

An Overview of the Biomaterials Used in Hydrogel Fabrication for Chronic Wound Healing Applications

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Abstract

Wound healing is a delicate, complex and challenging medical process. Hydrogel is a material that possesses properties aligned with the ideal characteristics required for wound dressings. Its mechanical properties, derived from the interconnection of fibers, closely resemble those of soft tissues regarding moisture retention, secretion absorption, and oxygen permeability. Additionally, hydrogels can be tailored to perform various functions, such as crosslinking with other materials and loading drugs, bioactive compounds and growth factors. This review focuses on the fabrication of multifunctional hydrogel wound dressings using both natural and synthetic biological materials, including silk fibroin, chitosan, alginate, cellulose, hyaluronic acid, polyvinyl alcohol, polyethylene glycol and polyvinyl pyrrolidone, each exhibiting distinct properties that enhance their efficacy as wound dressings. Consequently, this review highlights significant advancements in developing more effective hydrogel wound dressings.

Keywords: Chronic wound, Hydrogel, Biomaterials, Wound dressing, Biocompatibility

Introduction

Chronic wounds, characterized by their prolonged duration and inability to heal properly, place substantial demands on healthcare systems worldwide [1,2]. Various factors contribute to chronic wounds, including chronic diseases, vascular insufficiency, diabetes, malnutrition, aging, excessive reactive oxygen species (ROS) production and localized issues such as pressure, infection and edema [3]. These wounds often exhibit complex pathophysiological processes, including impaired angiogenesis, persistent inflammation and extracellular matrix (ECM) remodeling [4-6]. Chronic wounds can lead to significant morbidity, diminished quality of life, and, in severe cases, amputation [7]. Consequently, chronic wounds have emerged as a silent epidemic, affecting over 40 million individuals

worldwide. The financial burden associated with their treatment is estimated to exceed 25 billion US dollars annually [8]. Traditional wound care approaches often fall short of addressing the various challenges associated with chronic wounds. These treatments have notable limitations, including inadequate moisture retention, susceptibility to infection and a limited capacity to promote tissue regeneration [2,7,9]. The development of innovative wound-dressing materials is essential for addressing these challenges and enhancing patient outcomes.

Tissue engineering, a multidisciplinary field that integrates biology, engineering and materials science, offers a promising strategy for overcoming the limitations of conventional wound dressings [10]. By

utilizing biomaterials to construct 3-dimensional (3D) scaffolds that emulate the natural ECM, tissue engineering to create an optimal environment for tissue regeneration and repair [9-11]. Hydrogels, a biomaterial fabrication technique distinguished by their hydrophilic network structure, have garnered significant attention due to their excellent biocompatibility, customizable properties, and ability to replicate the hydrated environment of native tissues [12-15]. Biomaterials play a crucial role in fabricating hydrogels with tailored properties to meet specific requirements, such as nontoxicity, porous surface structures and mechanical properties appropriate for skin tissue [15,16]. A diverse array of biomaterials has been explored for hydrogel fabrication in chronic wound healing applications. Natural polymers such as collagen, chitosan, alginate and gelatin provide excellent biocompatibility and biodegradability [17-19]. Conversely, synthetic polymers such as polyvinyl alcohol (PVA), Polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) allow for the fabrication of hydrogels with customizable properties [20-22]. Despite the promising potential of these biomaterials, challenges such as cost, scalability and possible immune responses must be addressed [17,19]. Furthermore, developing effective wound dressings requires a comprehensive evaluation of various factors, including biocompatibility, mechanical properties, moisture retention and the ability to promote cell adhesion, proliferation and migration [15,16,23]. In addition to possessing these ideal properties, the design of wound dressings should also prioritize mitigating risk factors that hinder wound healing, such as reducing inflammation and eliminating bacteria that can lead to infections [24,25]. Addressing these factors is essential for enhancing the effectiveness of wound dressings.

Therefore, in this review, we summarize the evolution of wound dressings, emphasize the relative properties of an ideal wound dressing with the properties of a hydrogel, and challenges in improving the properties of wound dressing materials to have a variety of functions including anti-inflammatory, antimicrobial and mechanical properties. Furthermore, we provide a thorough analysis of the research on the development of wound dressings utilizing various materials, highlight the essential properties of biomaterials and examining their effects on wound healing as well as their physical and biological properties. This review focus on the

performance properties of biomaterials as a hydrogel wound dressing in the laboratory process. Lastly, we address the gap in laboratory research and clinical study of hydrogel-based wound dressings, as well as the future direction of their development.

Evolution of wound dressings

Historically, efforts have been made to apply substances that protect wounds and promote enhanced healing. The first people to have evidence of attempts at using wound dressings were the Egyptians around 2,000 BC. The Egyptians began by cleaning wounds, applying honey to them, and creating plasters out of resin. Then, in 400 BC, records indicate that the Greeks cleaned wounds with wine and vinegar [26]. In the past era wound dressings are made from the application of natural materials that can be found around them through observation of wound healing characteristics under the belief in healing and knowledge in each era.

After that during the 19th century, it was believed that wounds healed more effectively in a dry environment, which was thought to encourage scab formation and facilitate subsequent healing [27]. As a result, sterile gauze has become a standard intervention for wound treatment. Nowadays, advancements in technology have demonstrated that dry environments can lead to the accumulation of exudates, which may foster infections and exert pressure on wounds. These conditions can alter cellular behavior and prolong the wound-healing process. Additionally, frequent changes of sterile gauze can cause discomfort due to adhesion between the wound and the dressing induced by dryness [28]. With ongoing advancements in technology and biomedical research, animal studies have demonstrated that maintaining fluid balance within wounds significantly enhances cellular migration and proliferation compared to dry conditions. Furthermore, effectively managing wound exudates reduces adhesion between the wound and dressings, making dressing changes easier [29]. Consequently, the focus has shifted toward promoting moist wound healing to enhance recovery efficiency. Maintaining a moist wound environment also allows for higher flexibility in wound dressings, as they can be constructed from various materials, bioactive agents, and medications to improve their healing properties [27].

Traditional dressing

Before the 1980s, conventional wound dressings primarily consisted of gauze and synthetic fibers, chosen for their ability to protect wounds and absorb exudates [30]. Traditional gauze dressings not only absorb wound exudate but are also economical and readily available [31]. However, these dressings can adhere to wounds, causing pain during changes and promoting drying, which increases the risk of microbial penetration and infection [32]. Recently, moist dressings have been made to address the challenges associated with traditional wound dressings and improve wound recovery efficiency. Innovations have focused on altering the structure of dressings to retain moisture and minimize adhesion between the dressing and the wound, thereby reducing pain during dressing changes and enhancing overall functionality. In addition, Liang *et al.* 2023 [33] revealed statistical data comparing the effectiveness of moist dressing with gauze dressing by a meta-analysis. It was found that moist dressing facilitates accelerated wound healing, mitigate infection rates, reduce overall treatment costs and decrease the frequency of dressing changes.

Modern dressing

Advancement in technology have enabled the development of wound dressing that interact directly with the wound to promote better healing. Modern wound dressing is achieved through the design of various types of wound dressings, such as (i) film dressings, (ii) foam dressings and (iii) hydrogel dressings, as well as the incorporation of bioactive agents or drugs. By utilizing different material properties and maintaining moisture balance, these innovations enhance the effectiveness of wound dressings [34,35].

Film dressing

Film dressing is a thin, viscous layer that permits oxygen and water permeability, facilitating wound healing to some extent while allowing for observation of the wound during the healing process. However, due to its film-like nature, its capacity to absorb exudates is limited, and the high viscosity may result in additional damage when changing the dressing [27].

Foam dressing

Foam dressing, typically made from polyurethane, possesses foam properties that allow it to effectively absorb exudate and retain moisture. However, the toughness of the foam is often insufficient to adhere properly and maintain its shape on the wound, resulting in the need for frequent adjustments and, consequently, more frequent dressing changes [36].

Hydrogel dressing

Hydrogel wound dressings consist of crosslinked fibers within their structure [37], which results in a high water content capacity and excellent efficiency in absorbing wound exudate. They also possess mechanical properties that stabilize wounds while minimizing softness and pain during dressing changes. Moreover, the hydrogel exhibits properties that closely resemble those of an ideal wound dressing [38] (a comparison of the hydrogel's properties with those of the ideal wound dressing is presented in the following section). Due to these advantageous characteristics and potential similar to that of an ideal wound dressing, hydrogels have become popular materials for wound dressings and hold significant potential for further research [27]. However, the single-component nature of hydrogel dressings limits their performance to that of a single material, leading to inadequate mechanical properties [37]. To address this, efforts have been made to combine hydrogels with other materials or to modify them through cross-linking, as well as incorporating bioactive materials or drugs to enhance the effectiveness of hydrogel dressings as a promising solution for patients [39]. **Figure 1** illustrates the advantages and disadvantages of each type of wound dressing.

To summarize, modern wound dressings overcome the limitations of traditional wound dressings by making the wound environment more suitable for healing [34,35]. For instance, the hydrogel form can enhance hemostasis and regulate exudate content by modifying swelling and mechanical properties [27]. However, the appropriate use of modern wound dressings depends on the material's properties, the type of wound, and its intended use.



Figure 1 Summarizing the pros and cons of each form of wound dressing (green and red letters define the benefits and drawbacks of each method, respectively). (Created with BioRender.com).

With the remarkable attributes of hydrogels as wound dressing materials, current research trends are extensively focused on developing hydrogel-forming wound dressings. The precursor materials for hydrogel formation typically consist of polymer fibers that can be cross-linked to achieve a 3-dimensional structure [39]. A variety of materials are currently being utilized to fabricate hydrogel wound dressings. The following research exemplifies how diverse materials can be employed for this purpose. Each material possesses unique characteristics that can be modified to customize the properties of the hydrogel, making it suitable for various clinical scenarios. Furthermore, these materials can enhance the effectiveness of wound dressings by incorporating functionalities such as antioxidants and antibacterial agents.

Ideal properties for wound dressing

Multiple factors influence the properties of wound dressings, facilitating effective wound healing and accelerating the healing process. Wound dressings must be compatible with the wound site to ensure nontoxicity [40]. Generally, the primary goal of wound dressings is to completely cover the wound and protect it from

external contaminants, such as germs and dust, thereby aiding in the prevention of infection [35]. Additionally, wound dressings must retain moisture to allow for the absorption of wound exudates [41]. Effective moisture management prevents the formation of scabs and subsequent aggregation of secretions into a mass that can exert pressure on the wound. Such conditions can disrupt cellular processes, including intercellular communication and cell diffusion, ultimately impairing the efficiency of wound healing [42]. Furthermore, moisture retention in the dressing reduces the pain associated with dressing changes [27]. Wound dressings should possess appropriate mechanical properties to maintain structural integrity while adhering to the wound site and must be sufficiently flexible to conform to the shape of the wound [43]. Additionally, a crucial characteristic of wound dressings is their ability to facilitate gas exchange [35]. The dressing should have an appropriate pore size and a cohesive, interconnected porous structure. This pore structure supports cell adhesion, migration and the diffusion of nutrients, thereby contributing to optimal wound healing [43]. **Figure 2** shows the ideal properties of wound dressings.

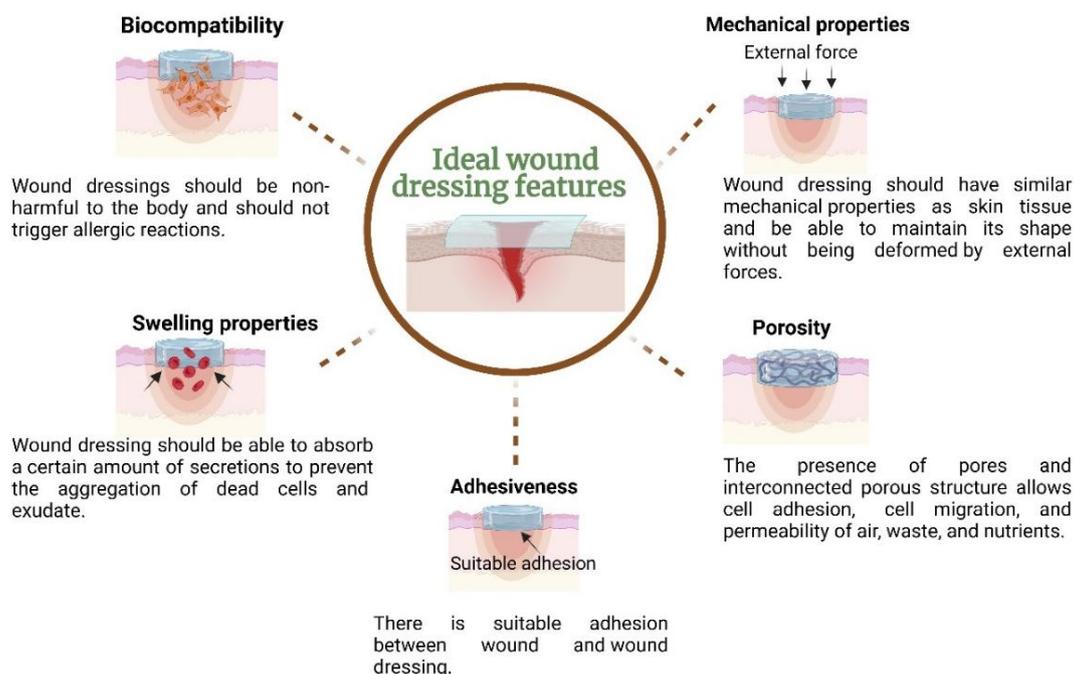


Figure 2 The conclusion of an ideal property for wound dressing. (Created with BioRender.com).

Challenges in wound dressing development

In addition to possessing ideal properties, wound dressings should also function to inhibit risk factors that delay wound healing, such as reducing inflammation and eliminating bacteria that can cause infection. These factors contribute to delayed wound recovery. Therefore, designing wound dressings with these capabilities presents a crucial challenge for enhancing their overall effectiveness (**Figure 3**).

Anti-inflammatory effect

During wound healing, the immune system eliminates microorganisms by secreting reactive oxygen species (ROS). These are highly unstable molecules with unpaired electrons produced by macrophages [44]. ROS kills bacterial cells by destroying intracellular structures, starting with the cell membrane and DNA, which leads to cell apoptosis [44]. While an appropriate amount of ROS facilitates the wound healing process, they also play a role in stimulating cell communication signals, as noted by Huang *et al.* [45]. However, prolonged or abnormal inflammation, such as that observed in conditions including diabetes, can lead to excessive ROS secretion. This overproduction adversely affects the tissue surrounding the wound, causing oxidative stress and sustained chronic inflammation,

which prolongs the wound-healing process [46]. Incorporating substances with anti-inflammatory properties into wound dressings can enhance their effectiveness for patients with chronic wounds. Many of these substances have aromatic structures that enable them to donate protons and electrons to free radicals, stabilizing them as less reactive molecules [45]. Examples of studies using natural anti-inflammatory agents include the fabrication of hydrogels containing piperine and aloe vera. *In vivo* testing in rat models demonstrated that the hydrogel with piperine demonstrated significantly higher wound healing efficiency compared to hydrogels without piperine. Piperine, a component of black pepper, exhibits antioxidant properties, making it an interesting alternative antioxidant agent for wound dressings [47]. In another study, a hydrogel based on hyaluronic acid was loaded with curcumin in nanomicelles. *In vivo* testing in rat models demonstrated that the hydrogel effectively resisted inflammation, accelerated wound healing and promoted the appearance of vascularization during the healing process [48]. Beyond these examples, other natural extracts with anti-inflammatory properties, such as gallic acid, tannic acid and polysaccharides, have also been identified as effective agents for enhancing wound dressings [45].

Antimicrobial effect

Infections must be carefully managed during wound recovery, as they can distinguish chronic wounds from normal wounds and complicate the healing process. To address this, efforts have been made to incorporate antibacterial substances into wound dressings. Achieving the desired antibacterial properties depends on various factors, including the type of wound, severity of infection, and cost considerations. Yousefian *et al.* [49], demonstrated the modification of antibacterial properties in wound dressings. Extensive research has focused on the development of antibacterial wound dressings. For example, the use of nanoparticles, metals and metallic oxides as antibacterial agents is well-established. Silver and gold nanoparticles, in particular, are known for their high ability to penetrate bacterial cell membranes, disrupt cellular activities and generate ROS, which induce cell apoptosis [50]. In another study, an injectable and degradable PEG hydrogel was developed as an antibacterial agent to promote wound healing. *In vitro* testing demonstrated that the PEG hydrogel exhibited antibacterial properties and supported cell migration and proliferation, as demonstrated by cell counting kit-8 (CCK-8) and scratch assays. *In vivo* testing in rat models further confirmed that the PEG hydrogel could effectively promote wound healing [51].

Mechanical properties

Wound dressings cover and protect the wound, making their mechanical properties a crucial consideration. The dressing must retain its shape and resist deformation during use. Ideally, the mechanical properties of a wound dressing should resemble those of the skin and be able to support a weight of

approximately 200 g [52], which is considered suitable for wound dressings. The pore size and interconnectivity of the pores directly influences these mechanical properties. A small pore size and high interconnectivity result in efficient water absorption, while a larger pore size allows for better absorption of wound exudate. However, if the pore size and interconnectivity are extremely large, it can lead to excessive diffusion of skin cells and other substances into the wound dressing, which interferes with the healing process [53]. Additionally, skin cells that migrate into the dressing can form connective tissue at the wound site, causing pain when the dressing is removed. Studies have demonstrated the impact of different pore sizes and interconnected porous structures on fibroblast cell migration and proliferation within a 3D scaffold made of SF. By controlling freezing temperatures, researchers have found that an optimal pore size for fibroblast migration and proliferation is between 200 - 250 μm , with a porosity of around 86 % [54]. The mechanical properties of wound dressings play a significant role in wound healing. Various methods have been developed to modulate the mechanical characteristics of hydrogels, including freeze-drying, particle leaching, electrospinning and gas foaming [55]. The mechanical properties of wound dressings are not only physically but also biologically significant. Research has demonstrated that physical forces such as H-bond, Van der Waals forces and hydrophobic and hydrophilic interactions influence cell behavior, with different types of forces exerting varying effects [56]. For instance, tension forces can cause cells to stretch, affecting cell proliferation, migration, and elongation. The influence of mechanical forces on wound healing has been comprehensively summarized by Barnes *et al.* [57].

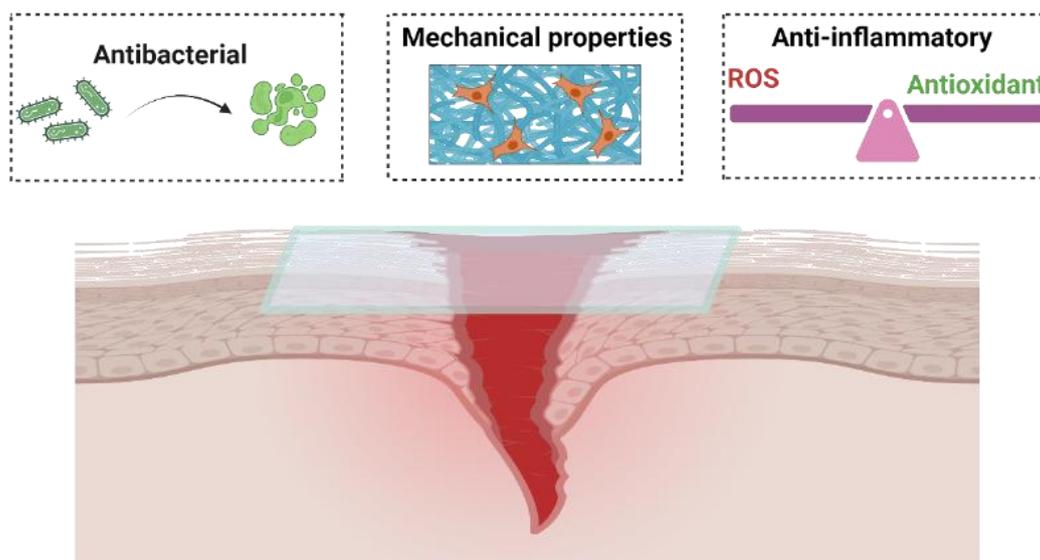


Figure 3 Antimicrobial properties, mechanical properties and anti-inflammatory properties, a challenge towards the development of more effective wound dressings. (Created with BioRender.com).

Natural polymer as a wound dressing

Natural polymers, synthesized by living organisms, typically consist of repetitive monomers that self-assemble into polymeric structures. Examples include polysaccharides, which are formed from monosaccharides and peptides, which are formed from amino acids [58]. These polymers are widely used in the biomedical field due to their biocompatibility, biodegradability and low immune response. Several natural polymers also offer additional beneficial properties for wound dressings, such as antibacterial and anti-inflammatory effects [45]. However, when used alone for crosslinking to form hydrogel structures, natural polymers often exhibit poor mechanical properties [59]. This limitation compromises their effectiveness as wound dressings, as their mechanical strength is typically inadequate for ensuring proper wound recovery [45]. To optimize hydrogels for wound dressings, it is essential to customize the hydrogel formation process to achieve the necessary mechanical strength. Moreover, enhancing these hydrogels by incorporating substances with antibacterial or anti-inflammatory properties has been demonstrated to improve wound healing efficiency [27].

Silk fibroin

Silk fibroin is a protein fiber derived from various sources, including silkworms, spiders, ticks and beetles

[60]. It is composed of a heavy chain weighing 390 kDa and a light chain of 26 kDa, with silk length estimated at approximately 10 - 25 mm. The heavy chain contains a sequence of glycine-serine-glycine-alanine-glycine-alanine (GSGAGA) repeats, as illustrated in **Figure 4** [61], which impart hydrophobic properties. In contrast, the light chain represents a shorter, hydrophilic segment. Silk fibroin's structural adaptability enhances its functionality through different crosslinking methods. Physical crosslinking occurs via intermolecular forces, leading to the formation of α -helical (silk I) structures or a transition to β -sheet (silk II) with improved mechanical properties [61]. Meanwhile, chemical crosslinking, which forms covalent bonds, offers the highest mechanical strength yet requires careful management of residual chemical toxicity [62]. Controlled modification of fibroin's structure expands its applications in drug and nanoparticle delivery systems. Additionally, silk fibroin exhibits biocompatibility, biodegradability, high oxygen permeability and low inflammatory response, making it highly suitable for biomedical applications, such as hydrogel wound dressings [63]. Research suggests that fibroin-based wound dressings can accelerate wound healing by activating signaling pathways that influence the healing process, including Nuclear Factor-kappa B (NF- κ B) helps control the expression of pro-inflammatory, cyclin D1 helps control cell divide,

Vascular Endothelial Growth Factor (VEGF) helps in growth of blood vessels and promote vascular endothelial growth factor (VEGF) expression, and vimentin plays a role in cell migration, which these signaling proteins regulate cellular behaviors in wound healing like adhesion, proliferation and inflammation [64]. Furthermore, the expression of cytokines such as IL-10, IL-6, IL-1a, tumor necrosis factor receptors (TNFR) and Toll-like receptors (TLRs) contributes to the wound's inflammatory response [65]. Silk fibroin also stimulates cell migration through pathways like MEK, PI3K and JNK kinase, promoting phosphorylation, a key factor in wound healing [66]. For example, a silk fibroin hydrogel combined with human acidic fibroblast growth factor 1 (FGF1) demonstrated sustained FGF1 release, enhancing cell migration in L929 fibroblast cells and improving wound healing in mice [67]. In another study, a hydrogel based on silk fibroin, acryloyl- β -cyclodextrin (Ac-CD) and 2-hydroxyethyl acrylate was developed to address

limitations of pure silk fibroin, such as lack of self-healing and slow gelation. The hydrogel, produced via photopolymerization under ultraviolet (UV) light, exhibited improved mechanical properties, rapid self-healing, biocompatibility, injectability and long-term stability. Loading curcumin into the hydrogel added anti-inflammatory properties and *in vitro* testing indicated that it could promote vascular endothelial growth factor (VEGF) expression and reduce inflammatory responses [68]. Another study developed a hydrogel wound dressing for diabetic patients, featuring silk fibroin as the hydrogel framework, with melanin for antioxidant properties and berberine for therapeutic effects. The matrix crosslinking enabled a slow, sustained release of berberine, suitable for prolonged wound treatment. *In vitro* tests showed good cell migration and control over oxidative stress, while *in vivo* testing confirmed the hydrogel's ability to promote wound healing in a diabetic type I Wistar rat model [69].

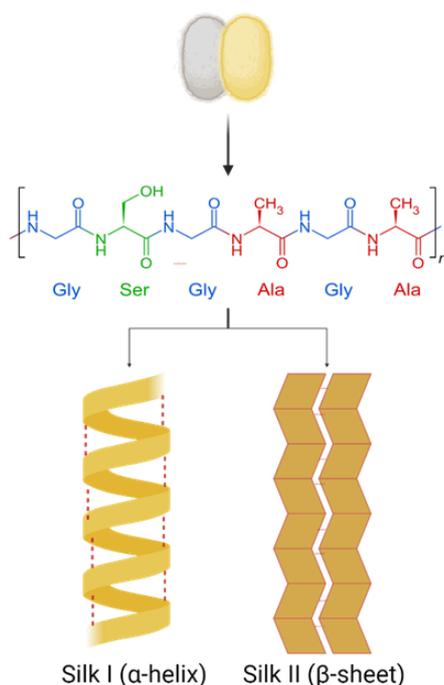


Figure 4 Silk fibroin chemical structure with protein sequence (GAGAGS), arrangement of silk fiber pattern: Silk I (α -helix) and silk II (β -sheet). (Created with BioRender.com).

Chitosan

Chitosan is a linear polysaccharide composed of β -(1-4) linked D-glucosamine and N-acetyl glucosamine, as depicted in **Figure 5** [70]. It is derived from chitin

through a deacetylation process, which involves the removal of acetyl groups until a minimum of 50 % of the amine groups remain [71]. Chitin is found in the exoskeletons of arthropods such as crabs, insects and

shrimp [72]. Chitosan exhibits several beneficial biological properties, including biocompatibility, biodegradability, antimicrobial activity and hemostatic capabilities [70]. These characteristics make it suitable for various biomedical and tissue engineering applications. Chitosan has demonstrated significant potential as a wound dressing due to its ability to interact with blood clots and platelets, as well as its notable antimicrobial properties [73]. While the exact mechanism behind its antimicrobial activity is not fully understood, one hypothesis suggests that the positively charged NH_3^+ groups in chitosan interact with the negatively charged phospholipids on bacterial cell walls, resulting in cell damage, as suggested by Teixeira *et al.* [74]. Recent research has focused on developing chitosan-based hydrogels for wound healing applications. For instance, Ansari *et al.* [75] prepared a

chitosan hydrogel loaded with guar gum and aloe vera (CS/GG/AV) and compared its efficacy with other formulations, including chitosan-only hydrogel, chitosan with guar gum and chitosan with aloe vera. In tests on wounded mice, the CS/GG/AV hydrogel demonstrated superior effects on epithelial regeneration and angiogenesis while also being non-cytotoxic compared to the other groups [75]. In another study, hydrogels were fabricated by crosslinking chitosan with polyacrylamide and coating the surface with poly(vinyl alcohol) and a polyacrylamide/glycerin (P-A) mixture. This P-A coating helped maintain a moist environment for extended periods and enhanced the mechanical strength of the hydrogel. *In vitro* tests confirmed the hydrogel's good antibacterial activity and cytocompatibility, while *in vivo* tests showed that it accelerated wound regeneration and closure [76].

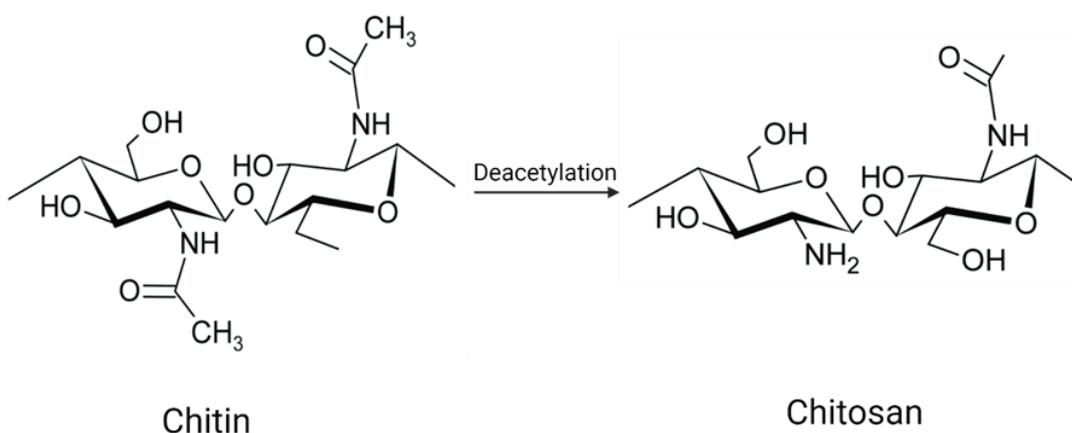


Figure 5 The deacetylation process of chitin, which is the removal of the acetyl group from chitin, the chemical structure of chitosan with D-glucosamine linked with β -(1-4) N-acetyl glucosamine. (Created with BioRender.com).

Hyaluronic acid

Hyaluronic acid (HA) is a naturally occurring substance found in various tissues, including connective tissue, joints, skin and eyes. It is a component of glycosaminoglycan (GAG), composed of repeating disaccharides-D-glucuronic acid and N-acetyl-D-glucosamine - linked by β -(1-3) and β -(1-4) glycosidic bonds, as illustrated in **Figure 6** [77]. Due to its composition, which includes carboxylic, acetamide and N-acetyl groups, HA has a high capacity for water absorption and retention [78]. HA's properties are also influenced by pH, temperature and environmental factors, making it suitable for injection in various forms under physiological conditions [78]. HA plays a critical

role in wound healing by regulating the secretion of interleukins (IL) such as IL-1 β , IL-8 and α -TNF, which are key mediators of cell communication during the inflammatory response [79]. Based on these properties, HA has been extensively researched for use in wound dressings. Recently, hydrogel wound dressings have been developed as homeostatic solutions. One example is a hydrogel based on N-succinyl chitosan and oxidized hyaluronic acid, loaded with calcium ions (Ca^{2+}) and amine-terminated poly(ethylene glycol) (4-arm-PEG- NH_2 , labeled PEG1). This hydrogel demonstrated injectable and self-healing properties, with the inclusion of Ca^{2+} enhancing the mechanical characteristics. Additionally, Ca^{2+} and PEG1 improved homeostasis,

wound healing and biocompatibility [80]. In another study, a hydrogel wound dressing was fabricated using *N*-dimethylbisacrylamide (NIPAM) and glutaraldehyde (GTA)-cross-linked HA. The hydrogel exhibited adhesive properties due to contraction induced by thermal stimulation. *In vitro* testing confirmed the

hydrogel's cytocompatibility and hemocompatibility, while *in vivo* tests on a mouse skin defect model demonstrated accelerated healing, reduced inflammation, enhanced angiogenesis and lower collagen deposition [81].

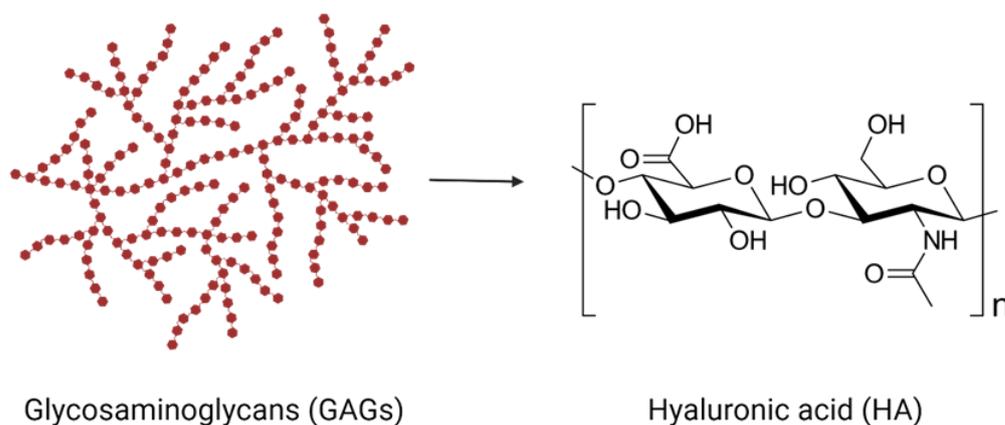
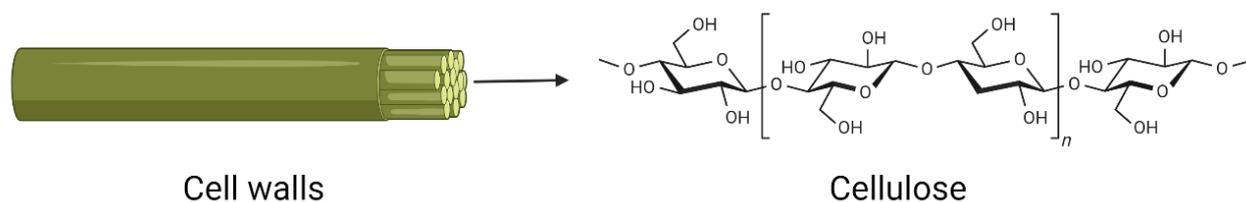


Figure 6 The chemical structure of hyaluronic acid, D-glucuronic acid and N-acetyl-D-glucosamine linked with β -(1-3) and β -(1-4) glycosidic bonds. (Created with BioRender.com).

Cellulose

Cellulose is an organic compound composed of β (1-4) linked D-glucose units, as illustrated in **Figure 7** [82]. It is a crucial component of the cell wall, where the arrangement of hydrogen bonds within each fibroin contributes to its relatively high strength. Due to its low toxicity and high compatibility with living tissues, cellulose is widely utilized in biomaterials and medical research. Additionally, cellulose can undergo structural modification at the hydroxyl group to produce cellulose derivatives with diverse properties for specific applications. Examples of these derivatives include methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC), sodium carboxymethylcellulose (NaCMC), hydroxypropyl cellulose (HPC), benzyl cellulose (BC), hydroxyethylmethylcellulose (HEMC) and hydroxyethylcellulose (HEC). The production methods, properties and applications of each cellulose derivative have been reviewed by Tudoroiu *et al.* [83]. Cellulose is also used in wound dressing applications. For example,

a composite hydrogel made from cellulose was reinforced with non-woven cotton, coated with TiO_2 and loaded with titania particles to impart antibacterial properties. This composite hydrogel demonstrated air permeability, effective moisture management and antibacterial activity due to the TiO_2 coating [84]. Another study combined a hydrogel based on bacterial cellulose with AgNPs to provide antibacterial properties and encapsulated curcumin, a naturally hydrophobic substance, in cyclodextrins. The findings demonstrated that the hydrogel maintained a moist environment, exhibited antibacterial effects from the AgNPs without associated toxicity, and provided anti-inflammatory benefits from the curcumin [85]. Furthermore, the fabrication of hydrogel wound dressings using gelatin and graphene oxide bacterial cellulose, crosslinked with tetraethyl orthosilicate, resulted in hydrogels with excellent water absorption capabilities. *In vitro* tests confirmed that the hydrogel was hemocompatible, and the incorporation of graphene oxide enhanced cell proliferation and viability [86].



Cell walls

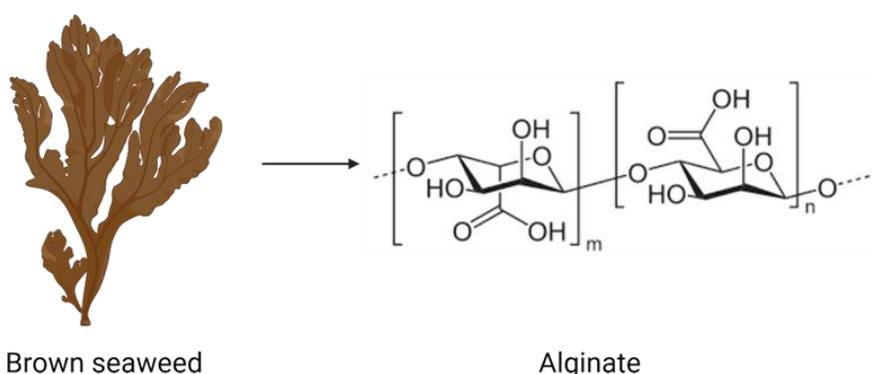
Cellulose

Figure 7 The chemical structure of cellulose, $\beta(1-4)$ linked D-glucose units. (Created with BioRender.com).

Alginate

Alginate is a hydrophilic polymer composed of (1,4) linked β -D-mannuronic and α -L-guluronic acids, as illustrated in **Figure 8** [87], and is primarily derived from brown seaweed found in the ocean. It is widely used in the biomedical field due to its hydrophilicity, biocompatibility and hemostatic properties [88]. Alginate's versatile properties allow for various applications, including gel formation for injections and the development of composite materials by incorporating nanoparticles and drugs [88]. Alginate is also employed in wound dressings. For instance, an alginate-based hydrogel containing hydrogen sulfide was developed, demonstrating good biocompatibility, degradability and swelling behavior during wound healing. *In vitro* testing identified 0.5 % as the optimal concentration of hydrogen sulfide, as higher levels led to cytotoxicity and hemolysis. *In vivo* experiments confirmed that the hydrogel effectively promoted

wound healing and achieved complete epithelialization [89]. Another study produced a composite hydrogel combining sodium alginate, chitosan, aloe vera and honey. The hydrogel exhibited a well-suited interconnected and porous structure that enhanced cell adhesion, migration and proliferation. The inclusion of Aloe vera, honey and chitosan contributed to high antibacterial activity [90]. A hydrogel wound dressing based on sodium alginate and gelatin loaded with AgNPs was also fabricated. This study showed strong intermolecular interactions between sodium alginate and gelatin through hydrogen bonding and electrostatic forces. *In vitro* testing indicated that the antibacterial properties of the AgNPs did not cause toxicity to fibroblasts. *In vivo* testing demonstrated that the hydrogel containing AgNPs was more effective in reducing wound size compared to the hydrogel without AgNPs [91]



Brown seaweed

Alginate

Figure 8 The chemical structure of alginate (1,4) linked β -D-mannuronic and α -L-guluronic acids. (Created with BioRender.com).

Synthetic polymer as wound dressing

Synthetic polymers are created through the crosslinking of monomers via covalent bonds. These polymers have found extensive applications in the biomedical field, including tissue engineering, drug

delivery, medical devices and wound dressings [58]. Although the medical use of synthetic polymers raises concerns regarding toxicity, their modifiability and flexibility have garnered significant interest in various applications [92]. This article presents a collection of

examples illustrating the use of polymers such as polyvinyl alcohol, polyethylene glycol and polyvinyl pyrrolidone as wound dressings and their impact on wound recovery.

Polyvinyl alcohol (PVA)

PVA is a hydrophilic polymer with the formula $[\text{CH}_2\text{CH}(\text{OH})]_n$, as illustrated in **Figure 9(a)** [93]. PVA possesses several properties that make it suitable for medical applications, including high solubility, excellent mechanical characteristics, biocompatibility and biodegradability [94]. Due to its strong crosslinking ability, PVA has been utilized as a hydrogel wound dressing. For instance, a hydrogel composed of PEBAX/PVA was coated with polyamide and Pistacia atlantica gum nanofibers while also being embedded with AgNPs. This composite hydrogel demonstrated impressive mechanical properties attributed to the incorporation of gum nanofibers, along with significant antibacterial activity and no cytotoxic effects [95]. In another study, a hydrogel incorporating silk sericin (SS), azithromycin (AZM), and PVA was crosslinked using genipin (GNP). The results indicated that SS improved the swelling ratio, cell attachment, proliferation, and porosity of the hydrogel; PVA enhanced its mechanical strength; and AZM contributed to its antibacterial properties. *In vivo* testing using an infected mouse burn model revealed that this hydrogel significantly promoted wound healing [96].

Polyethylene glycol (PEG)

PEG is a synthetic polymer with the formula $\text{H}-(\text{O}-\text{CH}_2-\text{CH}_2)_n-\text{OH}$, as depicted in **Figure 9(b)** [97]. Due to its high hydrophilicity, PEG is utilized as a surfactant to facilitate micelle formation, serving as carriers for various particles, including drugs and metallic nanoparticles, which enhance the stability and functionality of these nanoparticles. The application of PEG for coating purposes can be customized to achieve either hydrophilic or hydrophobic properties, depending on the specific requirements of the application [98]. Additionally, PEG possesses several advantageous properties for biomedical and tissue engineering applications, including biodegradability, non-immunogenicity and biocompatibility [97]. Given these attributes, PEG has been explored as a biomaterial for wound dressings. For example, a hydrogel wound

dressing designed for diabetic wounds was developed based on metalloproteinase and PEG (MMP-PEG) and loaded with adipose-derived stem cells and exosomes (ADCS-exo) to promote wound healing. The results indicated that this hydrogel effectively reduced reactive oxygen species (ROS), which are critical for wound healing in diabetic patients, and also facilitated angiogenesis and cell proliferation [99]. In another study, injectable hydrogels were created for diabetic wounds using hydroxypropyl trimethyl ammonium chloride chitosan (HACC) crosslinked with octafunctionalized POSS of benzaldehyde-terminated polyethylene glycol (POSS-PEG-CHO) via a Schiff base reaction. The findings demonstrated that these hydrogels exhibited good mechanical properties, excellent self-healing and antibacterial activity and injectability. *In vitro* testing revealed that the injectable hydrogels promoted cell migration and proliferation. Furthermore, *in vivo* testing on diabetic mouse wounds demonstrated rapid wound healing [100].

Polyvinyl pyrrolidone (PVP)

PVP is a soluble polymer derived from the monomer N-vinylpyrrolidone, which has the chemical formula $\text{C}_6\text{H}_9\text{NO}$, as illustrated in **Figure 9(c)** [101]. The structure of PVP endows it with properties suitable for use as a biomaterial, including high wettability, strong adhesion, heat resistance, biocompatibility and biodegradability [102]. Recent investigations have explored the use of PVP as a wound dressing. A hydrogel composite made from PVP fibers was fabricated using an electrospinning technique and loaded with hydroxycinnamic acid derivatives, specifically *p*-coumaric and ferulic acids, produced via thermal annealing. *In vitro* testing demonstrated that the hydrogel fibers facilitated the sustained release of antioxidants and offered protection to cells against oxidative stress. *In vivo* tests on mouse skin burns revealed a significant reduction in oxidative stress within the wounds. Additionally, *ex vivo* testing on human skin indicated effective skin regeneration and highlighted the beneficial effects of the hydrogel fibers during the inflammatory process [103]. In another study, a bioadhesive hydrogel capable of absorbing fluid and blood from wounds was created by crosslinking a polyacrylic acid (PAA) and PVP (PAA/PVP) complex. The swelling and degradation capacities of the hydrogel

were found to depend on the crosslinking density and molecular weight. *In vivo* testing using rat models with induced wounds demonstrated that upon application of

the PAA/PVP complex, the hydrogel formed rapidly and effectively absorbed fluid and blood from the wounds [104].

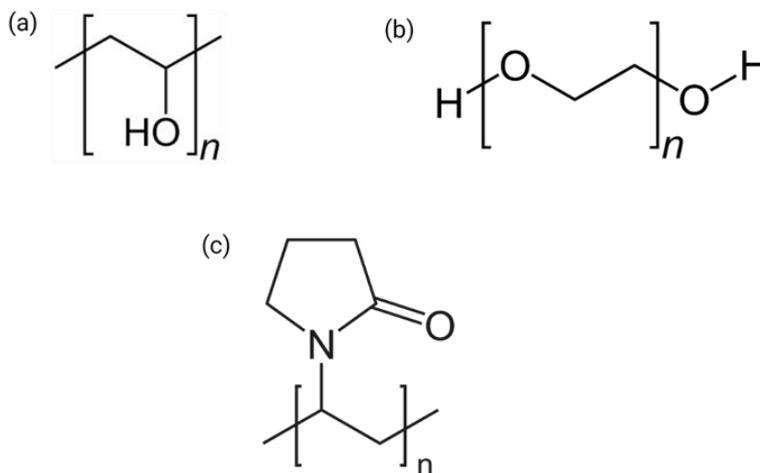


Figure 9 The chemical structure of polyvinyl alcohol $[\text{CH}_2\text{CH}(\text{OH})]_n$ (a), polyethylene glycol $\text{H}-(\text{O}-\text{CH}_2-\text{CH}_2)_n-\text{OH}$ (b) and polyvinyl pyrrolidone $\text{C}_6\text{H}_9\text{NO}$ (c). (Created with BioRender.com).

Comparison of the properties of natural and synthetic polymers on wound healing

Natural polymers offer significant advantages in terms of biocompatibility, biodegradability, inherent healing properties and rich sources, but natural polymer are often limited by their mechanical strength, necessitating further modification for optimal performance as wound dressings. In contrast, synthetic polymer allows greater control over mechanical

properties and can be tailored to specific needs, but they may present challenges such as high cost, lack of inherent healing, concerns regarding biocompatibility and environmental impacts [58]. Therefore, both natural and synthetic polymers have distinct strengths. The choice of use biomaterials depends on properties and functional roles in wound healing which is summarized in **Table 1**.

Table 1 Summary of properties and highlights the role of natural and synthetic polymers in wound healing.

Biomaterials	Properties of biomaterials and highlight in wound healing	Ref
Natural polymers	General properties: High biocompatibility and biodegradability	[58]
Silk fibroin	Properties: High oxygen permeability, low inflammatory response and Highlights: The efficiency to induce signaling pathways that involved with inflammatory response and cell migration	[63]
Chitosan	Properties: Hemostatic, blood clotting Highlights: High antibacterial properties	[70]
Alginate	Properties: Hydrophilicity, injectability and hemostasis properties Highlights: Minimize bacterial infection	[88]
Cellulose	Properties: Rich source, low cost and diversity in structural modifications (derivative cellulose) Highlights: Moisture control	[83]

Biomaterials	Properties of biomaterials and highlight in wound healing	Ref
Hyaluronic acid	Properties: Injectability and hydrophilicity Highlights: Induce cell adhesion and the efficiency to stimulate immune response	[79]
Synthetic biomaterials	General properties: Ability to control properties appropriately with specific applications	[58]
Polyvinyl alcohol (PVA)	Properties: High solubility, excellent mechanical properties, biocompatibility and biodegradability Highlight: Monitoring healing progress	[94]
Polyethylene glycol (PEG)	Properties: Biodegradability, non-immunogenicity and biocompatibility Highlight: Delivery active molecules	[98]
Polyvinyl pyrrolidone (PVP)	Properties: High wettability, high adhesion, heat resistance, biocompatibility and biodegradability Highlight: High antimicrobial properties	[102]

The impact of integrating biomaterials with distinct properties in hydrogel form on wound healing

As mentioned above, each biomaterials exhibit distinct properties that influence their use in biomedical applications. Then, the design of hydrogel wound dressings involves combining different materials to provide the hydrogel wound dressing with additional

functions and appropriate uses according to the situation. A summary of the characteristics and effects of designing hydrogel-based wound dressing materials on wound healing is presented in **Table 2**. However, the effects of wound healing as presented in **Table 2** were evaluated in preclinical research (limited to *in vitro* and *in vivo* testing).

Table 2 Summary of the features and effects on wound healing of combining biomaterials and bioactives used as hydrogel wound dressing.

Natural biomaterials			
Biomaterials	Hydrogel compositions	Effects of wound healing	Ref
Silk fibroin	Silk fibroin/FGF1	- Sustain the released of FGF1, which increase cell migration of cell fibroblast L929	[67]
	Silk fibroin/acryloyl- β -cyclodextrin (Ac-CD)/2-hydroxyethyl acrylate/curcumin	- More rapid self-healing and long-term stability - Anti-inflammatory, promote VEGF	[68]
	Silk fibroin/melanin/berberine	- Showed sustained release of berberine, and the hydrogel exhibited good cell migration and controlled oxidative stress, which is appropriate for diabetic wound	[69]
Chitosan	Chitosan/guar gum/aloe vera	- Showed the effects on epithelial regeneration and increased angiogenesis	[75]
	Chitosan/polyacrylamide -poly(vinyl alcohol) and polyacrylamide/glycerin (P-A)	- The hydrogel coated with P-A showed the ability to hold a moist for a long time, increase mechanical properties - Excellent antibacterial cytocompatibility and accelerate wound regeneration	[76]

Natural biomaterials

Biomaterials	Hydrogel compositions	Effects of wound healing	Ref
Alginate	Alginate-hydrogen sulfide	- Showed good biocompatibility, degradation, the hydrogel exhibited promising wound healing with the optimized concentration of hydrogen sulfide	[89]
	Sodium alginate/chitosan/ aloe vera/honey	- Cell migration and cell proliferation were promoted by suitable interconnect porous structure - High efficiency to antibacterial	[90]
	Sodium alginate/gelatin loaded AgNPs	- Strong crosslinking of sodium alginate and gelatin - Antibacterial properties and AgNPs have no toxicity with fibroblast cells	[91]
Cellulose	Cellulose/nonwoven cotton/titania-TiO ₂	- Showed air permeability, moisture management, and good antibacterial properties	[84]
	Bacterial cellulose/AgNPs curcumin encapsulated in cyclodextrins	- Showed moisture environment, antibacterial and anti-inflammatory	[85]
	Gelatin/graphene oxide bacterial cellulose/tetraethyl orthosilicate	- High water absorption - Hemocompatible properties increase cell proliferation and cell viability.	[86]
Hyaluronic acid	N-succinyl chitosan-oxidized/hyaluronic acid/poly(ethylene glycol) (4-arm-PEG-NH ₂ /calcium ion (Ca ²⁺))	- Showed self-healing good potential to adjust mechanical properties - Increase homeostasis, wound healing	[80]
	N-dimethylbisacrylamide /glutaraldehyde/hyaluronic acid	- Cytocompatibility and hemocompatibility - Ability to accelerate skin healing, reducing inflammatory, angiogenesis, and collagen deposition	[81]

Synthetic biomaterials

Biomaterials	Hydrogel compositions	Effects of wound healing	Ref
Polyvinyl alcohol (PVA)	PEBAX/PVA-polyamide/Pistacia atlantica gum nanofiber/AgNPs	- Exhibited strong mechanical properties - High antibacterial properties with no cytotoxic of the composite hydrogel	[95]
	Silk sericin/azithromycin/PVA/genipin	- High swelling ratio, mechanical strength - Showed antibacterial and wound generation	[96]
Polyethylene glycol (PEG)	Metalloproteinase/PEG/adipose-derived stem cells and exosomes	- Showed effectiveness in reducing ROS	[99]

Natural biomaterials

Biomaterials	Hydrogel compositions	Effects of wound healing	Ref
	Hydroxypropyl trimethyl/ammonium chloride chitosan/octafunctionalized POSS of benzaldehyde-terminated polyethylene glycol	- Exhibited good mechanical properties, excellent self-healing, and injectability - Antibacterial properties, promote cell migration and cell proliferation	[100]
Polyvinyl pyrrolidone (PVP)	PVP/hydroxycinnamic acid derivatives/ferulic acids	- Demonstrated sustained release of antioxidants and reduced oxidative stress on wounds	[103]
	Polyacrylic acid/PVP (PAA/PVP)	- Exhibited high ability to self-healing and high ability to absorb fluid from wounds	[104]

Furthermore, the development of hydrogel wound dressings has incorporated recent advanced technologies. For example, the fabrication of drug-loaded hydrogel wound dressings. Research has shown that the inclusion of growth hormones, antibacterial agents and anti-inflammatory substances in these hydrogel dressings can enhance wound healing [105-108]. Studies have demonstrated that these methods aid in the long-term controlled release of therapeutic agents at the wound site [107,109,110]. The customized release kinetics provided by these drug delivery systems present a promising approach for precise and efficient wound management strategies, establishing a basis for a more personalized and targeted method for healing chronic wounds [106,109]. Another example is the integration of 3D printing hydrogel dressings. This method has revolutionized wound treatment by allowing customized dressings for specific wound shapes [111]. Research has shown that 3D-printed hydrogel dressings are more adaptable and effective for irregular wound shapes and sizes, improving wound coverage and healing results [111,112]. In animal models, 3D-printed dressings with growth hormones and antibacterial substances reduce infection rates and promote tissue regeneration, improving wound closure rates [113,114].

Regarding ISO 10993, which is a series of international standards that provide guidelines for the biological evaluation of medical devices. The main idea of these guidelines is to ensure the biocompatibility and safety of medical devices. By following these guidelines, manufacturers can evaluate the possible risks linked to their devices and implement required

measures to minimize them. This protects patients from adverse effects and guarantees the effectiveness of medical devices. Regrettably, clinical studies have provided limited information on the use of novel hydrogels as wound dressings. Therefore, there is a vast area to study their effectiveness and safety in humans. One such gap is research on the long-term effects of utilizing hydrogel dressings in chronic wound therapy. There is a lack of rigorous continuing research examining the long-term usage and impact of these dressings on wound healing, scar formation, and general tissue regeneration [115]. To bridge the gap between laboratory research and clinical application, it is crucial to discuss translational aspects and potential barriers to implementing hydrogel-based dressings in healthcare settings. This discussion should encompass regulatory hurdles, cost-effectiveness considerations and healthcare provider education. By addressing these challenges, the adoption of novel hydrogel dressings can be accelerated, and patient outcomes can be improved.

Future perspectives for hydrogel-based wound dressing development

The trajectory of hydrogel wound dressing development demands a paradigm shift towards enhanced functionality and innovative applications to address the limitations of current approaches and optimize patient outcomes. A pivotal area of focus lies in the advancement of multifunctional hydrogels that synergistically facilitate wound healing, prevent infection, and enable precise medication delivery [105,115].

Incorporating cutting-edge technologies, such as the integration of sensors within the hydrogel matrix to monitor key wound parameters like temperature, pH and exudate levels, offers real-time feedback, enabling clinicians to dynamically adjust treatment regimens and optimize patient care [109]. Furthermore, incorporating bioactive molecules, such as growth factors and extracellular matrix components, within the hydrogel matrix can significantly enhance tissue regeneration and accelerate wound closure. A comprehensive understanding of the intricate interactions between these bioactive molecules within the hydrogel environment and their influence on cellular responses is crucial for maximizing therapeutic efficacy [110].

Lastly, the development of biodegradable hydrogel wound dressings is essential for sustainability. This necessitates a concerted effort in designing and synthesizing hydrogels from sustainable and biocompatible materials while ensuring their efficacy and safety within the wound healing process. Interdisciplinary collaboration among researchers, clinicians and engineers is essential to address the problems and fully exploit the promise of hydrogel-based wound dressings.

Conclusions

The evolution of wound healing underscores the critical need for innovative wound dressings that effectively address the complexities of this physiological process. Hydrogels are an excellent choice for wound dressings due to their ability to absorb secretions, retain moisture, and allow oxygen to penetrate soft tissues. Leveraging advancements in materials science and bioengineering, researchers are developing innovative hydrogels that incorporate a range of bioactive agents, such as antimicrobial compounds, growth factors, and extracellular matrix components, to enhance wound healing process.

A key advancement lies in the development of multifunctional hydrogels that synergistically address multiple facets of the wound healing cascade. These advanced materials not only provide a moist wound environment but also facilitate controlled release of therapeutic agents, effectively combating infection and promoting tissue regeneration, empowering clinicians to maximize patient outcomes.

Translating these advancements into clinical practice requires an integrated approach. Extensive clinical trials are imperative to evaluate the efficacy and safety of novel hydrogel dressings in diverse patient populations as well as the long-term effects of wound dressing treatment. Furthermore, developing patient-specific therapies and leveraging advanced bio-fabrication techniques are crucial for optimizing patient outcomes.

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