

Review

Hydrogel Dressings for the Treatment of Burn Wounds: An Up-To-Date Overview

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Abstract: Globally, the fourth most prevalent devastating form of trauma are burn injuries. Ideal burn wound dressings are fundamental to facilitate the wound healing process and decrease pain in lower time intervals. Conventional dry dressing treatments, such as those using absorbent gauze and/or absorbent cotton, possess limited therapeutic effects and require repeated dressing changes, which further aggravate patients' suffering. Contrariwise, hydrogels represent a promising alternative to improve healing by assuring a moisture balance at the burn site. Most studies consider hydrogels as ideal candidate materials for the synthesis of wound dressings because they exhibit a three-dimensional (3D) structure, which mimics the natural extracellular matrix (ECM) of skin in regard to the high-water amount, which assures a moist environment to the wound. There is a wide variety of polymers that have been used, either alone or blended, for the fabrication of hydrogels designed for biomedical applications focusing on treating burn injuries. The aim of this paper is to provide an up-to-date overview of hydrogels applied in burn wound dressings.

Keywords: hydrogels; burn injury; skin regeneration; wound healing; wound dressing

1. Introduction

Without discredit, the skin is the most exposed to various impairments, such as injuries, scratches, and burns, among all human body organs. Injuries of the epithelium and connective structures are associated with a weakened ability of the human body to assure adequate protection against harms from the outer environment [1]. As stated by the World Health Organization, burn injuries represent a major public health crisis, and are among the most severe injuries with over 180,000 annual deaths worldwide [2–4]. Burns are defined as damages of the skin caused by excessive heat or caustic chemicals, as the most common causes [3,5,6]. Among the three types of burns, third-degree burns, also known as full-thickness burns, will destroy the entire thickness of the skin, provoking immediate cell death and matrix destruction, with the most devastating damage at the surface of the wound (see Figure 1) [7,8]. During the last years, development in acute burn management has decreased mortality rate, allowing the survival of patients with burn injuries covering up to 100% of the body surface [9–12].

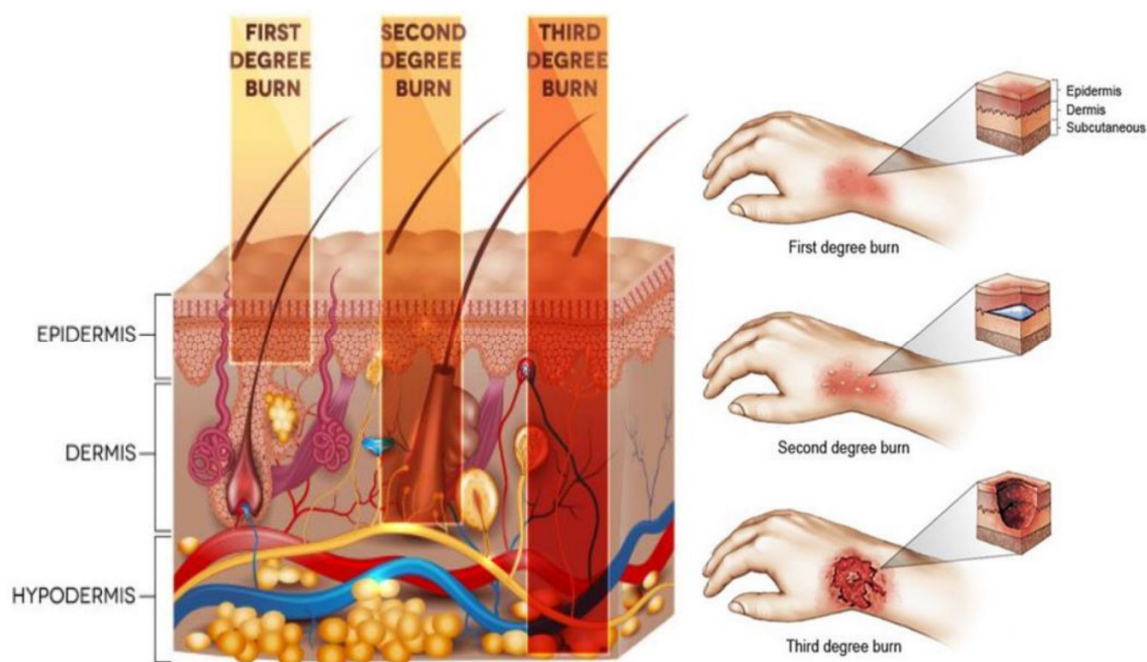


Figure 1. Different depth of invasion for burn injury [13]. Reprinted from an open-access source.

Burn injuries cause disruptions of the normal skin barrier and impairments of numerous host defense mechanisms that prevent infections [14,15]. Consequently, until full epithelialization occurs, burn patients remain vulnerable to various invasive microbial infections [16]. An inappropriate repair process could induce severe damage, like the initiation of an infection or the loss of skin, which could consequently harm the subjacent tissues and even the whole organism [17,18]. The installation of infection represents one of the most usual and inevitable obstacles in the process of wound healing, especially in chronic wounds [19–21], and one of the most important and serious complications that could appear during the acute period subsequent to burn injury [22,23]. Although numerous dressings are already commercially available (Figure 2), there is an urgent need for the development of novel wound care treatment options to address the increasing number of burn injuries [1].



Figure 2. Structure of different types of dressings [24]. Reprinted from an open-access source.

As previously mentioned, there is a great variety of wound dressings on the market that are used for burn wound healing. While cotton gauze is extensively used for burn care, there are some disadvantages that must be considered, namely the pain caused by its removal and possible delays in the wound healing process [22,25]. Since wound healing is a considerably dynamic process, the performance requirements of dressing should be modified as healing progress [6,26,27]. Nevertheless, a warm and moist environment has been widely accepted as the key factor that promotes fast healing, and, therefore, most modern wound care products are designed to assure these conditions [28–30]. Based on the “wet wound healing theory”, a wet healing environment is optimal for the growth of the granulation tissue and for facilitating skin cells division, further promoting complete wound healing [31–34]. An optimal dressing (Figure 3) is thus capable of preserving high humidity levels at the wound site whereas also erasing excess exudates; in addition, it must be non-toxic, non-allergenic, comfortable, and cost-efficient, allow for oxygen and water vapor exchange and protect against microbial invasion [19,35–49]. Modern wound dressings are developed as carriers for the delivery of therapeutic agents at the wound site in a variety of forms, including nanofibrous mats [50–52], sponges [41,53–55], films [30,56–60], foams [61–65], and hydrogels [1,24,66–73].

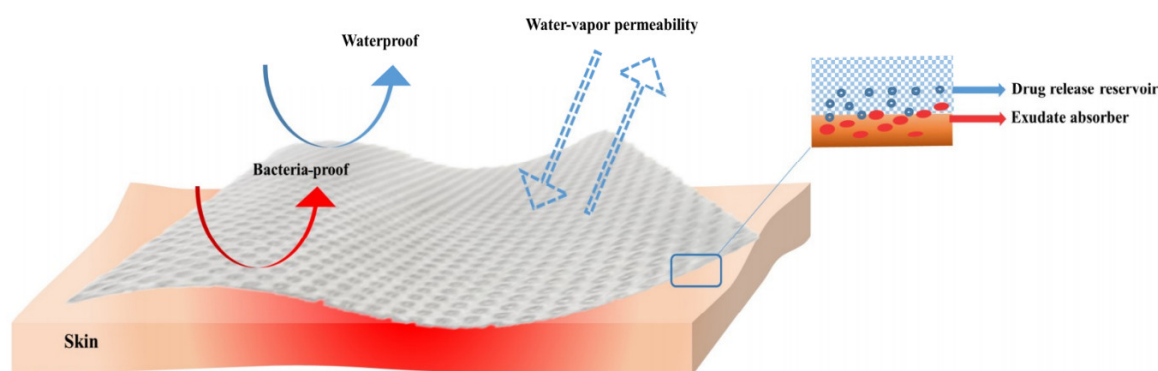


Figure 3. Properties of an ideal wound dressing [19]. Reprinted from an open-access source.

Hydrogels are generally obtained by mixing two different polymers in order to achieve a mixture with excellent wound dressing characteristics compared to the pure polymers. In this manner, hydrogels could potentially combine the characteristics of moist wound healing with an adequate fluid absorbance, while also allowing for the monitorization of the healing process owing to their transparency [28,73,74]. The intrinsic ability of hydrogels for promoting skin healing and regeneration has been an increasing studying focus, with clinical setting applications since 1980 [75].

As they are capable of satisfying important dressing requirements, wound dressings based on hydrogels are one of the most promising materials applied in wound care. Such requirements include maintaining the wound moist whereas absorbing excess exudate, covering the sensitive underlying tissue without adherence, decreasing pain through cooling effects, and actively intervening in the wound healing process [1,76,77]. However, as hydrogels cannot eliminate the pathogenic microbes by themselves, the problem associated with burn wound infections is still challenging [22]. The innovation in advanced wound care is directed to the development of active dressings, where hydrogels are combined with components that enhance the primary purpose of providing a beneficial environment for wound healing [78]. In this regard, novel strategies focus on developing hydrogels as burn wound dressings with antimicrobial properties. This paper aims to provide an up-to-date overview of the most recent strategies for developing hydrogel dressings for the treatment of burn wounds and the prevention of burn wound infections.

2. Inert Hydrogels for Treatment of Burn Wound Dressings

Owing to their hydrophilic character and properties similar to soft tissues, polymeric hydrogels are considered as the first biomaterials candidates in the development of wound dressings for the treatment of burn wounds [1,79–81]. In this context, polymeric hydrogels assure an ideal moist environment for the healing process, while also being comfortable to the patient owing to their cooling effect and non-adherent character [20,75]. More importantly, recent studies in the field of regenerative medicine demonstrate at least a partial skin regeneration *in vivo* through the action of bioactive hydrogels (Table 1) [75].

The wound healing process is directly affected by various local factors, oxygenation, and infection. The development of a suitable material for covering the wound and further prevent infection is a long-established requirement [82]. Researchers have been using different natural polymers, such as alginate [81,83–85], chitosan [81,86–88], collagen [89,90], dextran [91,92], hyaluronan [2,93], xanthan [94,95], konjac [95], and gelatin [96] for the production of hydrogels. Their wide application in wound dressing fabrication is based on their similitude to the extracellular matrix (ECM), which further improves acceptance by biological systems through the inhibition of the immunological reactions frequently observed for synthetic polymers [81,97].

Owing to its good elasticity and capacity to absorb a high amount of fluids, which further induces adequate moisture at the site of the wound, alginate is considered a great wound dressing material [81]. Stubbe et al. [83] developed a gelatin-alginate hydrogel for burn wound treatment. The hydrogel dressings proved good biocompatibility with adaptable cell attachment properties. Nuutila et al. [84] used a Platform Wound Device (PWD) based on alginate hydrogels embedded with high concentrations of topical antibiotics for studying the immediate treatment of burn wounds. The PWD represents a platform technology that starts as a first point treatment strategy that protects the wound and allows for the administration of topical therapeutics. The device can be adjusted to suit any size burn over any body contour. They proved a safe delivery of the antibiotics in high concentrations embedded in the alginate hydrogel using the PWD and, therefore, a successful treatment method for burn infections.

Moreover, chitosan promotes wound healing through a series of mechanisms, including fibroblasts activation, deposition, and arrangement of collagen fibers regulation, cell migration, granulation, and vascularization promotion [81]. Hence, chitosan is one of the most widely used biomaterials for hydrogel production, which is further applied for wound dressing development [87]. A hydrogel sheet (HS) composed of chitosan, honey, and gelatin was developed by Wang et al. [86] as a burn wound dressing. The histological examination showed a complete repair of the epidermis on day 12 after treatment with the HS. In addition, the toxicological evaluations demonstrated that HS is non-toxic and non-irritant material for the body and skin. Furthermore, Mingcui et al. [88] developed a porous nanocomposite hydrogel based on keratin, chitosan, and zinc oxide nanoparticles using the lyophilization technique. The results proved good tensile strength, antibacterial activity, sustained swelling and biodegradation, and excellent cell feasibility. In addition, the animal model results confirmed that the developed dressing assures about 92% repair of fractional depth injury in two weeks. In this manner, they proved that these hydrogels could be used in first-degree burn wound healing applications.

Table 1. The properties of the burn devices under inert hydrogels.

Polymeric Hydrogel Dressing	System Description	Tensile Strength	Antibacterial Activity	Swelling and Biodegradation	Degree Burn	Healing Time	Healing Process	Reference
Alginate	Alginate hydrogel/ZnO NPs	-	Against <i>E. coli</i> , <i>S. aureus</i> , <i>C. albicans</i> , and methicillin resistant <i>S. aureus</i>	16–20 swelling ratio; biodegradation in PBS (up to 40% in 3 weeks);	3rd degree	48 h	Hemostatic potential evaluated through blood clotting ability; Ex-vivo epithelialization shown through keratinocyte cells proliferation and migration towards the wounded area; effect favoured by release of Zn ²⁺	[98]
	Gentamicin loaded Mannuronic alginate/amidated pectin blend microparticle	-	Against <i>S. aureus</i> and <i>P. aeruginosa</i>	11.91 ± 0.87–14.81 ± 0.96 swelling ratio	3rd degree	-	Optimal healing environment assured through good powder flowability, high fluid absorbing capacity and water permeability at equilibrium	[99]
	Photocrosslinkable functionalized gelatine-alginate hydrogels	6–12 kPa storage modulus	-	More than 1200% swelling ratio	-	-	Good biocompatibility with adaptable cell attachment properties for HFF-1 foreskin fibroblast cells	[83,100]
Chitosan	Keratin-chitosan/ZnO NPs	0.31 MPa	Against <i>S. aureus</i> and <i>E. coli</i>	Up to 30 swelling ratio in 7 days; Biodegradation up to 64% in 7 days	1st degree	7–14 days	Migration of keratinocytes in epidermis	[88]
	Crosslinked carboxymethyl chitosan-dialdehyde-modified cellulose nanocrystal	4 kPa maximum storage modulus	-	Up to 350% swelling ratio	Deep partial thickness skin burn	14 days	Biocompatibility for normal adult human primary dermal fibroblasts in vitro in 2D and 3D cell models; healing at 14 days in deep partial thickness skin burn in vivo model; formation of hair follicles and blood vessels; densely packed collagen fibers with regular arrangement	[101]
	IGF-1C chitosan hydrogel							
Collagen	Collagen hydrogel/ <i>Saccharomyces cerevisiae</i> probiotic	Ultimate tensile load approx. 60 N	-	Complete biodegradation at 20 days		22 days	Improved the wound closure, cosmetic appearance and decreased scarring at 12 and 22 days post injury (DPI); Epidermal proliferation at 12 DPI, lower inflammation and granulation tissue formation, complete re-epithelialization at 22 DPI; normal appearance of the skin	[89]
	Acid soluble collagen/pepsin soluble collagen	-	-	-	2nd degree	28 days	Formation of new epidermis on day 14; apparition of hair follicles, sebaceous glands, dermal papillae and maturation of skin appendages on day 21; ordered fibrous tissue and high formation of skin appendages on day 28	[90]

Table 1. Cont.

Polymeric Hydrogel Dressing	System Description	Tensile Strength	Antibacterial Activity	Swelling and Biodegradation	Degree Burn	Healing Time	Healing Process	Reference
	Collagen I-hyaluronic acid hydrogel	-	Against <i>S. aureus</i> and <i>E. coli</i>	Up to 95% swelling ratio at day 3; 59% maximum degradation at 7 days in enzymatic medium and 30% in enzyme free medium	-	14 days	Proliferative activity of HMEC human microvascular endothelial cells and COS-7 fibroblasts cultured within the hydrogel; increase of vascular endothelial growth factor level in HMEC; weak inflammatory behaviour at 4 days after in vivo implantation; no systemic toxicity; complete in vivo wound healing after 14 days; complete normal structure of the epithelial tissue and less inflammatory response	[102]
Dextran	Dextran- hyaluronic acid hydrogel-sanguinarine/gelatin microspheres	Tensile load 15N in dry state and respectively 35N in wet state	Against methicillin-resistant <i>S. aureus</i> and <i>E. coli</i>	Swelling ratio 29 (in water) and 25 (in PBS); Biodegradation in PBS 31% and in hyaluronidase 24% (at day 21)	-	More than 20 days	Enhancement of NIH-3T3 fibroblast cell proliferation in vitro; improvement of re-epithelialization and enhancement of extracellular matrix remodelling in rat full-thickness burn infection models; efficient scar inhibition	[92]
	Dextran hydrogels	-	-	Biodegradation promoted by early inflammatory cell infiltration	3rd degree	3–5 weeks	Early inflammatory cell infiltration; Endothelial cell penetration at day 7; mature epithelium, presence of hair follicles and sebaceous glands at day 21; new hair growth and normal epidermal morphology at 5 weeks	[103]
	Dextran/bacterial cellulose hydrogel	Up to 16 ± 2.3 MPa	-	96.7 ± 0.49% water content	-	14 days	In vitro biocompatibility for fibroblast cells; complete wound healing at 14 days; significant skin maturation, mature epithelial layer and formation of hair follicles	[104]
Hyaluronan	Hyaluronic acid-benzaldehyde terminated F127 triblock copolymer	Adaptable mechanical strength	-	2600–4500% swelling ratio in 3–5 min	Deep partial-thickness burn model	21 days	Moderate tissue adhesiveness; good exudation-absorption; good compatibility for 3T3 fibroblast cells; increased wound close rate with time; more typical epidermis and skin appendages compared to controls at day 21; complete epidermal wound healing at day 14	[93]
	Hyaluronic acid-poloxamer hydrogel	-	Against <i>E. coli</i> migration	-	-	14 days	Complete wound healing in rat models by day 14; promotion of fibroblast cells accumulation and collagen deposition, granulation tissue formation, angiogenesis	[105]
	Aminoethyl methacrylate hyaluronic acid-methacrylated methoxy polyethylene glycol hydrogel/chlorhexidine diacetate-nanogel	-	Against <i>E. coli</i> and <i>S. aureus</i>	Up to 2657.24% swelling ratio after 24 h	-	14 days	Rapid homeostasis; accelerated healing process	[106]

As collagen plays fundamental roles in ECM formation and cell and tissue development and migration, collagen-based hydrogels have been considered as potential wet dressings for wound treatment. They are highly advantageous in terms of closely fitting the wound and providing adequate moisturizing, while also preventing bacterial infections. Moreover, collagen molecules may promote wound epithelialization and accelerate wound healing [90]. Oryan et al. [89] designed a study for investigating the impact of collagen hydrogel scaffold dressing with or without the topical use of *Saccharomyces cerevisiae* on cutaneous burn wound healing in rats. The results proved increased wound healing by enhancing epithelialization and decreasing scar size, and good biomechanical properties at the wound site. Using the self-aggregating property of collagen, Ge et al. [90] prepared a novel hydrogel dressing based on a high concentration of pepsin-soluble collagen. The experiments provide clear proof and essential data for the use of aquatic origin collagen as hydrogel-based wound dressings for the treatment of refractory wounds like extensive deep burn wounds (see Figure 4).

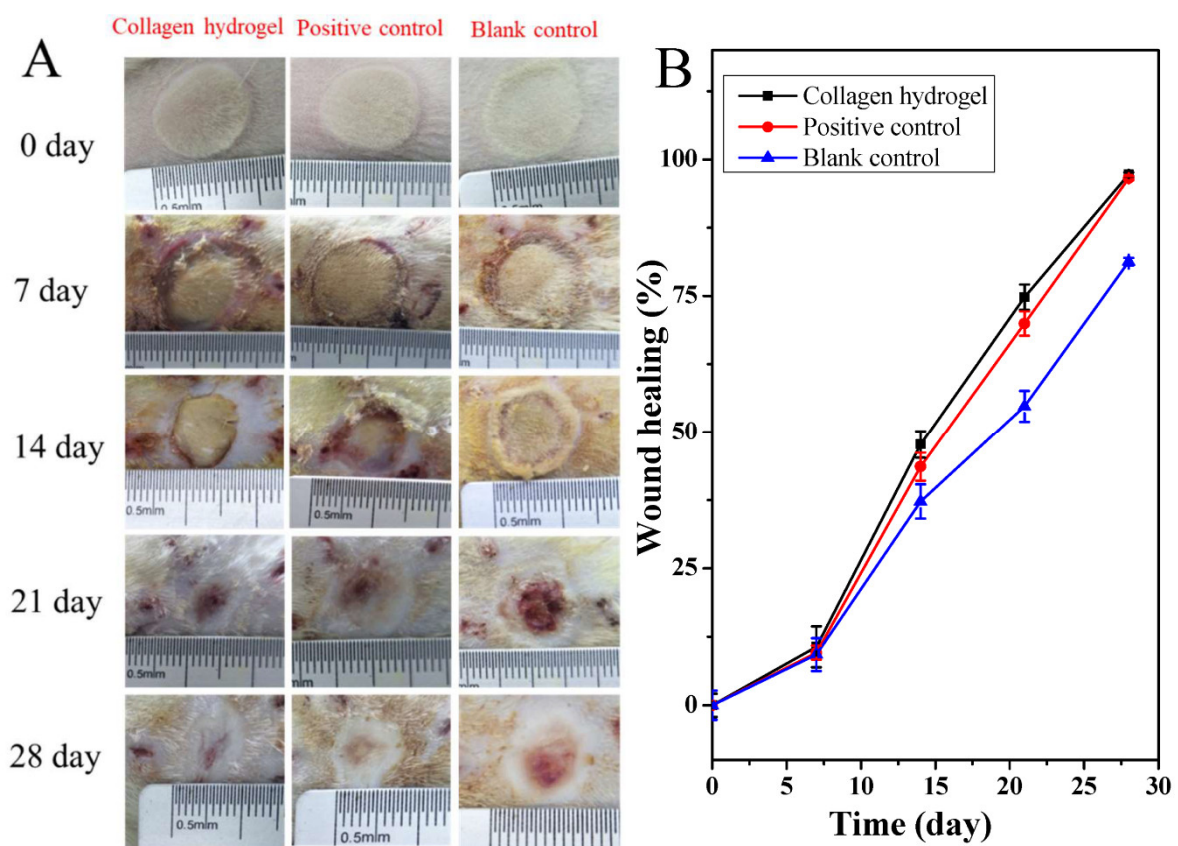


Figure 4. Healing of deep second-degree burn of rat skin with different treatments. (A): Photographs of deep second burn wounds at 0, 7, 14, 21 and 28 days. (B): Wound healing rate with different treatments. Positive control group, treated with commercial product (3MTM Tegaderm™ hydrocolloid dressing); Collagen hydrogels group, treated with collagen hydrogel dressing containing 10 mg/mL PSC; Blank control group, without any treatment after wound burned [90]. Reprinted from an open-access source.

Dextran, a polysaccharide that can potentially increase hemocompatibility of the associated materials, has numerous effects on blood coagulation homeostasis, such as diminished fibrin polymerization, platelet activation inhibition, and erythrocyte rouleaux formation [91,107]. In 2018, Zhu et al. [92] manufactured a dextran-hyaluronic acid hydrogel enriched with sanguinarine-containing gelatin microspheres. Characterized by large porosity and high swelling ratio, these systems improved fibroblast cell proliferation and sustained the release profile of sanguinarine. The results suggest that the hydrogel provides a potential high-quality strategy for the treatment and scar inhibition of infected burn wounds. A hydrogel dressing was prepared by Zheng et al. [108] using a solution blend

comprised of polyvinyl alcohol and dextran-aldehyde, that was crosslinked via the freeze-thaw method and freeze-drying. Thorough evaluations revealed an excellent acceleration of the wound healing process and improved wound contraction rate and skin regeneration in a full-thickness skin defect model. Thus, the suitability of this hydrogel for application as a wound dressing has been proved.

Hyaluronic acid is a natural glycosaminoglycan that may be found in numerous human tissues, such as connective tissues, skin, synovial fluid, and umbilical cord. As a result of its biodegradability, biocompatibility, and ease of chemical modification, hyaluronic acid-based biomaterials have been largely applied in tissue engineering and for the treatment of inflammatory diseases and wounds [2,109–111]. Li et al. [93] developed a promising hydrogel based on hydrazide-modified hyaluronic acid and benzaldehyde-terminated F127 triblock copolymers. The obtained hydrogel combined multiple functions (i.e., adaptable mechanical strength, rapid gelation, liquid-absorption, self-heal ability, drainage, tissue adhesion, and excellent biocompatibility) in one system, proving its potential for promoting burn wound healing. Dong et al. [2] developed an improved method of adipose-derived stem cells (ASCs) delivery for the treatment of burn wounds. Specifically, the method used an in situ-formed hydrogel system consisting of hyperbranched polyethylene glycol diacrylate polymer, a commercially available thiol-functionalized hyaluronic acid, and a short RGD peptide. The developed hydrogels provided an effective niche that could enhance the regenerative potential of ASCs and promote burn wound healing.

Xanthan gum is a high molecular weight anionic heteropolysaccharide. Its backbone consists of (1,4)- β -D-glucose residues with a trisaccharide side chain linked at the C3 position to alternate glucose residues [94,112]. Xanthan gum is a microbial and exo-polysaccharide, which has been utilized in biomedical applications owing to its great biocompatibility and gelling properties [113,114]. Shawan et al. [94] fabricated xanthan gum and gelatin hybrid composite hydrogels for evaluating its skin wound healing efficiency using experimental skin burn wounds in rats. The results proved good polymeric networks, with adequate porosity of the hydrogels, biodegradability, and good wound healing ability.

Therefore, it can be observed that natural polymers are biomaterials of significant importance for wound dressings development, as they promote wound repair and healing processes through a variety of physiological mechanisms. Moreover, their efficiency is also based on their intrinsic antimicrobial characteristics, which prevent wound infections.

3. Active Hydrogels for Treatment of Burn Wound Dressings

Although a moist environment is required at the wound site, it may also increase the risk of microbial infections, which will further extend the wound and/or affect the wound healing process [115]. Microbial colonization is not desired, as it may conduct serious infections, which can result in disease, disability, or even death [116]. The natural reparative and regenerative phases implicated in the healing process fail to occur when wounds are colonized by opportunistic microbes [117]. Additionally, uncontrolled infections may impede the regeneration of the anatomical and physiological structures and culminate in chronic non-healing wounds [70]. To prevent and combat infections, advanced medicine relies on antimicrobial agents like antibiotics, which act by either destroying pathogens or inhibiting their growth [118]. Hence, hydrogels with antibacterial characteristics have great potential in clinical applications [119]. Unfortunately, the wrong use of antibiotics has led to the development of increasingly multi-resistant microbes [118]. The rise of multi-resistant bacterial and fungal infections in burn wounds has increased the need for novel burn wound treatment strategies' development [120]. Generally, there are two categories of antimicrobial agents, namely organic agents, including antibiotics and organic mineral salts, and inorganic agents, including silver [120–122], zinc [88,119], and copper [119,123]. In recent years, antimicrobial agents-embedded wound dressings have appeared as a viable alternative to decrease wound microbial colonization and infection for improving the healing process [19].

3.1. Active Hydrogels Based on Quaternary Ammonium Salts for Wound Dressings

In this context, Gharibi et al. [91] developed quaternary ammonium salts (QAS)-containing wound dressing membrane and utilized dextran to counterbalance the adverse effects of the antimicrobial agent. Despite the high antimicrobial efficiency of quaternary ammonium salts, their hostile hemolytic effect on red blood cells is a challenging problem for using them as an active antiseptic agent in wound dressings. Wound dressings were prepared using the sol-gel hydrolysis and polycondensation reaction of a methoxysilane-functionalized quaternary ammonium compound and a methoxysilane-terminated polyurethane prepolymer, at various concentrations, and subsequently surface-modified with dextran. The antimicrobial activity of the dextran-grafted samples was maintained, while also proving potential hemocompatibility and good cytocompatibility in fibroblast cell cultures.

Additionally, Li et al. [124] evaluated the potential of maleopimaric acid quaternary ammonium cation (MPA-N⁺) based on rosin acid as a bactericide for modified cotton textiles (CT) considering the fact that antimicrobial CT show great promise for wound dressings. Obtained results confirmed that MPA-N⁺ modified CT (CT-g-MPA-N⁺) can be applied for wound dressings and CT modification using MPA-N⁺ demonstrates a new strategy for using renewable resources to control the spread of infectious diseases.

Furthermore, Zhou et al. [125] prepared an eco-friendly dressing using a chitin-derived membrane with amphipathic anion/quaternary ammonium salt designed for antibacterial purposes. Successfully prepared chitin-amphiphilic ion/quaternary ammonium salt dressing present antibacterial and antipollution effects and promote wound healing. Overall, this study reveals a promising new material for a natural dressing for wound application.

3.2. Active Hydrogels Based on Silver for Wound Dressings

Many silver-based products have become effective substitute agents in burn management in order to avoid the use of antibiotics, with an increased number of studies stating their effectiveness against a large range of microbes [126–129]. The important antimicrobial activity of silver nanoparticles has been previously reported [120–122,130]. As silver treatments applied in burn wound care have also been associated with toxicity for human cells [120], the balance between cytotoxicity and antimicrobial activity of wound dressings must be considered when applied at the wound site [120,130]. Nonetheless, the increase of antibiotic-resistant bacteria has forced to re-evaluate the character of silver and silver derivatives as antibacterial agents for restraining the colonization of bacteria in burn injuries [131]. Boonkaew et al. [120] compared the antimicrobial efficiency of a novel silver hydrogel dressing with two commercially available silver wound dressings for burns, namely Acticoat™ and PolyMem Silver®. They proved that after 24-h exposure, the silver hydrogel decreased most of the tested microbial strains below the detection limit and reduced the viability of bacteria by 94–99%. Furthermore, a thermo-sensitive hydrogel consisting of methylcellulose and embedded silver oxide nanoparticles was prepared by Kim et al. [121] through the one-pot synthesis method in which a silver acetate precursor salt induces a salt-out effect in the methylcellulose solution. They proved that the obtained thermo-responsive methylcellulose hydrogel has important potential for wound regeneration, considering its great antimicrobial and burn wound healing activity. In a study performed by Banerjee et al. [122], a novel treatment for promoting vascularization in burn wounds was proposed. They developed a two-step treatment method based on the controlled time and dose release of silver sulfadiazine and the subsequent delivery of ASCs, which aids in preventing silver toxicity related to traditional topical delivery methods and stimulates the regeneration of the wound. A PEGylated fibrin hydrogel containing 50 mg of silver sulfadiazine-loaded chitosan microspheres was applied on the wounds and results demonstrated that the proposed sequential treatment for infected burn wounds reduces bacterial infection, while also promoting neo-vascularization and improved matrix remodeling.

The hydrogels based on 2-hydroxyethyl acrylate and itaconic acid were synthesized by Vuković et al. [132] and used for silver(I) ions incorporation. The obtained hydrogels presented

promising antibacterial activity against methicillin sensitive *S. aureus* (MSSA) and methicillin resistant *S. aureus* (MRSA), indicating the capacity to treat the life-threatening infections.

Therefore, it can be observed that silver nanoparticles are widely applied in wound dressings due to their low toxicity for human cells, naturally availability, and strong antimicrobial effects.

3.3. Active Hydrogels Based on Zinc for Wound Dressings

Zinc is a highly necessary element for the human body, and, owing to its complex antibacterial mechanisms, it is significantly efficient on various antibiotic-resistant strains [119]. Zinc oxide nanoparticles possess bactericidal character, and it is currently applied as a part of a large variety of restorative materials [133,134]. Mingcui et al. [88] fabricated a nanocomposite hydrogel consisting of keratin, chitosan, and zinc oxide nanoparticles as an antimicrobial strategy for burn wound healing. The mechanical properties, swelling ability, bactericidal effect, and biocompatibility of the nanocomposite were evaluated for its effectiveness for burn wound treatment. Khorasani et al. [135] incorporated zinc oxide nanoparticles into heparinized polyvinyl alcohol/chitosan hydrogels for wound dressing applications. Based on the results, the obtained bionanocomposite hydrogels improved the performance in the wound healing process as it efficiently protected the surface of the wound against exudate accumulation and dehydration, while impeding bacteria growth and infection development.

Furthermore, Rakhshaeia and Namazi [136] prepared flexible nanocomposite hydrogel films through combination of zinc oxide impregnated mesoporous silica (ZnO-MCM-41) as a nano drug carrier with carboxymethyl cellulose (CMC) hydrogel. The antimicrobial property of the obtained CMC/ZnO-MCM-41 samples is a result of intrinsic antibacterial activity of ZnO nanoparticles and confirmed the prolonged release of TC. The authors affirm that the obtained hydrogels could serve as a kind of promising wound dressing with sustained drug delivery properties.

Additionally, Khorasani et al. [137] prepared polyvinyl (alcohol)/chitosan/nano zinc oxide nanocomposite hydrogels using the freeze-thaw method. The results of toxicity and antibacterial activity of samples indicated that obtained hydrogels were non-toxic and biocompatible and were significantly capable to protect the wounds against microorganisms.

3.4. Active Hydrogels Based on Growth Factors, Cytokines, and Cells for Wound Dressings

Regardless of the great number of active compounds that could be considered as therapeutics for promoting wound healing, the wound inflammatory environment inhibits their activity to improve healing, with a limited number of candidates proving clinical effects [1,2]. Analgesics such as morphine [138], ibuprofen [139,140], or lidocaine [141,142] are of significant interest in extensive burns, infected wounds, or in palliative medicine [1,143]. Additionally, hydrogels may also deliver growth factors [1,144,145], stem cells [2,146], peptides [147–149], and various drugs, such as anti-inflammatory drugs [144,150,151], amino acids [152], antioxidants [70,153], vitamins [154,155] and nutrients [135,156], which may decrease the inflammatory reaction, nourish the wound tissue, and promote wound healing [119,126]. One of the recent classes of bioactive hydrogel wound dressings is based on the healing properties provided by growth factors [1,157], cytokines [158], or cells [1,158]. This section also contains recently published literature studying the effects of applying natural alternatives, such as honey, bacterial cellulose, or aloe vera as regenerative and antibacterial agents that further accelerate wound healing processes.

Nimal et al. [126] prepared an injectable hydrogel comprising nano tigeicycline and chitosan platelet-rich plasma with an anti-staphylococcal activity using *Drosophila melanogaster* model for infectious wounds. This hydrogel provided an appropriate medium for the delivery of antibiotics and effectively prevented skin infections.

Furthermore, Wang et al. [144] produced a hydrogel consisting of chemically modified hyaluronic acid, dextran, and β -cyclodextrin and integrating resveratrol and vascular endothelial growth factor (VEGF) plasmid, which acts as an anti-inflammatory and pro-angiogenic components for burn wounds. The hydrogel scaffold was loaded with plasmid DNA encoded with VEGF and conjugated with

polyethyleneimine. Wounds treated for 21 days with these hydrogels demonstrated enhanced wound healing by inhibiting inflammation and promoting angiogenesis compared to untreated wounds and hydrogel-alone treated wounds, suggesting that the in situ formed hydrogels may be applied for wound healing and tissue regeneration applications. Moreover, Mohamad et al. [158] performed an in vivo evaluation of bacterial cellulose and acrylic acid wound dressing hydrogels containing keratinocytes (HEK—human epidermal keratinocytes) and fibroblasts (HDF—human dermal fibroblasts) for burn wounds. Wound healing was accelerated in mice treated with hydrogels and hydrogels embedded with cells healed quicker, by contrast to when no treatment was administered, with best results associated with the delivery of HEK and HDF cells. Therefore, the prepared hydrogels can act as potential materials and cell carriers for the rapid healing of burn wounds.

Based on their broad-spectrum antimicrobial activity and reduced probability of inducing drug resistance, antimicrobial peptides are a new generation of potential antimicrobial molecules [148]. Zhou et al. [147] investigated a bioactive peptide amphiphile nanofiber-based hydrogel biomaterial that may stimulate burn wound healing. Burn wounds in rats were treated with the bioactive Arg-Gly-Asp-Ser (RGDS)-modified gel that proved important cell proliferation in vitro. The in vivo assays showed that the RGDS- peptide amphiphile gel notably improved the burn wound healing process between day 7 to 28 through enhanced re-epithelialization. Application of these gels accelerates deep partial-thickness burn wound recovery by stimulating fibroblasts and creating a suitable environment for the proliferation of epithelial cells and closure of the wound.

Additionally, Khan et al. [148] developed a hydrogel that has the potential for treating bacterial wound infections. The hydrogel formulation is based on an antimicrobial peptide, ϵ -poly-L-lysine, and catechol, which was cross-linked via mussel-inspired chemistry between the amine and phenol groups. In addition to its antimicrobial properties, they demonstrated that the hydrogel presents antibiofilm activity toward multidrug-resistant bacteria. In addition, in vivo studies indicated a considerable reduction in more than four orders of magnitude of the bacterial burden in the infected burn wounds. As it is biocompatible and noncytotoxic to mammalian cells, this hydrogel could be applied in burn wound care.

Since they are appropriate carriers for low soluble drugs or bioactive molecules, liposomes are able to overcome this hydrogel limitation. Hence, by combining these two delivery systems, an encouraging alternative to reach controlled dermal drug delivery, and effective localized skin therapy could be developed [159]. Wu et al. [160] studied the liposome-encapsulated farnesol in order to improve tissue repair in rat models of third-degree burns. The wounds were treated for 1 and 2 weeks with a formulated gel comprising different ratios of 2% hydroxypropyl methylcellulose and 4 mM liposomal farnesol. The liposomal gels prepared in this study enhanced collagen production and wound healing both in vitro and in vivo, but inhibited fibroblast proliferation at high concentrations. The gels exhibited notable effects on wound healing of third-degree burns compared with the untreated or the hydroxypropyl methylcellulose gel alone and commercial silver sulfadiazine cream treated groups. Moreover, the capacity of liposomes to provide sustained drug/substance release could allow for targeted drug delivery to specific skin layers. The rapid liposome clearance from the skin site may be prevented through the use of this hydrogel, which ensures additional protection against fast degradation by conserving the liposomal membrane integrity. The characteristics of the hydrogel in terms of mesh size, porosity, and polymer composition and the physicochemical properties of the liposomes, such as size, composition, and surface charge, directly determine the release of drug/substance [159].

3.5. Active Hydrogels Based on Natural Agents for Wound Dressings

As antibiotics are progressively becoming resistant by infection-producing strains, researchers are currently focusing on the large bioresource repertoire. They mainly consist of herbs but can also include animal and mineral ingredients [19,161–164]. There are a lot of natural agents with bioactive effects on wounds with complications from polymicrobial infections mentioned in the literature. At

the biofilm level, the bactericidal effects of such agents target both the initial and the advanced phases of wound infections [19,164].

Not long ago, naturally-occurring materials gained renewed attention for biomaterial applications due to their important biocompatibility, antimicrobial, and environmentally friendly properties [19,81,165]. Konjac glucomannan, a plant derivative from the *Amorphophallus konjac* corm, a native plant from China and Japan, is an example of such natural biomaterials [41,53,166–168]. Zhou et al. [168] fabricated matrine-loaded composite hydrogel consisting of Konjac glucomannan and fish gelatin as an antimicrobial wound dressing. The bioactive compound improved the antibacterial activity of the gels by maintaining the physiological environment for wound healing and preventing bacteria growth on the surface of the wound. Alves et al. [95] obtained a thermo-reversible hydrogel comprising of xanthan gum and konjac glucomannan (Figure 5) at different concentrations and ratios. The obtained hydrogels showed a transparent and moisturized appearance (Figure 6), which permitted the continuous observation of the wound healing process without dressing removal. The obtained hydrogels are hydrophilic, thus providing a moist environment, while also absorbing the excess exudate and suitable biological properties for promoting cell adhesion, migration, and proliferation [95].

In addition, the therapeutic features of honey in regard to wound healing applications, such as ensuring a topical nutrition to the wound, stimulating granulation, angiogenesis, and wound epithelialization, and reducing inflammation, are the main criteria that make it suitable for introduction into wound dressings [19,169–171]. Zohdi et al. [172] developed a crosslinked Malaysian honey-incorporated hydrogel dressing, which exhibited excellent physical properties, such as proper transparency, exudate absorbance, and acidic pH values, as ideal characteristics of burn wound dressings.

While bacterial cellulose is chemically identical with plant cellulose, the degree of polymerization for bacterial cellulose is approximately 2000–6000 and for plant cellulose, approximately 13,000–14,000 [81]. Bacterial cellulose has great hydrophilicity, water-uptake capacity, permeability, and tensile strength, characteristics that have attracted great interest as wound dressing material [81]. Moreover, bacterial cellulose is currently considered a promising functional biomaterial with various applications in different fields, including skin tissue repair, scaffolds for tissue engineering, and wound healing applications [151,158,173,174]. Loh et al. [173] performed an *in vivo* evaluation of a keratinocytes and fibroblasts-containing wound dressing hydrogel composed of bacterial cellulose and acrylic acid for burn wounds. They demonstrated that these hydrogels are promising for burn wound dressing and cell carrier applications.

Aloe vera has a healing action that occurs due to the maintenance of the moisture of the wound, reduced inflammatory process, enhanced cell migration and proliferation, and maturation of collagen. Its effects appear by the synergistic action among the different active components that act on the tissue during the novel epithelium formation [146,175,176]. Yates et al. [177] patented an antimicrobial therapeutic hydrogel composition comprised of a pharmaceutical and/or medical-grade silver salt, and an aloe vera gel or extract. Additionally, it may also include a non-ionic surfactant, stabilizing agents, and polyol and hydrophilic hygroscopic polymers. The so-obtained hydrogel has potential antimicrobial activity against bacteria, fungi, viruses, and protozoa, acting as an efficient treatment for burns, and as a wound/lesion dressing, that maintains adequate moisture levels and provides a physiologic environment that stimulates wound healing and pain relief. Oryan et al. [146] evaluated the *in vivo* effects of allogeneic ASCs-loaded aloe vera hydrogel on a rat burn wound model. They proved that aloe vera enhanced the anti-inflammatory effect of ASCs by decreasing the TGF- β 1 and bFGF expression level, diminishing scar formation. Combining ASCs with aloe vera hydrogels could bring advancements in the field of regenerative medicine as it promotes the pro-angiogenic effect of ASCs, increases the expression level of cytokines and growth factors, and improves wound repair and regeneration.

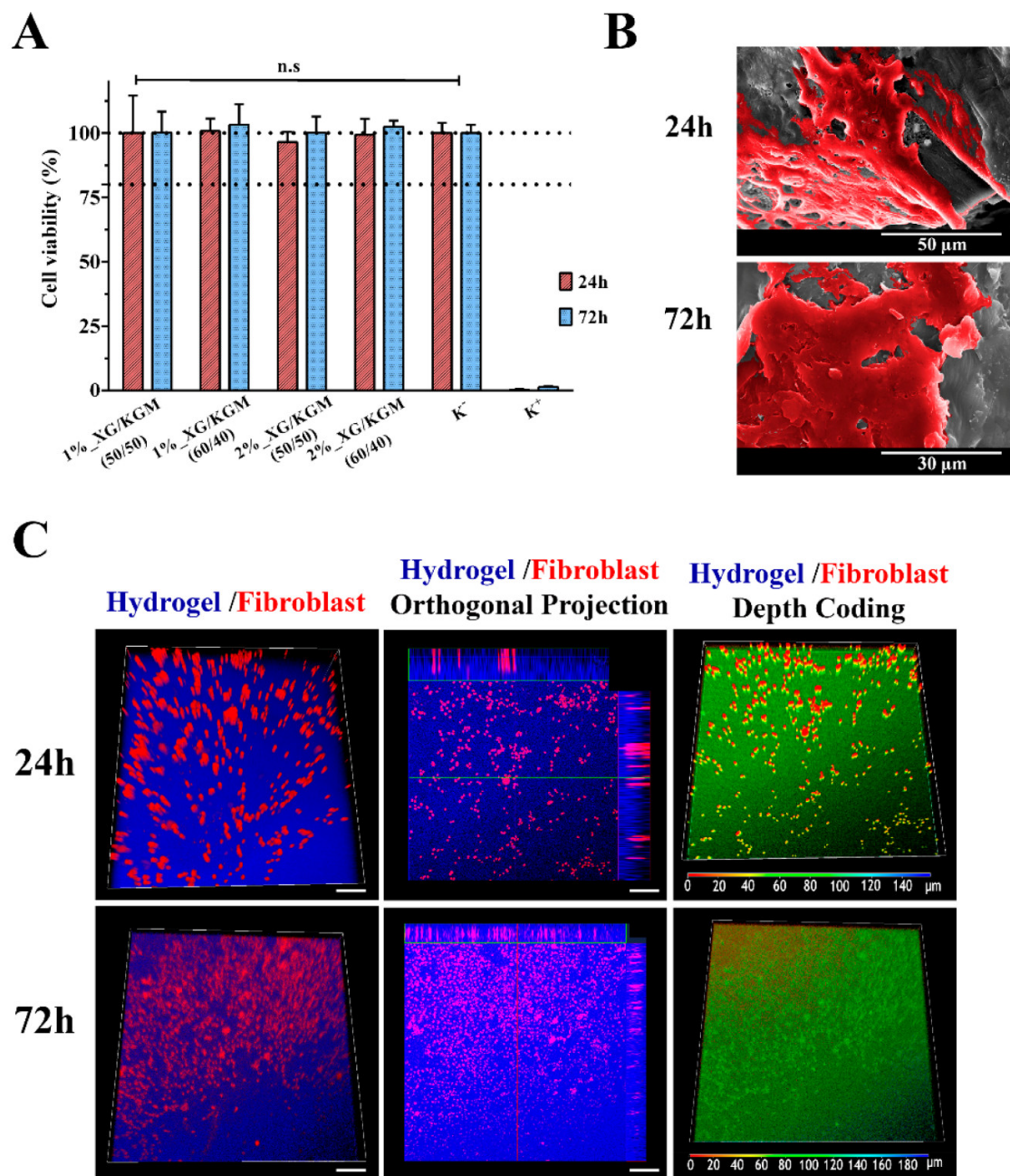


Figure 5. Characterization of the cytocompatibility of the hydrogels. (A) MTT assay of human fibroblast cells grown in the presence of different hydrogels. Wells treated with ethanol were used as positive controls. n.s.: no statistically significant groups. The data are shown as means \pm standard deviations ($n = 3$). (B) Representative SEM images of fibroblast cell adhesion and proliferation on the surface of the 1%_XG/KGM_(60/40) hydrogel, after 24 h and 72 h of incubation. (C) Confocal laser scanning microscopy (CLSM) images of cell internalization in 1%_XG/KGM_(60/40) after 24 h and 72 h, where different colors correspond to distinct depth values (as indicated in the color-coding scale) [95]. Reprinted from an open-access source.

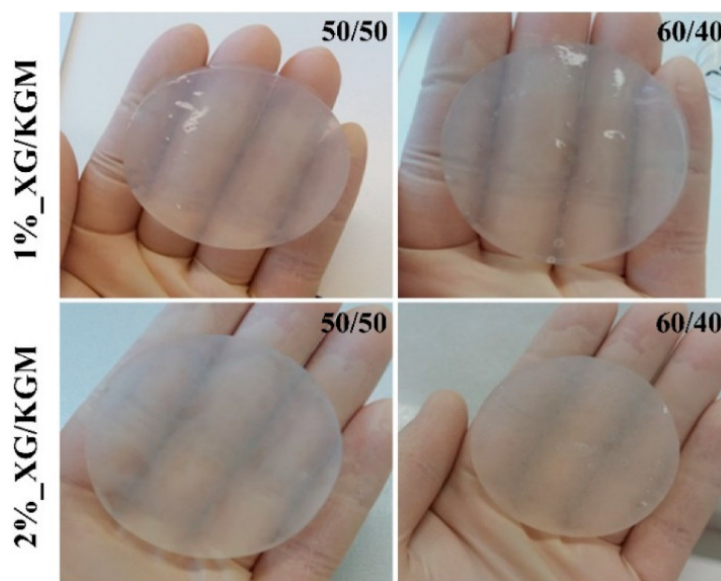


Figure 6. Macroscopic images of the hydrogels XG/KGM [95]. Reprinted from an open-access source.

Amniotic membrane, the innermost lining of the human placenta, is a globally accepted biomaterial for the treatment of second and third-degree burns, as it contains numerous proteins, growth factors, and stem cells that enhance the wound healing process [178–184]. A study by Hossain et al. [184] proved the efficiency of amniotic membrane and *Moringa oleifera* are decisive agents for higher epithelialization, quicker wound healing, no rejection phenomena, decreasing number of suffering patients, and cost-efficiency. Another study was realized by Rahman et al. [178], which prepared a gel by combining amnion and aloe vera extract, which showed promising effects in internal epithelialization and diminished scar formation.

While currently available therapeutic agents are generally inadequate in regard to their efficacy and numerous adverse severe effects, natural biocompounds have been applied in medicine since ancient times as they are well known for their capabilities of promoting wound healing and preventing infection without causing significant side effects. Therefore, this class of materials should be an alternative strategy for the development of hydrogels used for the treatment of burn wounds.

4. Conclusions

Among the wound dressings developed, hydrogels have gained the consideration of researchers as a result of their intrinsic ability to mimic the 3D structure of the skin ECM. Moreover, hydrogels are hydrophilic 3D networks, which can absorb optimal quantities of biological fluids (e.g., wound exudate) or water. Additionally, hydrogels are capable of maintaining dry, sloughy, or necrotic wounds clean by rehydrating dead tissues (moist healing), thus leading to an increase of autolytic debridement and surface wound cooling. Consequently, hydrogels could aid in pain relief and, thus, improve patient acceptance of the dressing. Further, hydrogel biodegradability eliminates possible complications related to wound dressing replacement, like tissue maceration, infection, and pain. Despite the numerous hydrogel-based products already available on the market, advanced hydrogel dressings development or optimization still represents an important research area, with the purpose of further improving skin healing in reports to specific clinical applications. Antimicrobial hydrogels represent an important class of macromolecular antimicrobial agents, which have proved significant efficiency in preventing and treating drug-resistant infections.

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