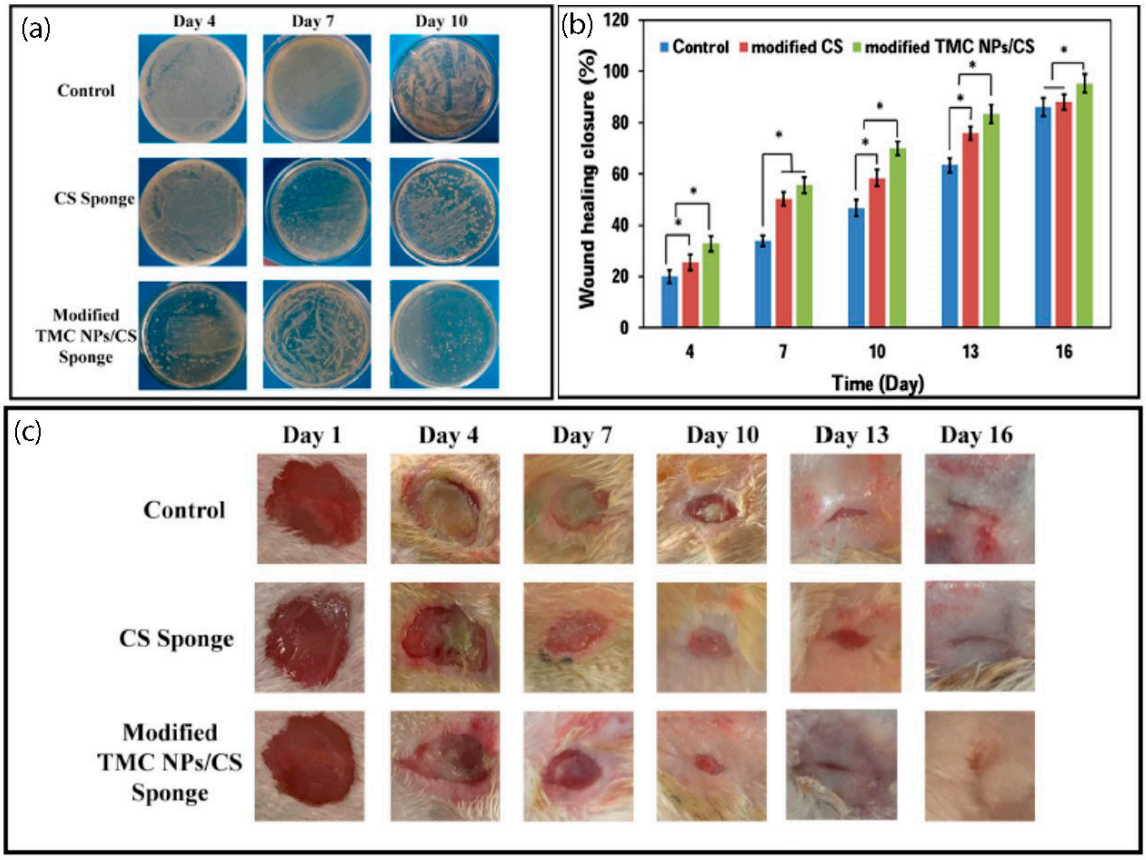

Figure 5. The impact of TMC NPs/CS on the wound healing process of diabetic mice. (**a**) Bacteria isolated from the mice wounds. (**b**) In vivo study of healed wounds in diabetic mice on days 4, 7, 10, 13, and 16 for each treatment regimen. (**c**) Appearance of wounds in diabetic mice with bacterial infection [84].

4. Electrospun Asymmetric Membranes

Researchers have verified that electrospun asymmetric membranes can be regarded as promising candidates for wound dressing because of their low degradation and satisfactory mechanical properties [85]. A biocompatible and biodegradable poly (α-ester) that can be broadly utilized in biomedical applications, especially wound dressing is polycaprolactone (PCL). Indeed, several physicochemical characteristics of this polymer like extraordinary spinnability, slow degradation, appropriate mechanical strength, and good hydrophobic properties have gained considerable attention in wound dressing [86]. It is necessary to mention that the role of poly(vinyl acetate) (PVAc) in different biomedical applications such as wound dressing, tissue engineering, and drug carrier has been highlighted during the last few years [87]. Such hydrogels like PVAc possess valuable functional groups, which are very biocompatible with tissues and body fluids. Riyajan and collaborators realized that the absorption capacity of PVAc capsules is satisfactory and they have verified its high (about 140%) swelling ratio after 15 h of exposure in aqueous medium [88]. Aragón et al. in their interesting experiment have stated that electrospun PVAc fibers were not being used before their report [57,89]. Most of the time, wounds need treatment with potent antibiotics because the presence of infection around the wound, which is mostly caused by sores, burns, or diabetic ulcers can prolong the duration of the healing process.

It has been observed that sustained local delivery can be a useful way because such local delivery setups can not only provide several advantages, but also they minimize the side effects. For instance, this delivery system enhances the efficiency of drug therapy and diminishes the frequency of bandage replacements, which is favorable to patients [87]. As a point, it can be stated that electrospinning is one of the most convenient methodologies that can simply incorporate compounds like antifungals, antiseptics, and antibiotics to the special polymer fibers. The appropriate relation between the surface area and volume and also high drug-absorption efficiency of electrospun membranes have made these membranes good agents for wound dressing [90].

The presence of microorganisms and antibiotic resistance are two major obstacles to wound management that can limit the therapeutic performance and even choices. So far many different natural products and herbal medicines have been introduced and utilized in related wound or ulcer treatments. Since ancient times, the extracts of the herbal medicinal plants are applied to hasten the healing process [86]. The researchers have claimed that thymol, eugenol, and carvacrol are regarded as major biological compounds of essential oils that have antioxidant, antifungal, antibacterial, and antiviral activities [91]. Hence, Aragón and collaborators have proposed the polycaprolactone (PCL)/polyvinyl acetate (PVAc) asymmetric membranes that have been loaded with monoterpene carvacrol. The antibacterial effects of these novel membranes have been demonstrated in Figure 6A. Additionally, the evaluation of cell viability under the presence and absence of these membranes has been illustrated in Figure 6B. Consequently the researchers have proved that these novel membranes possess good mechanical properties, high antibacterial effects with acceptable fluid handling capacity, which can pave the route in the wound healing process [92].

A group of researchers have reported a new asymmetric membrane that was fabricated through the routine electrospinning method [56]. They have produced the top layer of the membrane with the combination of poly(caprolactone) and silk fibroin. Their goal was to reproduce the waterproof ability and dense nature of epidermis. Additionally, hyaluronic acid loaded with thymol and silk fibroin were applied to fabricate the bottom layer of these membranes. Based on the results that verify the wettability, biocompatibility, and good mechanical properties of the aforementioned membranes, it can be concluded that these membranes are very good candidates for wound dressing. The presence of thymol on the bottom layer of the membrane can promote the antibacterial and antioxidant effects of the final product as demonstrated in Figure 7. Although various properties belong to these membranes, it seems the incorporation of proteins and growth factors is a promising way to enhance the biological performance of such membranes.

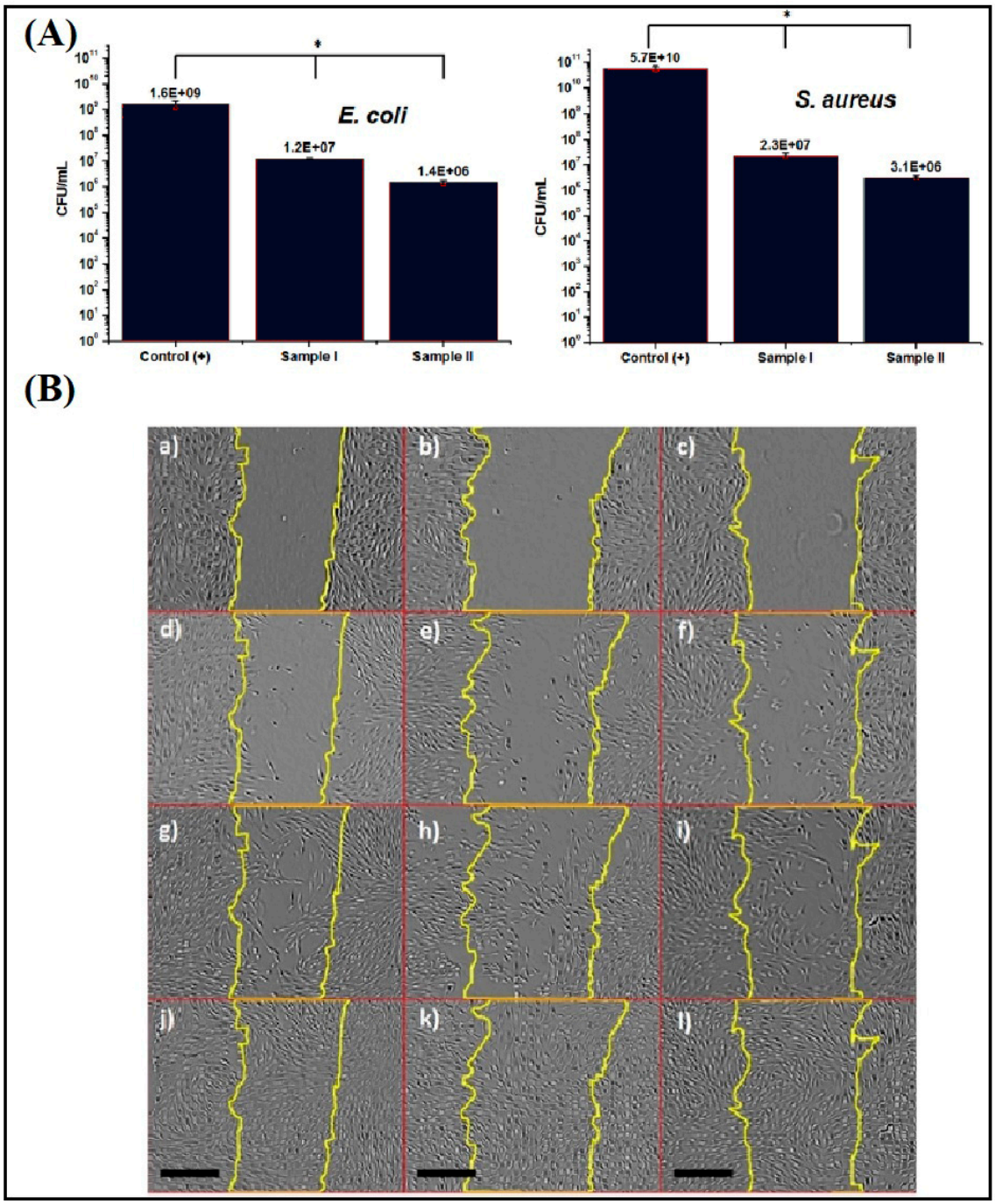

Figure 6. (**A**) Antibacterial effect of asymmetric membranes against *Escherichia coli* and *Staphylococcus aureus*. (**B**) Evaluation of cell viability under the effect of carvacrol release by the wound healing assay in human dermal fibroblasts incubated without membrane (control; **a**,**d**,**g**,**j**), with Sample I (**b**,**e**,**h**,**k**) or with Sample II (**c**,**f**,**i**,**l**) at the different time points studied: 0 h (**a**–**c**), 24 h (**d**–**f**), 48 h (**g**–**i**), and 72 h (**j**–**l**). Scale bar, 500 μm [92].

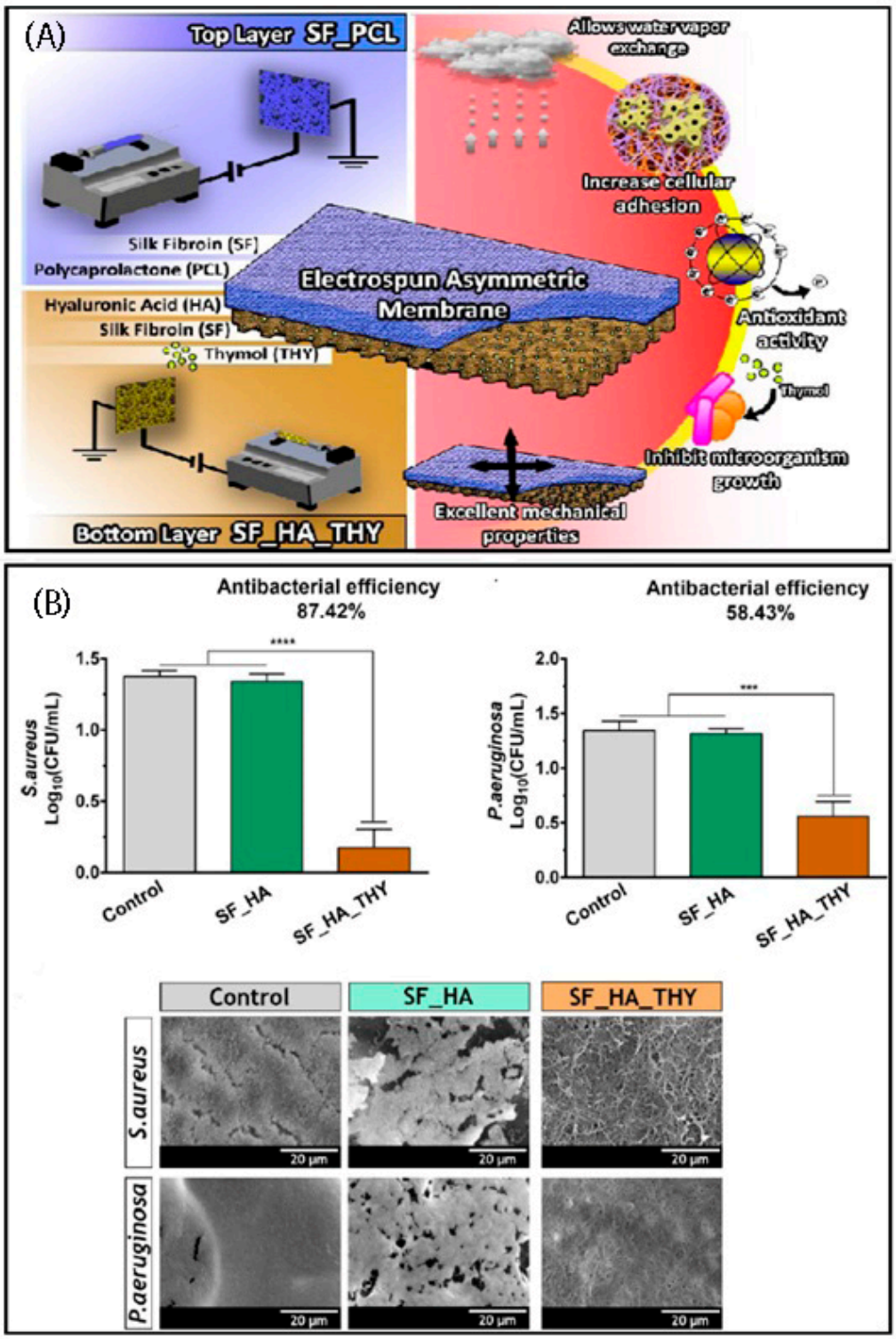

Figure 7. (**A**) Schematic illustration of electrospun asymmetric membrane's production method (**B**) Investigation of the antibacterial activity of the SF_HA and SF_HA_THY nanofibrous layers against *S. aureus* and *Pseudomonas aeruginosa* with SEM images of control, SF_HA and SF_HA_THY nanofibrous layers incubated with *S. aureus* and *P. aeruginosa* [56].

5. Conclusions and Future Prospects

Asymmetric membranes with extraordinary properties and high similarity with the native skin have gained considerable attention and they have played a vital role in wound healing applications. In other words, the asymmetric membranes possess a denser outer layer that can imitate the epidermis skin layer, which protects the scarred area from bacterial, chemical, and physical threats and also manages the exchange of gaseous membranes. The major goal of this short review was to summarize the intrinsic properties and abilities of asymmetric membranes to act as wound dressing agents. Although there are several methods to produce these membranes, new preparation methods that are affordable and non-time-consuming are essentially required. It has been confirmed that electrospun and chitosan-based asymmetric membranes with extraordinary characteristics are potent agents for preventing bacterial contaminations and they can facilitate the tissue growth process. Nevertheless, although highly promising results obtained with chitosan-based asymmetric membranes, until now no ideal wound healing agent has been fabricated. Hence, researchers have concentrated on the fabrication of asymmetric membranes through the bioprinting technique. Despite the many efforts that have been made to promote wound healing agents, the incorporation of patient-derived skin cells or even stem cells can be considered as excellent candidates for this purpose. Additionally, the fabrication of novel asymmetric membranes with high antibacterial, anti-inflammatory, antiseptic, and antinociceptive properties can reinforce the wound dressing process and reduce the treatment duration. As a point, it can be stated that the inclusion of growth factors and proteins may be the key factor to enhance the biological performance of these membranes however is still obscure and needed more experiments to verify.

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