# Review Paper: Biomimetic Wound Dressings: Advancements, Applications, and Challenges in Modern Wound Care

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## ABSTRACT

Wound dressings are critical in managing various injuries, including pressure ulcers, venous ulcers, and diabetic foot ulcers. Various dressing materials are employed in wound care, such as traditional dressings, interactive materials, skin substitutes, bioactive dressings, and dermal grafts. These materials, both synthetic and biological, contribute to effective wound healing by supporting the regeneration of skin tissues. However, biomimetic wound dressings are emerging as a superior alternative to conventional dressings due to their ability to align more closely with the natural wound healing process. Among these, hydrogels are particularly promising for their capacity to replicate the biological properties of human skin, offering enhanced moisture retention, flexibility, and biocompatibility. Biomimetic wound dressings are available in various forms, including films, gauzes, injectable gels, and sprays, catering to different wound types and healing stages. In recent years, the development of novel wound dressings has become a focal point in biomedical engineering, with a strong emphasis on leveraging the benefits of biomaterials. These advanced dressings promote faster healing and offer various advantages, such as reduced infection risk and improved patient comfort. However, despite their potential, biomimetic dressings also present specific challenges, such as production costs and variability in performance across different wound types. This review explores the strengths and limitations of biomaterial-based wound dressings, highlighting their growing significance in modern wound care and future therapeutic applications.

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## 1. Introduction

Biomedicine, in particular, uses the term "bioinspiration" to refer to developing novel materials by copying biological structures, functions, processes, or occurrences to achieve specific goals [1]. The characteristics of bioinspired elements can vary, mimicking an organism's chemical composition, nano- and microstructure, and architecture. Numerous innovative, nature-inspired adhesive materials in the form of hydrocolloids, films, foams, hydrogels, and micro/nanofibers have been developed to address the drawbacks of conventional formulations. Researchers have investigated the reversible wet adherence of these organic materials, drawing inspiration from polymers inspired by mussels, paste inspired by barnacle glue, secretions inspired by insects, and artificial octopus suckers [2, 3].

Much work has been done to develop bioinspired adhesive formulations with strong biocompatibility and adhesive characteristics for wound treatment and drug delivery. These bioinspired adhesive formulations can replace standard surgical wound dressings and tissue adhesives. Due to their excellent biocompatibility, bioinspired adhesives can accommodate dynamic tissue mobility and promote internal and exterior wound healing. Effective wound treatment requires understanding the healing process and the properties of various dressing materials [4]. Maximizing the treatment's efficacy is the main objective of all wound care procedures. To prevent tissue maceration, excessive exudates should be removed from the wound. An optimal dressing should encourage autolytic debridement, preserve moisture, and offer sufficient oxygen and water vapor permeability. It must be adhesive and flexible enough to allow the desired mechanical compliance for the affected person's frame and be simple to apply and remove. Deliverable bioactive substances with antibacterial, antifungal, and antiseptic properties, such as antibiotics, palatable oils, and herbal antioxidants, can facilitate the interaction between dressing and the wound microenvironment and speed up the healing process. Film-casting, electrospinning, self-assembling, freeze-drying, emulsifying, microsphere injection, and other fabrication techniques have created wound dressings entirely made of synthetic macromolecules or natural materials [5].

### *1.1 Diversity of wound dressings*

Wound dressings are essential in treating a wide range of injuries. Their main features include uptake of excess exudates, protection from pathogens, mechanical support, gaseous exchange, removal of dead tissue and foreign particles, non-toxicity, adherence to the per wound area but removal without damaging the wound bed, cost-efficiency, and maintaining a moist environment to hasten healing [6]. Existing dressings can sometimes be associated with disadvantages, such as delayed wound healing, poor air permeability, inability to maintain moisture, and allergic reactions. Therefore, the development of effective dressing materials remains crucial.

Bandages can be classified into five groups: traditional dressings, interactive materials, skin substitutes, bioactive dressings, and skin grafts [7].

- **Traditional dressings:** These include gauze, fluff, bandages, and cotton wool. They are dry and used as primary or secondary dressings to protect the wound from infection and bleeding and to cushion the wound bed. Made of cotton, rayon, and polyester (woven and non-woven fibers), they offer some protection against bacterial infections; however, they require frequent changes to prevent healthy tissue maceration [8].
- **Interactive dressings:** These include composites, films, gels, and foams. They can accelerate wound healing, particularly for pressure and diabetic foot ulcers, by providing a moist environment that promotes good water transfer and improves re-epithelialization and granulation. These dressings can also be loaded with bioactive agents. Interactive dressings can actively interact with wound exudate, tissue, cells, and growth factors to promote healing [9].
- **Skin substitutes:** These are a heterogeneous group of biological, synthetic, or biosynthetic materials providing temporary or permanent open wound coverage. Ideally, they possess the composition and function of the skin or have the potential for autologous regenerative healing. Skin substitutes are often derived from cell co-culture or cell scaffold material and are effective in skin regeneration. However, they can be expensive, have a limited lifespan, may be rejected by the body, and carry a risk of infection or disease transmission [10].

•**Dermal grafts:** These are among the most essential materials in dermatology and plastic surgery. Examples include cell-free xenografts, autologous transplants, and allogenic transplants. These materials are used for various purposes, such as treating traumatic wounds, regenerating burns, managing defects after oncological resection, eliminating wound contracture, promoting hair recovery, and treating congenital skin defects [11].

•**Bioactive dressings:** These deliver wound-healing agents by incorporating bioactive compounds or being composed of endogenously active materials. Examples include hydrophilic colloids, sponges, foams, nanofibers, hydrogels, collagens, and films. Bioactive dressings are typically biodegradable and biocompatible and act as drug-delivery systems for nanoparticles, growth factors, vitamins, and antibiotics. The various categories of wound dressings, highlighting their unique properties and applications in modern wound care, are shown Figure 1. They accelerate the wound-healing process. While nanofibers and hydrogels are distinct types of dressings, they can both be loaded with drugs to achieve controlled release and transformed into bioactive bandages through the incorporation of bioactive agents [12].

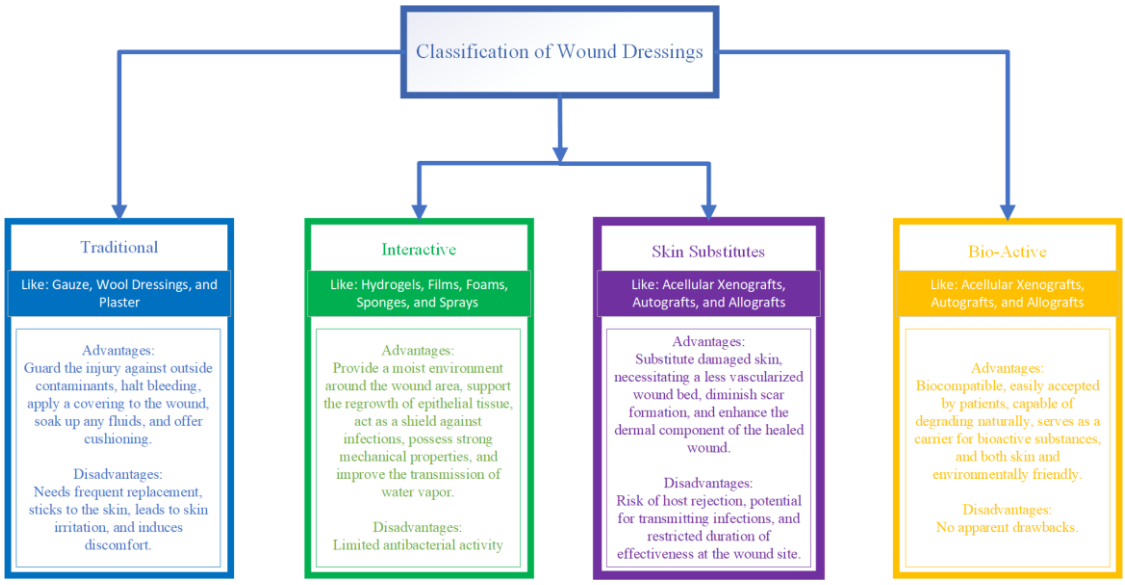


**Figure 1.** Classification of wound dressing

Wound healing is a dynamic and complex process requiring a suitable environment, material, and surrounding to promote efficient wound closure [13]. It involves four phases: hemostasis, inflammation, proliferation, and maturation. Understanding these mechanisms is crucial for developing new hydrogels with valuable properties for wound management [14]. Given the variety of wounds and advancements in medical technology, different products have been produced to repair various wounds. Recent scientific and technological advances suggest that appropriate materials for a modern and clinically advanced hydrogel should consider factors such as biocompatibility, composition, mechanical properties, gelation behavior, self-healing ability, shape, pore size, responsiveness to external stimuli, and adhesiveness [15]. Scientists face a significant challenge in developing an ideal dressing material that combines all these characteristics while providing optimal conditions for the most effective regeneration process.

Materials used in wound dressings have evolved with scientific progress to offer better conditions for wound healing. Choosing the proper material from various options for a specific wound is critical for adequate healing. The selection of a dressing is based on various factors, such as the wound's kind, depth, location, size, discharge amount, presence of infection, and adhesion properties [16]. Traditional wound dressings, such as cotton bandages and gauze, absorb much of the wound's moisture. This drying effect slows the healing process and causes discomfort during removal. In contrast, a wide variety of polymers have been developed in films,

foams, and gels that can provide optimal conditions for wound healing [17].

Wet dressings demonstrably accelerate wound healing compared to dry dressings. Skin regeneration occurs more efficiently and painlessly only in a moist environment [18]. Traditional dry healing dehydrates wounds, while moist wound healing promotes faster healing through various mechanisms, including preventing scab formation and drying of exudates containing nutrients, oxygen, growth factors, and white blood cells [13]. Different wound types require specific dressings based on their individual needs. For instance, necrotic wounds involve separating dead tissues from healthy ones. Here, the dressing should maintain a moist environment to prevent dehydration [19]. Sloughy wounds, such as burns and ulcers, require cleansing but benefit from exudate-absorbing dressings. As a result, using moist dressings has become the standard practice for treating chronic wounds. Studies have shown that a humid environment speeds up wound healing by minimizing dehydration, fostering the formation of blood vessels (angiogenesis) and collagen, and enhancing the breakdown of fibrin and dead tissue. This approach also reduces pain while improving the wound's appearance [17].

Several methods can accelerate wound healing in a controlled, moist environment. These include faster epithelialization (formation of the skin's outer layer), easier migration of epidermal cells on a wet surface, the proliferation of keratinocytes (skin cells) and fibroblasts (connective tissue cells), enhanced activity of growth factors, improved angiogenesis, collagen synthesis, better wound aesthetics, and overall quality. Therefore, an ideal wound dressing should possess the following characteristics: high gas permeability, efficient removal of excess exudates, protection from infections and microorganisms, reduction of wound surface necrosis, mechanical safety, ease of application and removal, biocompatibility, biodegradability, elasticity, non-toxicity, pain relief, cost-effectiveness, a long shelf life, conformability to wound shape, and minimal dressing change frequency [20]. The key characteristics that define an ideal wound dressing, such as biocompatibility, flexibility, and antimicrobial properties, are summarized in Figure 2. Wound dressings provide the skin with immediate protection, minimizing functional impairment. The ideal wound dressing material should possess healing activity, antibacterial activity, and non-toxicity property, be cost-effective, available, and capable of being adapted into novel products based on specific wound conditions [21].


**Figure 2.** Ideal wound dressing features

## 2. Materials and Methods

### *2. Biomimetic materials*

### *2.1. Natural Biomimetic Materials*

Natural polymers are widely used in regenerative medicine for wound and burn dressings owing to their biocompatibility, non-cytotoxicity, biodegradability, non-immunogenicity, inherent bioactivity, special antibacterial, and cell-adhesive/binding properties, as well as capacity to be a component of the extracellular matrix (ECM). Natural polymers, such as chitosan, hyaluronic acid (HA), and alginates, are used to form hydrogels that mimic the structure of the extracellular matrix. Different types of polymers used in biomimetic materials are categorized, focusing on their structural and functional properties in Figure 3. Biomaterial hydrogels, with their three-dimensional cross-linked polymer networks saturated with water or biological fluids, find applications in the pharmaceutical and biomedical industries, particularly for wound treatment, tissue engineering, drug delivery, and organ transplantation [22]. Natural polymers are crucial in restoring damaged tissues during wound healing, ultimately leading to skin regeneration [23]. Additionally, irradiation can create new biomaterials based on biodegradable, non-toxic, and renewable polymers [24]. Consequently, hydrogels made from cross-linked natural polymers offer a promising approach to treating wounds and burns. Indeed, the unique advantages of natural polymers, such as their hemostatic, anti-inflammatory, and cell proliferation properties, have made natural hydrogels attractive candidates for wound dressings. Polymers derived from natural sources are advantageous as biomaterials and in regenerative medicine because of their similarities to the extracellular matrix and other polymers found in the human body [25]. However, one drawback of some biomaterials is their limited functionality and weak mechanical properties. Therefore, future research in developing cutting-edge biological and medical dressings will likely focus on modifying natural biological materials, combining them with other materials, and incorporating them with drugs for enhanced functionality [26].

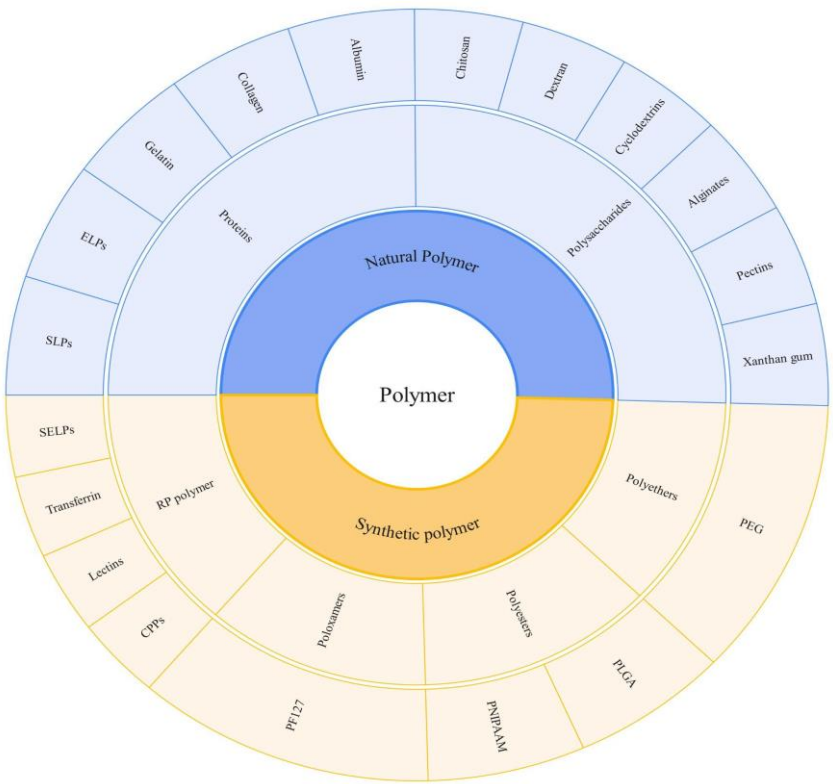


**Figure 3.** Classification of polymers

### 2.1.1. Protein-based polymers

Collagen, the most abundant animal protein, provides tissues with mechanical strength and promotes cell attachment and proliferation. Only a few of the 46 distinct collagen types, characterized by their triple-helical structure, are used to create collagen-based biomaterials [27]. Recombinant collagen produced by *Escherichia coli* or via heterologous expression in mammalian, insect, and yeast cells offers an alternative to animal-derived proteins, which can cause allergic reactions and transmit pathogens [28]. Due to its remarkable resemblance to native collagen within the body, collagen exhibits excellent biocompatibility and biodegradability, making it a valuable material for various biomedical applications [29]. In wound healing, fibroblasts play a crucial role by synthesizing collagen molecules that self-assemble into fibrils with diameters ranging from 10 to 500 nanometers. This intricate collagenous network plays a pivotal role in facilitating the migration of cells toward the wounded area, thereby promoting tissue repair [30, 31]. Simple chemical functionalization of the protein structure allows for diverse dressing designs [32, 33]. Collagen-based wound dressings in the form of hydrogels, electrospun fibers, or scaffolds containing nanocrystals have been used to treat burn wounds, heal ulcers, reduce tissue contraction and scarring, and accelerate epithelialization [34, 35] . Collagen sponges and fibrous membranes exhibit promising wet strength, allowing suturing to soft tissues and acting as a template for new tissue formation [36, 37]. A vast body of research has investigated the development of constructs for tissue engineering applications. These constructs often combine collagen with synthetic biopolymers (e.g., poly-hydroxyl esters) or natural materials (e.g., dextran, chitosan, hyaluronic acid, alginate) to create composite scaffolds [38, 39]. Additionally, acetylated, succinylated, methylated, or biotinylated collagen has been used to control drug delivery and immobilize therapeutic enzymes or growth factors [40]. An example of a multifunctional collagen-based dressing is the one proposed by Albright et al. The current study investigates a novel electrospun wound dressing composed of a poly-ε-caprolactone/collagen matrix (PCL/COL). This matrix is loaded with transforming growth factor beta-1 (TGF-β1) to promote tissue regeneration and further modified with polypeptide-based nanocarriers encapsulating gentamicin and tannic acid. This design offers a multifunctional platform that exhibits antibacterial and anti-inflammatory properties while maintaining a favorable topography for cell proliferation. These characteristics collectively contribute to accelerated wound healing and closure. Karri et al. (2016) presented a comparable design utilizing a collagen-alginate composite scaffold loaded with curcumin-encapsulated chitosan nanoparticles, highlighting the potential of natural biomaterials in wound dressing development [41]. Gelatin, a collagen derivative with potential applications in biomedicine, is obtained from collagen in bones, skin, and connective tissues through incomplete denaturalization [42-46]. Gelatin has created robust hydrogel-like membranes, microspheres, sponges, and electrospun mats for cutaneous tissue applications, particularly for treating severe burn wounds [47]. Several blends with modified chitosan and poly-vinyl alcohol based on enzymatic cross-linking have also been proposed to enhance fibroblast culture and proliferation. Despite their widespread use as biomaterials for scaffold construction, collagen and gelatin remain promising materials with significant untapped engineering potential [41, 48-50].

### 2.1.2. Elastin

Elastin, an ECM protein, is crucial for the elastic properties of tissues (rebound and recoil) and is abundant in blood vessels, ligaments, tendons, lungs, and skin. Insoluble elastin is formed by cross-linking tropoelastin, its soluble precursor [51, 52]. This protein has a high molecular weight (6072 kDa), and its structure is rich in hydrophobic sequences containing aliphatic residues, such as valine (V), proline (P), leucine (L), alanine (A), isoleucine (I), and glycine (G) [53, 54]. However, the linker domain contains proline-rich regions with lysyl residues. Cross-linking elastin at the injury site helps organize damaged tissue and reduces scarring by promoting less scar tissue formation, as scar tissue lacks elastin [55, 56]. Additionally, cross-linked elastin promotes chemotaxis in fibroblasts, endothelial cells, and inflammatory cells, aiding

wound healing. Following skin damage, elastin proteins are not properly produced, leading to an inadequate elastic fiber network and compromised physical properties of scars compared to healthy skin [57, 58]. Therefore, it seems like a good idea to design and create novel materials based on elastin or polypeptides that resemble elastin. These conclusions have led several researchers to concentrate on creating elastin and elastin-like materials in various forms utilizing a variety of cross-linking agents. At wound sites, elastin and elastin-like polymers are also employed as carriers for cells, antibiotics, growth hormones, and other matrix proteins that promote healing [59]. Elastin and elastin-like polymers can also transport cells, antibiotics, growth factors, and other matrix proteins to wound sites, promoting healing [59,60]. Keratin proteins, made by skin cells, are a major building block of hair, skin, nails, and other external structures. These proteins contain high levels of sulfur-containing building blocks. The high concentration of cysteine creates disulfide bonds essential for the structural integrity of tissues [61, 62]. These bonds link cysteine residues in the protein, making it strong and lightweight. Keratins are categorized into diverse groups based on factors such as production method (primary and secondary), biochemical characteristics (type I-acidic and type II-basic), molecular weight (low, medium, and high), and distribution (soft and hard) [63, 64]. Several studies suggest the importance of keratin in protein synthesis, cell differentiation, and wound healing. Upon skin damage, keratinocytes near the wound change gene expression, upregulating three specific keratin subtypes: Keratins 6, 16, and 17 (KRT6, KRT16, and KRT17) [65, 66]. These alterations influence the cellular viscoelastic properties, promoting tissue repair. Additionally, keratin proteins possess an inherent ability for self-assembly and polymerization, allowing for the creation of porous scaffolds, sponges, fibers, films, and hydrogels [67]. Keratin and its derivatives exhibit specific cell-binding motifs, such as glutamate-aspartic acid-serine and leucine-aspartic acid-valine sequences, which promote cellular attachment [68]. Beyond their role in cell adhesion, keratins also perform regulatory functions that influence cell behavior, including cell invasion and proliferation. Due to their natural abundance, inherent bioactivity, biocompatibility, and biodegradability, keratin and keratin-based dressings have been shown to accelerate wound healing and promote overall well-being [66, 69]. These dressings promote cellular migration into the wound, releasing keratin peptides that enhance healing. Research overwhelmingly demonstrates the importance of keratin and its derivatives, sourced from either chicken feathers or human hair, in all phases of wound healing [70, 71].

### *2.1.3. Polysaccharides-based polymers*

Alginate, a linear anionic polysaccharide derived from the cell walls of some bacterial species and brown marine algae, comprises D-mannuronic acid and L-guluronic acid. Highly hydrophilic and biocompatible, it absorbs wound exudate and maintains a moist microenvironment, promoting healing [72,73]. While alginate promotes wound healing, combining it with antibacterial, enzymatic, or other components can further aid in eliminating necrotic tissue and microbial bodies [74,75]. The most common alginate dressings are formed by cross-linking a sodium alginate solution with divalent cations (calcium, barium, cadmium, magnesium, zinc, cobalt, and strontium). These can then be processed into foam-like or fibrous dressings [76] . The backbone of alginate, consisting of poly-hydroxyl and poly-carboxyl groups, allows for easy modifications, making it versatile for various applications, including wound healing [77]. Alginate wound dressings are formed by either cross-linking a solution with $Ca^{2+}$, $Mg^{2+}$, $Zn^{2+}$, and $Mn^{2+}$ or freeze-drying the material into porous structures [78, 79]. Notably, the high concentration of $Ca^{2+}$ ions in the dressing interacts with $Na^{+}$ ions in wound fluids, making them particularly effective for exudating wounds [80]. Alginates with a high G block content are often preferred for biomedical applications due to their ease of processing and low immunogenicity [81]. Alginate-based wound dressings come in various forms, including nanofibers, films, foams, hydrogels, or topical formulations. These dressings can absorb excess exudate, maintain a moist wound environment, mitigate bacterial colonization, and promote granulation tissue formation [82, 83]. Incorporating antibacterial agents or metallic nanoparticles can further enhance their antibacterial activity [84]. For

instance, Roudkenar et al. investigated the use of a combined alginate hydrogel and gelatin-based wound dressing to promote new blood vessel formation (revascularization) and epithelial tissue regeneration (re-epithelialization) in skin wounds (in vivo). In vitro findings showed that conditioned media obtained from mesenchymal stem cells significantly stimulated umbilical cord mesenchymal stem cells to migrate and upregulate vascular endothelial growth factor [85].

Hyaluronic acid is an anionic, linear glycosaminoglycan (GAG) formed by alternating β-1,3 and β-1,4 glycosidic linkages between monosaccharide units of N-acetyl-D-glucosamine and D-glucuronic acid [86, 87]. HA polymers can adopt various structures and morphologies depending on their size, salt content, pH, and associated cations. Found in both bacterial and eukaryotic cells, HA is particularly abundant in human skin, vitreous humor, umbilical cord, and synovial fluid. However, it is present in all body tissues and fluids, including bone tissue, heart, lung, and aorta valves, the prostate, tunica albuginea, cavernous, and spongy penis, and plays a role in cellular signaling that promotes wound healing [88, 89]. HA and its derivatives are used as medications or additives in some products, such as wound dressings in the medical field. Numerous studies have demonstrated that HA participates in fibroblast and endothelial cell organization and proliferation during the initial stages of wound healing [90, 91]. Notably, migrating and proliferating cells often have HA-rich ECM around them, allowing them to interact with cell surface receptors [92]. Additionally, research suggests that the molecular weight of hyaluronic acid affects the growth, migration, and neovascularization of endothelial cells [93]. In a study by Wang et al., a topical formulation containing short-chain hyaluronan fragments (2-10 disaccharide units) demonstrated positive effects on wound healing in diabetic rats. The study observed that HA significantly enhanced the proliferation, migration, and formation of endothelial cells even under hyperglycemic conditions (high glucose) [94].

Chitin (CT), the second most abundant natural polysaccharide after cellulose, is found in the exoskeletons of many species, including protists, diatoms, sponges, arthropods, mollusks, insects, and arachnids, particularly shellfish, such as shrimp and crab [95, 96]. Traditionally, CT was isolated from the exoskeletons of crustaceans and fungi. Extraction methods include chemical processing, microbial fermentation, or bio-enzymatic hydrolysis [97]. Chitosan, a derivative of CT, is produced by partially deacetylating CT (poly-N-acetyl glucosamine). It consists of β-1,4-linked D-glucosamine and N-acetyl-D-glucosamine units. It is valued for its excellent biocompatibility, biodegradability, non-toxicity, and ease of processing, leading to its extensive use in various fields [98]. The field of bionics utilizes the intersection of biology, chemistry, and physics to study the structure, function, and optimization of natural biomaterial systems. Inspired by millions of years of natural selection, researchers are designing various structural and functional chitosan-based biomimetic materials [99]. Chitosan's diverse properties make it applicable for adhesion, hemostasis, controlled release, and adsorption. To better understand its role in different biomedical applications, chitosan-based biomimetic materials can be categorized into scaffolds, hydrogels, films, and composite materials [100].

Biosynthetic cellulose is beneficial as a healing scaffold or matrix for chronic wound dressings, minimizing discomfort and accelerating healing. It promotes granulation and epithelialization in partial and full-thickness wounds [101]. Modified cellulose dressings can incorporate co-immobilized active molecules, such as enzymes, antioxidants, hormones, vitamins, and antibacterial medications [102]. Due to its exceptional nanostructure, strong mechanical strength, and superior physicochemical properties, the flexible biomaterial known as biosynthetic cellulose is employed in regenerative medicine as a wound-healing scaffold for severely damaged skin and small-diameter blood vessel replacement. Its similarity to the ECM makes it particularly suitable for these applications [103].

Agarose, a well-known biocompatible polymer abundant in seaweed, comprises D-galactose and 3,6-anhydro-L-galactopyranose units. Affordable and easy to obtain, agarose can self-assemble into a fibrous network in an aqueous solution without cross-linking agents [104]. Wet-spun natural agarose fibers and agar polysaccharides show promise as biomaterials for wound dressings.

Researchers have produced continuous fibers using a suitable solvent (dimethyl sulfoxide-water, 9:1 v/v) and an ethanol coagulation bath [105]. These smooth and uniform agarose fibers exhibit high tensile strength (30-50 MPa) and swelling capacity (400-500%). While agar fibers boast a higher water swelling capacity, agaropectin has been shown to introduce flexibility limitations [106].

Heparin, a highly sulfated anionic GAG, is primarily composed of three repeating units: HA, 2-deoxy-2-sulfamino-6-O-sulfo-α-D-glucose, and 2-acetamido-2-deoxy-α-D-glucose. 1,4-glycosidic bonds link these units [107]. Found mainly attached to the ECM and protein core on the cell surface of higher organisms, heparin interacts with various essential proteins. Recent in vitro and in vivo studies have demonstrated its involvement in numerous biological functions, including blood coagulation, inflammation, cell proliferation, angiogenesis, viral infectivity, and development [108, 109]. Heparin's interaction with proteins is primarily mediated by electrostatic interactions between its sulfate and carboxylate groups and clusters of positively charged amino acid residues (e.g., arginine and lysine) on these proteins. These interactions are crucial for initiating and regulating wound healing processes, such as cell movement and growth, deposition of the ECM, blood vessel formation, and tissue reorganization [110]. In addition to electrostatic interactions, heparin-binding domains can involve amino acids, including asparagine and glutamine, which bond hydrogen with heparin. These interactions contribute to ECM construction by stabilizing proteins and influencing their affinity for molecular receptors and resources [111]. Researchers have developed heparin-mimetic peptide nanofibers that facilitate wound contraction, re-epithelialization, and the growth of skin appendages, all of which contribute to full-thickness burn injury recovery. These nanofibers also promote neovascularization and deposition of a highly cross-linked collagen matrix, further enhancing wound healing [112].

### *2.2. Synthetic-based Wound Dressings*

In recent years, there has been a surge in research investigating biopolymer synthesis and its applications in bioinspired materials science. Naturally occurring degradable polymers, such as chitosan, hyaluronan, collagen, and gelatin, can create scaffolds [113]. Biopolymers offer several advantages over synthetic polymers, which may exhibit inadequate mechanical properties, neutral charge distribution, slow degradation rates, and hydrophobicity [114]. Chitosan and sodium alginate are just a few examples of natural, non-toxic, non-immunogenic, biodegradable, and biocompatible biopolymers. These properties contribute to their widespread applications in pharmaceuticals and biomedicine [115, 116]. Historically, synthetic polymers were adopted due to their lower cost and perceived functional superiority, although potential immune responses and toxicity were not always considered [117]. Poly (lactic-co-glycolic) acid (PLGA), poly(caprolactone) (PCL), polyethylene glycol (PEG), and poly (glycolic acid) (PGA) are some of the synthetic polymers that have gained attention for scaffold creation. By combining synthetic and natural polymers, researchers can address concerns about hydrophilicity, cell attachment, and biodegradability [118,119]. Synthetic polymers offer advantages in controlled synthesis and consistent physicochemical properties and stability compared to natural polymers. An overview of commonly used synthetic polymers, highlighting their properties and applications in wound healing, is provided These hydrogels combine self-healing properties, ecological stability, in Table 1. However, they often lack inherent biological activity and may be associated with some toxicity, unlike natural polymers with therapeutic benefits [120]. They can be categorized as hydrophilic or hydrophobic and are frequently used in wound healing applications.

**Table 1.** Commonly used synthetic polymers for wound healing

| Type of polymers | Properties |
|---|---|
| Polyvinyl alcohol (PVA) | Biocompatible, Nontoxic, Hydrophilic, Water-soluble, pH-sensitive |
| Polylactic acid (PLA) | Biocompatible, Biodegradable, Nontoxic, Hydrophobic, Structurally stable, the degradation products are absorbed by the body through natural metabolic pathways |

| | |
|---|---|
| Polyglycolic acid (PGA) | Biocompatible, Biodegradable (by hydrolysis; it produces $CO_2$ and lowers the local pH, leading to cell and tissue necrosis, more hydrophilic than PLA, High tensile strength |
| Polyurethane (PU) | Biocompatible, Degradation rate can be adapted, Potential side effects of degradation products, Tough and durable |
| Poly (lactic-co-glycolic) acid (PLGA) | Biocompatible, Biodegradable, Degradation rate can be controlled by adjusting monomer ratios |
| Polycaprolactone (PCL) | Biocompatible, Biodegradable, Slower degradation rate than other polyesters, Hydrophobic, Semicrystalline, Good elastic properties |
| Polyethylene glycol (PEG) | Biocompatible, Nonbiodegradable, Bioinert, Hydrophilic, Resistant to protein adsorption |
| Polydimethylsiloxane (PDMS) | Bioinert, Nonbiodegradable, Compatible with blood, Low toxicity, Hydrophobic surface, Anti-adhesive properties, Exceptional elasticity when lightly cross-linked, Good thermal stability |
| Polyethylene oxide (PEO) | Non-toxic, Biocompatible, Non-immunogenic, Hydrophilic, Flexible |
| Polyvinyl pyrrolidone (PVP) | Biocompatible, Biodegradable, Environmental stability, Low cytotoxicity, High chemical and thermal resistance, Affinity to complex hydrophilic and hydrophobic substances, Excellent solubility in water and organic solvents |

## 3. Results

### *3. Multifunctional wound dressings*

Multifunctional wound dressings are consumable products widely used in clinical settings. Hydrogels with high biocompatibility generate less environmental waste [121]. Therefore, ecological considerations play a critical role in developing wound dressings. In recent years, research and development efforts have focused on creating multifunctional composite wound dressings, a key area of interest for medical and chemical advancements [122]. While multifunctional composite wound dressings hold significant promise, their development presents significant challenges, particularly regarding their ability to promote wound healing through performance [123].

### *3.1. Hydrogel-based multifunctional dressings*

Among these multifunctional dressings are hydrogels. Hydrogels can be designed and manufactured following green chemistry principles, producing environmentally friendly materials [124]. A simple preparation process can yield multifunctional hydrogels that integrate cell compatibility, antibacterial properties, and wound-healing ability [125]. These hydrogels combine self-healing properties, ecological stability, high mechanical strength, and drug-loading capacity. A comprehensive comparison of multifunctional hydrogels, detailing their composition, functions, and potential biomedical applications, is presented in Table 2. Combining these essential properties for effective wound healing makes multifunctional hydrogel-based dressings unique materials [126, 127]. The design and fabrication of hydrogels significantly impact their functionality, influencing antibacterial activity, electrical conductivity, adhesion to tissues, mechanical properties, and ability to promote tissue regeneration. These factors include the type of polymer used, any modifications made to the polymer, incorporating nanomaterials and nanostructures, and adding active materials to the hydrogel network [128, 129]. Wound infections can significantly prolong hospitalization, delay healing, and increase costs and mortality rates. Infection can lead to a pronounced immune response, potentially accompanied by sepsis or septic shock, which can cause hypotension and multiorgan failure [130, 131]. Skin damage is painful and can catastrophically compromise the integrity and protective functions of the skin. Traditional dressings, such as gauze, cotton wool, dressings delivering bioactive constituents, and antimicrobial and regenerative agents, are currently used in clinical practice [132]. With the advent of flexible electronics and the development of novel biomaterials, several advanced dressings have emerged that can measure the physicochemical properties of acute and chronic wounds [133]. Mirani et al. proposed a novel, advanced multifunctional hydrogel-based wound dressing with wound monitoring and drug delivery capabilities called

GelDerm. GelDerm offers several advantages over existing technologies. This multifunctional hydrogel is based on alginate, a hemostatic agent, and glycerol. The hydrogel was created using three-dimensional (3D) printing with a microfluidic coaxial extruder [134]. The multifunctional dressing comprises an array of porous, color-changing pH sensors and drug-eluting scaffolds. This sensor array allows for measuring spatial variations in pH within the wound, which can indicate different types of bacterial infections. The recorded data is uploaded to a cloud drive, enabling medical personnel to access patient data and monitor wound conditions in real-time [135]. While many dressings are available on the market, GelDerm is unique because it integrates diagnostic and therapeutic components into a single dressing. This advanced dressing has received approval from the American FDA and is also commercially compatible with other dressings, such as Mepitel, without causing any physical or chemical irritation [136]. The proposed technology holds great promise for managing chronic and acute injuries caused by trauma, surgery, or diabetes. The ability to diagnose and treat infections at the site of injury reduces the need for manual wound inspection and systemic administration of antibiotics to patients. The formulation used in the design and fabrication of this proposed multifunctional dressing can be lyophilized and sterilized for long-term storage [137, 138].

### *3.1.1. Nanostructural components for wound healing in multifunctional hydrogels*

Hydrogels can be incorporated with various nanostructured components, such as cellulose, hydroxyapatite, nanoparticles based on Si, Au, Ag, and Fe, carbon nanotubes, graphene, metal-organic frameworks, genes, and proteins. This integration leads to the formation of novel composites with improved properties for biomedical applications [145].

**Table 2.** Some multifunctional hydrogels for enhanced wound healing

| Hydrogel composition | Functions | Ref. References |
|---|---|---|
| Quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly (ethylene glycol)-co-poly (glycerol sebacate) (PEGS)-FA | This material exhibits a desirable combination of properties, including strong adhesion, rapid self-healing behavior, and efficient blood clotting ability, significant antibacterial activity, good biocompatibility, and the capacity to scavenge reactive species. Additionally, it demonstrates electroactive properties. | [139] |
| PVA and benzaldehyde-capped PEG, Phenylboronic modified Chitosan (CSPBA) | Indicates the material's ability to change its properties based on pH and glucose concentration fluctuations. Suggests the material can respond to the presence of insulin, potentially by releasing it in a controlled manner. The material can create an environment or provide cues that stimulate cell growth and multiplication. | [140] |
| Thiolated chitosan (TCS), and gallic acid (GA) | These materials serve as investigational agents for their potential in: Exerting antibacterial activity Demonstrating antioxidant properties Modulating the activity of matrix metalloproteinases (MMPs) and myeloperoxidase (MPO) | [141] |
| Poly (glycerol sebacate)-co-poly (ethylene glycol)-g-catechol / synthon-modified gelatin (GTU)/Fe | Light-activated (near-infrared) and pH-responsive materials can convert light into heat (photothermal) and boast self-healing properties. They can also be injected and adhere to tissues while offering antibacterial and antioxidant capabilities. This combination makes them promising for targeted therapies. | [124] |
| BG/HAS/ succinimidyl succinate (SSPEG) | These materials hold promise for promoting angiogenesis, the formation of new blood vessels. This characteristic could be particularly beneficial for applications where improved tissue vascularization is necessary. | [124] |
| Piperazine di-acrylamide (PDA)–polyacrylamide | Strong adhesion to biological tissues promotes excellent cell attachment, exhibits good affinity for extracellular matrix (ECM) proteins, and preserves the biological activity of loaded Epidermal Growth Factor (EGF). | [142] |
| Gelatin methacryloyl | These hydrogels can be conveniently sprayed onto wounds, minimizing invasiveness. Their | [143] |

| | | |
|---|---|---|
| (GelMA) /MA-modified tropoelastin | elastic nature allows them to conform to uneven surfaces, while their adhesive properties promote good contact with the tissue. An additional benefit is their antimicrobial activity, which helps combat infection, a major concern in wound healing. | |
| Hyaluronic acid (HA)-epigallocatechin-3-gallate (EGCG) conjugates | It can adhere to tissues, enhancing its interaction and effectiveness within the body. Furthermore, it exhibits anti-inflammatory activity, which could help reduce inflammation, a common factor in many diseases. Additionally, its antioxidant properties contribute to combating oxidative stress, potentially protecting cells and tissues from damage. | [144] |

### *3.2. Self-healing wound dressings*

Hydrogels, 3D cross-linked networks of polymers containing a high-water concentration, have recently gained significant attention. Self-healing hydrogels, capable of regaining their original structure and function after physical damage, are particularly attractive due to their versatility [154, 155]. Some self-healable hydrogels possess properties such as injectability, adhesiveness, and conductivity, making them suitable for various applications, including drug/cell delivery vehicles, glues, and electronic devices. Biocompatibility refers to a material's ability to be tolerated by the living human body. Polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyacrylic acid meet this criterion due to their simple chain structures. Similarly, biocompatible polymers can be derived from polypeptides and polysaccharides, such as collagen, alginate, cellulose, and HA. PLGA, a non-toxic, hydrophilic, and bioerodible polymer derived from amino acids, is another example of a biocompatible material. It is non-immunogenic and non-allergenic and can be modified to create self-healing hydrogels for tissue scaffolds [156].

### *3.3. Injectable Hydrogels*

Injectable hydrogels formed by in situ chemical polymerization or sol-gel transition have recently gained significant attention. These materials are flowable aqueous solutions before administration but rapidly gel under physiological conditions upon injection. This gel formation offers several advantages: injectable matrices can be implanted minimally invasively, and bioactive molecules or cells can be easily incorporated through pre-injection mixing. Following gelation, these matrices become drug-delivery depots for pharmaceuticals or cell-growing depots for tissue regeneration. Thermosensitive hydrogels are particularly attractive for injectable applications due to their ability to spontaneously gel at body temperature, eliminating the need for additional chemical treatment [157].

An ideal injectable medical hydrogel should meet the following requirements [158]:

1. **Injectability:** Before administration, the system should be in a solution state, ideally with a sufficiently low viscosity to enable injection through a narrow needle, minimizing patient discomfort.
2. **Gelation:** Gelation via either chemical cross-linking or physical association should occur or be completed after injection.
3. **Biodegradability:** The gels should be biodegradable or gradually dissolve into bioresorbable products.
4. **Biocompatibility:** The polymer itself, its degradation products, and any necessary additives (e.g., cross-linking agents) should be biocompatible.
5. **Specific functionalities:** Depending on the application, additional requirements may be necessary, such as a sustained release profile for drug delivery or cell-adhesive properties for tissue engineering.

### *3.4. Drug-Loaded Wound Dressings*

Wound healing is a complex biological process focused on tissue regeneration and restoration of integrity [159]. The primary goal in wound healing is to achieve rapid closure with optimal functional outcomes. Therefore, medical researchers have continuously strived to develop highly effective wound care strategies [160]. Wound dressings are frequently used to promote wound repair and can offer various functionalities depending on the wound type and severity [161]. They act as a barrier against the external environment, protecting wounds from microbial infection. Furthermore, they should possess other vital characteristics, such as biocompatibility, moisture retention, and gas permeability. Drug-loaded wound dressings

represent a novel approach in this field. To achieve these desired properties, wound dressings can encapsulate natural and active therapeutic components, such as cellulose, silk fibroin, gelatin, and chitosan [162]. These components can accelerate wound healing by regulating fundamental biological processes, such as inflammation, cell migration, and immunity [163]. Chen et al. demonstrated that HA and collagen I in wound dressings can mimic the extracellular matrix, promoting wound closure. This structure also enhances in vitro cell proliferation, essential for wound repair [164]. Polyvinyl alcohol/chitosan wound dressings loaded with a controlled release of antiseptics facilitate faster wound recovery than conventional treatments. These drug-loaded dressings exhibit antibacterial activity, supporting the immune system in fighting infection [165]. Curcumin loaded with tetracycline hydrochloride on wound dressings has also been shown to exert antibacterial effects on wounds [166] . Nanotechnology offers various properties that are desirable as an ideal wound dressing material. Studies by Iram et al. suggest that drug-loaded silver nanoparticles can promote wound healing by stimulating the immune system. Similarly, nano-based dressings loaded with chloramphenicol have effectively controlled infection at the wound site. These nano-based dressings are advantageous because they do not adhere to the wound bed and maintain a moist environment throughout the healing process. The controlled release of drugs from nano-based dressings allows therapeutic compounds to persist at the wound site for a sustained period [167, 168].

## 5. Conclusion

In conclusion, biomimetic strategies have emerged as a promising approach for treating skin wounds. Researchers are exploring a diverse range of biomaterials and synthetic materials to design effective wound dressings that mimic the structure and function of skin tissue. It is crucial to recognize the unique pathophysiology of each chronic wound and tailor the dressing accordingly. Biomimetic wound dressings hold significant potential to replace conventional dressings due to their alignment with natural wound healing processes. Furthermore, utilizing biological waste as a cost-effective material source presents an attractive prospect. Notably, biomimetic hydrogels demonstrate a superior ability to mimic the biological properties of human skin compared to other materials. These hydrogels can be fabricated in diverse forms, including films, gauzes, injectable gels, and sprays, offering versatility for different applications. However, several commercially available biomimetic dressings require further refinement. The limited effectiveness of current formulations and a lack of robust clinical trials hinder their widespread adoption. Therefore, further research is warranted, focusing on optimizing formulations, conducting rigorous in vivo studies, and ensuring cost-effective, ease-of-use, and optimal biocompatibility.

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### Compliance with ethical guidelines

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### Authors’contributions

E GhN: Conceptualization of the review, primary drafting of the manuscript, and coordination of revisions. M Sh: Contributed to the design and structure of the review, critical revision of content, and interpretation of data from literature sources. SA FM: Assisted with literature search, data collection, and initial drafting of sections related to biomaterials and their applications. A F: Provided input on the technical aspects of wound dressings, assisted in analyzing data, and contributed to manuscript editing. B A: Involved in drafting and revising the manuscript, with a focus on the biomedical engineering aspects, and provided critical feedback on the review’s final version.

### Conflict of Interests

The authors declare no conflict of interest.

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