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Biomaterial-Based Hydrogels for Chronic Wound Healing: A Comparative Review of Natural Polymers

Cing Wun Yang
elinelleyang@gmail.com

ABSTRACT

Chronic wounds have been both a problem and a challenge to both patients and healthcare systems all over the world. Standard treatments like gauze dressings are generally not adequate to promote the active tissue regeneration that chronic wounds lack. Hydrogels based on biomaterials have appeared as a promising alternative treatment that provides a moist environment for healing, mechanical support, and the possibility of being modified to include therapeutic agents. This review assesses and compares four main natural biomaterials used in the formulation of hydrogels for chronic wound healing, examining their structural characteristics, mechanisms of action, and evidence for effectiveness across different types of chronic wounds. The results indicate that no single biomaterial is superior for all chronic wound types; instead, material selection may be guided by properties suited to specific wound traits. Alginate's fluid-absorption capacity suggests utility for highly exudative wounds; chitosan's antimicrobial properties suggest utility for infection-prone wounds; collagen's cell-adhesion properties suggest utility for structurally damaged wounds; and hyaluronic acid's moisture-retention properties suggest utility where long-term moisture retention and regenerative support are needed. These associations are based on mechanistic and preclinical evidence rather than direct comparative clinical trials.

Nevertheless, evidence for these materials is still uneven, with a shortage of large-scale randomized controlled trials and a strong dependence on data from animal studies for composite systems. This review points out these gaps in the evidence. It sets out priorities for future research, such as conducting standardized clinical trials, designing studies that are specific to the type of wound, and further developing composite biomaterial systems, to help create more effective and evidence-based hydrogel treatments for the management of chronic wounds.

INTRODUCTION

1.1 Biomaterials Used in Wound Healing Gel

Biomaterials are classified as either natural materials derived from the environment or synthetic materials engineered by humans, used for medical applications such as supporting cellular structure, improving wound healing, or replacing damaged tissues or biological functions. Biomaterials can be made from metals, ceramics, plastics, and glass, which are synthetic materials engineered by humans; living cells or

tissues can also be collected to make natural biomaterials. These materials can then be reengineered into different forms, such as biodegradable fibers, foams, and fabrics, for biomedical applications (NIH, 2019).

Conventional treatments, such as gauze dressings and topical ointments, reduce pain and infection and promote wound closure. Those materials are insufficient for chronic wound healing and can lead to permanent scarring. Therefore, an alternative treatment to promote cell regeneration is essential (Dang et al., 2018). Tissue engineering has sought to address the risks of infection and insufficient graft volume due to donor availability by providing a solution: scaffolds (with better biocompatibility and biodegradability that promote cell regeneration) that can transport growth factors to cells and injured tissues and accelerate the formation of new cells. Natural biomaterials have appeal and are broadly used in tissue regeneration due to their high compatibility with natural tissues in both biological and chemical traits, cost-effectiveness, availability, biocompatibility, biological activity, biodegradability, and low cytotoxicity compared to synthetic biomaterials that do not have biological function domains, which leads to a restraint of bonding biological signals to cell adhesion or direct phenotypic expression. In contrast, their degradation products can lead to inflammation (Chen & Liu, 2016; Kim et al., 2008; Su et al., 2021).

Natural biomaterials can be extracted from natural polysaccharides, phenolic compounds, and proteins. They are often used because their biological and chemical properties are similar to those of natural tissues. Natural polysaccharides occur in plants and animals, including chitin, chitosan, hyaluronan, and alginate (Rinaudo, 2008). Chitosan is a type of polysaccharide that can be produced by deacetylation (removal of an acetyl group from chitin) or by enzymatic hydrolysis, in which chitin deacetylase cleaves the chitin-chitin bond with water. It is usually found in the exoskeletons of arthropods and fungi (Ali Khan et al., 2019). Chitosan is a useful biomaterial for its biocompatibility, degradability, and ability to enhance cell attachment, proliferation, and viability, and to support the migration of inflammatory cells that release large amounts of proinflammatory products and cytokines, thereby triggering or heightening inflammation at an early stage of healing (Alsarra, 2009). Hyaluronic acid can also be used in wound healing, as it is extracted from cows, fish, combs, or umbilical cords (Rinaudo, 2008). Nevertheless, alginate is also another type of polysaccharide used to accelerate wound healing due to its hemostatic and antimicrobial characteristics. It can produce electrospun nanofibers with a higher surface area-to-volume ratio, enabling lightweight construction and the absorption of large quantities of liquid within their fiber structures (Su et al., 2021).

1.2 Burden of chronic wounds

A chronic wound is a type of skin injury that does not heal in a normal or timely way, typically lasting longer than 4 to 12 weeks or failing to progress through the normal stages of repair. This usually results from poor blood flow, diabetes, venous insufficiency, or sustained pressure on a specific area that cuts off blood supply (Institute for Quality and Efficiency in Health Care (IQWiG); 2006-., 2025).

Chronic wounds carry a substantial burden worldwide, including an economic one. There are estimated to be 8 million people globally who live with some form of chronic wound, whether it is infected or not. According to data from the Global Burden of Disease project, patients with skin and subcutaneous

conditions increased rapidly over a decade, from around 493 million cases in 2005 to an estimated 605 million by 2015 (Vos et al., 2016). In addition, the five-year mortality rate for chronic wounds (30.5%) is nearly the same as cancer; however, research funding related to or devoted to wound care is largely behind cancer research (Armstrong et al., 2020). Patients who live with chronic wounds often experience considerable pain, psychological and physical strain, reduced mobility, and social withdrawal.

In some cases, these wounds can progress to disability or amputation when the treatment is no longer working (Järbrink et al., 2017). Health outcomes such as disease progression, wound healing, and overall life expectancy are shaped not only by biological factors but also by social and economic factors, including income, education, employment, physical surroundings, psychological stress, and the strength of an individual's support network. Food insecurity (lack of consistent access to sufficient food to support a healthy lifestyle) affects about 11% of people in the U.S. and is associated with chronic conditions such as obesity and diabetes, both of which impair wound healing (Sen & Roy, 2019; Sen, 2023).

Another major risk factor is age; as patients with chronic disease grow older, particularly individuals with diabetes and obesity, they might face risk from neuropathy, autoimmune disease, cardiovascular disease, and chronically elevated blood sugar. According to data from the U.S. senior population, chronic wounds are expected to become a pressing issue for older adults (Sen, 2021; Olsson et al., 2019). Economic impacts are another significant factor associated with chronic wounds, including both direct expenses, such as medical and healthcare costs, and indirect expenses, such as decreased productivity due to illness and early retirement. The global market for advanced wound care is projected to reach USD 30.532 billion by 2020, growing at an annual rate of roughly 4.61% from 2023 onward (Sen, 2023). In wealthier nations, chronic wound treatment is estimated to consume between 1 and 3 percent of total healthcare spending (Falcone et al., 2021; Sen, 2021; Olsson et al., 2019; Freedman et al., 2023). Because chronic wounds are biologically complex, numerous modern technologies have been developed and explored. Researchers have turned toward more sophisticated and biomimetic treatment approaches. However, further advancement of the field depends on a thorough grasp of the wound-healing process and its key stages. Current research integrates traditional wound care with new tools to build a more complete picture of how wounds heal (Alberts et al., 2025).

1.3 Limitations of conventional wound care

Wounds have been a longstanding problem for patients for years and impose a substantial burden on medical assistants and doctors. They are also called a "silent epidemic." There are an estimated 4 million cutaneous wounds documented annually, and the number of cases in developing countries has been increasing progressively (Lindholm & Searle, 2016; Y. Chen et al., 2023). Skin injuries destroy the integrity of the skin's framework and trigger a series of cellular and molecular reactions aimed at recreating or replacing injured tissues. Wounds with a healing process that is orderly and uninterrupted during cell regeneration are usually referred to as "acute wounds". When the healing process is affected by severe oxidative stress, infection, or underlying medical conditions, it results in a "chronic wound". These kinds of wounds exhibit unique attributes such as recurrent infection, a heightened inflammatory phase, and impaired responsiveness of epidermal cells (A. C. de O. Gonzalez et al., 2016; Xiang et al., 2020; Firlar et al., 2022). Due to the scarcity of donors and the development of hypertrophied scars,

current industry-standard therapies, including skin grafts and flaps, dermal substitutes, and skin growth procedures, face significant challenges for mass production. These limitations also reflect a financial strain on the healthcare sector, especially given the need for efficient wound treatment. This results in a need for alternative, efficient treatments to overcome the limitations of current approaches (Tavakoli & Klar, 2020; Gounden & Singh, 2024).

According to data from Gounden and Singh (2024), various forms of dressing have varying degrees of suitability depending on lesion characteristics. Moist dressings can improve skin regeneration. Dry dressings might lead to additional pain and tissue damage. Another conventional treatment is Negative pressure wound therapy (NPWT). This non-invasive approach applies controlled suction to draw out fluid and debris from a wound site, typically using a sealed or foam dressing connected to a collection canister. It helps raise oxygen levels and maintain moisture around the wound, which supports the healing process. However, NPWT is not suitable for every kind of wound, such as cancer, bone infection, or dead tissue covered by a hard eschar. It is also limited by the patient's mobility (Kantak et al., 2017). Surgery is an option for wound management, ranging from straightforward closure to skin grafts, skin flaps, and musculocutaneous flaps. These approaches are chosen based on factors such as the wound's location, the patient's health condition, and the goals of treatment. However, these options require special surgical expertise and well-resourced medical facilities, making them both resource-intensive and expensive. Lastly, Hyperbaric Oxygen Therapy (HBOT) requires patients to breathe 100% oxygen inside a pressurized chamber set above normal atmospheric pressure. This accelerates tissue regeneration in wounds and shortens the wound-healing process(Wenhui et al., 2021; Gounden & Singh, 2024). It is mainly used for wounds that fail to heal on their own. However, it is limited to specific cases, such as diabetic and pressure ulcers, due to the cost and time commitment of the specialized equipment involved. HBOT carries risks of potential lung collapse (pneumothorax) and ear damage (Kantak et al., 2017; Gounden & Singh, 2024).

1.4 Rationale for biomaterial-based hydrogel dressings

There are numerous conventional wound treatments available, but they still exhibit various drawbacks, which lead us to explore an alternative treatment that is better for the patient. The alternative plan should demonstrate both antibacterial and antimicrobial traits to mitigate infection. When infected, bacteria enter the site of injury and release compounds that inhibit the ability of immune cells to eliminate these bacteria, resulting in a prolonged healing process (Holloway & Harding, 2022). The system is aimed to be biodegradable, biocompatible, and non-toxic while also maintaining a moist environment by supporting the healing process through angiogenesis and collagen formation, and providing non-adherence, which reduces pain and scab formation (Varaprasad et al., 2020). It also requires the system to have the capacity to absorb wound exudate and facilitate gas exchange between the damaged tissues and the environment, since oxygen is critical for cell growth and angiogenesis (B. Sheokand et al., 2023). Finally, it must enhance tissue regeneration while remaining cost-effective (Gounden & Singh, 2024).

Hydrogel is classified as a substance of extensive application in skin regeneration. It is a three-dimensional structure that forms through either physical or chemical cross-linking of hydrophilic polymer chains (Koehler et al., 2018). It is synthesized using numerous techniques, including radiation,

freeze-thawing, or chemical processes. It is also a reversible gel that is structured by molecular entanglement or ionic and hydrogen bonds. A permanent gel can also form when it is structured with covalent bonds. Its network can expand with water until it reaches a state of equilibrium, returning to its initial structure. This leads to considerable capacity to absorb exudate from ground wounds, accelerate oxygen flow, and sustain a better moisture environment in the injury location, which ultimately facilitates the healing process (Van Vlierberghe et al., 2011; Gounden & Singh, 2024).

Hydrogel's distinctive physical qualities help it be fabricated into various sizes and forms, resulting in complete coverage of the irregular shape of the wound (Bilici et al., 2016). Hydrogel has the characteristics of biodegradability and biocompatibility that allow it to serve as a short-term model throughout the re-epithelialization (new epithelial cells cover a wound to restore the skin barrier) and remodeling of chronic wounds. In addition, it has sufficient bioadhesion to maintain stability and improve hemostasis and moisture levels in the wound. Moreover, hydrogel has also been incorporated with several components, including antibacterial and antimicrobial agents, drugs, and other biomolecules, to improve overall wound-healing efficacy. This suggests that hydrogels are a well-suited biomaterial class for covering skin wounds and supporting the healing process, among the several biomaterial types discussed in this review (Bilici et al., 2016; Arif et al., 2021; Gounden & Singh, 2024).

1.5 Objectives

This review aims to critically evaluate and compare the four major biomaterials currently used to formulate hydrogels for chronic wound healing, including alginate, chitosan, collagen, and hyaluronic acid, with respect to their structural properties, mechanisms of action, and evidence of efficacy across different chronic wound types, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, and arterial ulcers. Specifically, this review seeks to summarize the cellular and molecular mechanisms underlying normal and chronic wound healing; characterize the properties, advantages, and limitations of each biomaterial as a hydrogel-forming agent; synthesize current evidence on composite and functionalized biomaterial systems; evaluate the clinical translational status of each material, including approved products and available trial evidence; and identify existing gaps in the literature to guide future research toward the development of more effective, evidence-based biomaterial hydrogels for chronic wound management.

2. METHODOLOGY

This comparative review was conducted across multiple databases, including PubMed/MEDLINE, Web of Science Core Collection, Scopus, ScienceDirect, and the Cochrane Library, supplemented by Google Scholar for grey literature and citation tracking, to identify peer-reviewed sources relevant to natural polymer biomaterials, wound healing gels, and chronic wound disease. The search strategy was to use a combination of keywords: "Edible Biomaterials", "Wound healing", "Wound healing process", "Biomaterial in wound healing gels", "Wound healing gel", "Hydrogel", "Chronic wounds", "hyaluronic acid", "chitosan", "Alginate", "Collagen", and "natural biomaterial".

Search terms combined controlled vocabulary and free-text keywords related to four core concept areas: (1) wound type ("chronic wound," "diabetic foot ulcer," "venous leg ulcer," "pressure ulcer," "arterial ulcer"); (2) material format ("hydrogel," "biomaterial," "wound dressing"); (3) specific polymer type ("alginate," "chitosan," "collagen," "hyaluronic acid," "hyaluronan,"); and (4) publication type ("review," "systematic review," "meta-analysis," "randomized controlled trial"). Boolean operators (AND/OR) were used to combine these concept groups, for example:("chronic wound*" OR "diabetic foot ulcer*" OR "venous leg ulcer*" OR "pressure ulcer*") AND (hydrogel* OR biomaterial* OR "wound dressing*") AND (alginate OR chitosan OR collagen OR "hyaluronic acid"). In each database, raw search returns were 1,454 (PubMed/MEDLINE), 2,264 (Web of Science), 160 (Scopus), 14,985 (ScienceDirect), and 99 (Cochrane Library).

Given the scope of this narrative review and the substantial variation in return size across databases, results were screened in order of each platform's default relevance ranking rather than title-by-title. Screening focused on the first two to three results pages per query, with records advanced to full-text review if they matched three or more core search concepts in the title or abstract. This process led to approximately 10 studies that were read in full and form the primary evidence base for the material-specific section of the review.

The remaining reference list was substantially built through citation searching (snowballing): reviewing the reference lists of these core studies, together with Google Scholar's to identify additional relevant primary and background literature. Approximately 80% of the total references in this review were identified through this citation-chaining process rather than direct database retrieval, which is a reflection of the uneven distribution of primary literature across the four biomaterials under review, with alginate, chitosan, collagen, and hyaluronic acid varying considerably in the depth of dedicated clinical and mechanistic research available.

Studies were included if they were published in peer-reviewed journals, addressed chronic wound healing, wound biomaterials, or hydrogel-based wound dressings, focused on one or more of the four biomaterials under review or provided relevant background on wound healing mechanisms and chronic wound pathophysiology, and were published in English. Eligible study types included original research, systematic reviews, meta-analyses, and narrative reviews with sufficient methodological transparency. Studies were excluded if they were not peer-reviewed, focused exclusively on acute wounds, surgical wounds, or burns without relevance to chronic wound pathology, addressed applications of the reviewed biomaterials unrelated to wound healing, were retracted publications as verified against journal retraction notices and the Retraction Watch database, or lacked sufficient methodological detail to assess study quality.

Due to the biomaterials-for-chronic-wound-healing literature being uneven across materials, such as alginate, chitosan, collagen, and hyaluronic acid supported by decades of research and, in several cases, clinical trial evidence. Some areas of the wound-healing biomaterials literature remain narrow and consist predominantly of preclinical or animal-model studies rather than controlled human trials, this review supplements the more limited material-specific literature with comparative evidence from the

better-established polymers and general biomaterials science, explicitly noted wherever such extrapolation occurs.

3. WOUND HEALING BIOLOGY AND THE CHRONIC WOUND PROBLEM

3.1 Stages of Wound Healing

There are four major stages of wound healing in the physiological response to tissue injury. Healing is a labyrinthine process involving interactions among numerous cell types, including cytokine mediators and the vascular system. When there is tissue damage, the initial phase, hemostasis, of recovery always occurs with a generous amount of lymphatic fluid (which collects fluid that leaks out of blood vessels) and blood to achieve sufficient hemostasis, which results in extrinsic and intrinsic coagulation (fluid thickening into a gel or solid mass) to stop blood loss. Then, adenosine diphosphate (ADP) causes platelet clumping and initiates thrombosis, followed by vasodilation (the widening of blood vessels by increasing blood flow), which increases the flow of white cells and thrombocytes. The inflammatory phase, as stage two, initiates hemostasis and chemotaxis, which both attract white cells and thrombocytes and accelerate the release of mediators and cytokines. All processes, such as collagen degradation, fibroblast transformation, new vessel growth, and re-epithelialization, occur simultaneously. Serotonin and histamine are two mediators released from platelets that increase cellular permeability. The proliferative, or granulation, phase would not occur at a distinct time but is an ongoing process throughout wound healing. Fibroblasts begin producing more collagen and glycosaminoglycans near the wound core, thereby stabilizing it. Reepithelialization then begins as cells migrate from the wound periphery and edges. The superficial epithelial cell layer starts to form and thicken over time. Then, neovascularization begins to form new blood vessels from the original vessels, and vasculogenesis results in the formation of new vessels from endothelial progenitor cells (EPCs). As collagen fibers form, the wound starts to mature (Wallace et al., 2023). The final phase of wound healing, remodeling, starts around week 3 and can last for 12 months. Excess collagen begins to degrade, and wound contraction peaks around week 3. The degree of wound contraction during secondary healing (the wound edges cannot be brought together) is much greater than that during primary healing (the wound edges are brought together) (Bowden et al., 2015).

3.2 Chronic Wounds' Pathophysiology and Classification

3.2.1 Diabetic foot ulcers

Diabetic foot ulcer (DFU) is defined by the International Working Group on Diabetic Foot (IWGDF) as a disease with multiple symptoms caused by either current or prior diabetes, including symptoms like skin dryness, ulceration, infection, or destruction of the foot tissues (Bus et al., 2020; X. Wang et al., 2022). It is also one of the most studied types of chronic wound due to its association with diabetes and lower extremity amputation (Falanga et al., 2022). Patients with diabetes who develop DFU face more than a tenfold increase in amputation risk relative to those without one, and individuals with DEU or LEA carry estimated two- and threefold higher mortality risk compared to diabetic patients who develop neither complication (Falanga et al., 2022). Various diabetic patients suffer from DFU and usually also have neuropathy and/or peripheral artery disease (PAD). Motor neuropathy directly affects the foot, which can

lead to muscle atrophy. PAD is the major reason for the neuropathy and leads to leg ulcers and potentially amputation. Due to diabetes mellitus (DM) majorly affecting the arteries and lower limbs, there is a higher frequency of lower limb amputation in patients with PAD (Alberts et al., 2025).

As the ulcer develops, the condition influences the healing process, which can be complicated due to numerous factors taking precedence at different periods. Persistent ulceration and infection erode the epidermis and dermis, compromise the skin's barrier function, and can progress to full-thickness tissue loss. DFU severity is most often graded using a standardized system, one of the most widely adopted being the Wound, Ischemia, and Infection classification. It scores three independent risks that could lead to lower limb amputation. Each of the three factors scores 0 to three and is based on size, depth, severity, and difficulty in the healing process. This grading helps predict severe amputation (Alberts et al., 2025). Reported DFU prevalence varies considerably by care setting, from about 1-20% among hospitalized diabetic patients to under 1-10% in the community population, with global incident estimates ranging from around 5 to 41 new cases per 100 people annually among people with diabetes. This variation reflects differences in age, comorbidity burden, and geography (Falanga et al., 2022).

3.2.2 Venous leg ulcers

Venous leg ulcers (VLUs) are the most severe form of chronic venous disease that is caused by venous hypertension. Their development involves both macroscopic and microscopic pathology. Macroscopically, hereditary changes in vein wall structure and valve function lead to varicose veins and impaired venous return, and this process sustains venous hypertension (Alberts et al., 2025). Microscopically, this causes ongoing leakage of macromolecules and breakdown products from red blood cells, resulting in local iron accumulation and persistent inflammation. This state draws white blood cells into the dermis and sustains cytokine release, which pushes fibroblasts toward a more contractile phenotype and increases tension in the dermis. Iron accumulation also keeps macrophages locked in a pro-inflammatory state that favors ongoing tissue damage rather than the shift toward tissue repair. Current treatment now focuses on both relieving venous hypertension and directly promoting wound healing. VLU typically takes around six months to heal and recurs in more than 58% of patients within five years (Crawford et al., 2017; Lim et al., 2018; Alberts et al., 2025).

VLUs are the second most common chronic wound after pressure ulcers, in an estimated 1.5-3 cases per 1000 persons (Díaz-Herrera et al., 2021; Nelson & Adderley, 2016; Margolis et al., 2002; Homs-Romero et al., 2021; Falanga et al., 2022). It is most common in women and also increases with age, reaching around 1.5%, and the annual incidence is 1.2% (Nelson & Adderley, 2016; Margolis et al., 2002). While overall prevalence has stayed consistent across countries, it still varies depending on whether data come from the general population or a primary care setting. In the case of VLU, epidemiological studies are over a decade long. This reflects the demand for new data (Forssgren et al., 2008; Berenguer Pérez et al., 2018; Falanga et al., 2022).

3.2.3 Pressure ulcers

Pressure ulcers (PUs) are also known as bedsore, decubitus ulcers, pressure sores, or pressure injuries. They develop when localized blood flow is disrupted, typically from prolonged pressure and/or shearing

forces acting on body tissue, often from body or limb weight, and this risk is heightened in patients with poor nutritional status. Extrinsic risk factors include prolonged immobilization, such as lying on a bed, table, or spinal board, and medical equipment that fits poorly against the skin. Intrinsic risk factors include smoking, diabetes, and malnutrition that further increase susceptibility. PUs are staged by severity: Category I involves non-blanchable redness with intact skin; Category II involves partial-thickness skin loss; Category III involves full-thickness skin loss; and Category IV involves full-thickness tissue loss with exposed bone, tendon, or muscle (Anthony et al., 2019; Boyko et al., 2018; Alberts et al., 2025). Effective PU treatment typically requires a multidisciplinary team spanning plastic surgery, physical therapy, infectious disease, orthopedic, internal medicine, general surgery, and neurology. Radical debridement followed by flap closure, which uses well-vascularized tissue of adequate volume, remains the primary surgical approach. At the same time, skin grafting has fallen out of favor due to its association with higher ulcer recurrence. Despite advanced surgical techniques, the recurrence rate still surpasses 80% in some cases, indicating that this remains a major clinical challenge (Irmak, 2018; Alberts et al., 2025).

3.2.4 Arterial ulcers

Arterial leg ulcers (ALUs) make up an estimated 22% of all leg ulcers and result from insufficient blood flow to the lower limbs due to narrowing or blockage from atherosclerosis. Unless the underlying arterial insufficiency is addressed, these ulcers may heal very slowly or fail to heal at all. In addition, vascular mixed ulcers are estimated to account for around 10% of lower leg ulcers. Mixed ulcers involve both venous and arterial pathology; effective treatment requires evaluating both the physiological and anatomical contributions of each condition rather than treating either in isolation (Broderick et al., 2020; Hedayati et al., 2015; Alberts et al., 2025).

ALUs arise from diminished arterial blood flow to the lower limb due to atherosclerotic narrowing of medium and large arterioles. Moreover, diabetes, thromboangiitis obliterans, vasculitis, pyoderma gangrenosum, thalassemia, and sickle cell disease are several conditions that can predispose patients to atheroma formation. Coexisting hypertension can compound arterial damage by injuring the vessel's inner lining. The resulting drop in arterial supply produces tissue hypoxia and subsequent tissue injury, while thrombotic or atheromobolic events can also contribute to tissue damage and ulcer development. ALUs usually develop over the toes, heels, and other bony prominences of the foot. They typically look as sharply defined punched-out lesions with a pale, necrotic, non-granulating wound bed. The surrounding skin often appears dusky, feels cool, and may be thin, hairless, brittle, and shiny in texture. Toenails are frequently thickened, become opaque, and may eventually be lost due to gangrene of the affected extremity in severe cases. On vascular examination, the dorsal pedis and posterior tibial pulses are often diminished or absent, and bruits may be audible over the proximal leg arteries, signaling underlying atherosclerosis (Falanga et al., 2022).

3.3 Why Chronic Wounds Fail to Heal

Treatment of chronic wounds often fails even with careful management when persistent infection develops. A range of aerobic and anaerobic pathogens, including Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, and beta-hemolytic streptococci, commonly colonize these

wounds, taking advantage of an impaired host immune response and further delaying healing. Support for the causal role of biofilms in chronic wounds comes from studies examining bacteria-wound tissue interactions, both in keratinocyte cell cultures in vitro and in animal wound models in vivo, with animal models proving particularly useful for distinguishing correlation from causation regarding biofilm effects on healing. Preventing infection requires aseptic technique, thorough debridement, and appropriate antimicrobial therapy (Wu et al., 2019; Firas Diban et al., 2023; Alberts et al., 2025). Topical antimicrobials have become increasingly important in wound care as antimicrobial resistance, driven largely by overuse of systemic antibiotics, continues to rise. Because they are applied directly to the wound, topical antimicrobials achieve high local drug concentrations, cause fewer systemic side effects, and carry a lower risk of promoting resistance (Thaarup et al., 2022; Punjataewakupt et al., 2018; Alberts et al., 2025).

Numerous factors, including bacterial infection, underlying illness, hypoxia, and chronic inflammation, can disrupt wound healing. Chronic wounds are marked by persistent inflammation tied to dysregulated immune activity, and this failure to properly regulate the immune response sustains inflammation and slows healing, contributing to wound chronicity. Hypoxia, or insufficient oxygen supply to the wound bed, is another key contributing factor. In the short term, hypoxia can actually promote angiogenesis by upregulating hypoxia-inducible factor 1 (HIF-1) and its downstream target, vascular endothelial growth factor (VEGF). However, when hypoxia becomes chronic, it instead impairs angiogenesis and disrupts cell signaling, contributing to delayed healing. Hypoxia can result from inadequate blood flow, tissue damage, or inflammation, and by interfering with angiogenesis, cell proliferation, and re-epithelialization, it can slow tissue regeneration, prolong healing time, and increase infection risk. Addressing hypoxia effectively therefore remains an important goal for improving wound healing outcomes (Han et al., 2023; Schilrreff & Alexiev, 2022).

3.4 Role and Characteristics of Biomaterials in Wound Healing

The skin is the largest organ. It is responsible for several major functions, such as playing a role as a protective barrier from the external environment, maintaining homeostasis, and functioning as a neuro-endocrine-immune organ to adapt its mechanism in either neural and humoral pathways in response to environmental stressors or pathological processes (Slominski et al., 2012; Slominski et al., 2015). Skin tissue engineering aims to develop higher-quality skin replacement products to enable faster wound repair. Two main skin replacement therapies are used to accelerate wound healing: allografts and autografts. An allograft is the implantation of tissues or organs from a donor of the same species as the recipient. An autograft, by contrast, is the transplantation of tissues from the same individual. Another technique used to aid tissue repair is the use of scaffolds or temporary biological structures composed of various biomaterials that support cell growth and differentiation (Hilmi, 2015). Biomaterials provide physical support, promoting cell growth and migration and accelerating the formation of new tissues in wound healing. To support the healing process efficiently, biomaterials should satisfy certain property criteria, including appropriate mechanical strength, flexibility, porosity, structure, biodegradability, and biocompatibility (Hilmi, 2015; Ma & Choi, 2001; Niculescu & Grumezescu, 2022). There are three types of biomaterials used in scaffolds for skin tissue engineering: synthetic, natural, and composite (Downer et al., 2023).

Synthetic biomaterials are the most commonly used in tissue engineering due to their flexibility, ease of processing, low toxicity, high mechanical strength, and nonbiodegradability (Chaudhari et al., 2016). Aliphatic polyesters are synthetic biomaterials composed of repeating units, such as polylactic acid (PLA) and polyglycolic acid (PGA). They serve as delivery systems that support skin regeneration by releasing bioactive molecules for tissue repair (Chaudhari et al., 2016; Cacciotti et al., 2018; Cacciotti, Chronopoulou, et al., 2018). Natural biomaterials derived from animals and plants, such as collagen, silk, gelatin, and fibrinogen, also help with skin reconstruction. Collagen is one of the major biomaterials used because of its large role in the healing process. Animal-derived biomaterials release beneficial GFs for wound-healing applications (Chaudhari et al., 2016). Composite biomaterials are created by combining two or more distinct materials with complementary features to address each material's limitations in the tissue repair process. Cellulose and chitosan can be combined with cellulose poly fiber to form an anti-infective bandage that separates the internal and external environments during the wound healing process (Chaudhari et al., 2016).

3.5 Advantages and Limitations of Biomaterials in Chronic Wound Healing Applications

Tissue damage can occur at different levels with varying sizes, depths, and shapes, resulting in either acute or chronic wounds depending on the duration of injury. An acute wound is created by a sudden event and heals faster than a chronic wound (Zhao et al., 2017; Saleh et al., 2019; da Silva et al., 2019; Wang et al., 2019; Lu et al., 2019).

Infection is one of the major challenges in efficient wound healing, especially in chronic wounds. Sustained inflammation and delays in tissue repair are usually caused by the consistent presence of pathogenic microorganisms at the wound site, especially bacteria capable of forming biofilms. Biofilms act as protection for bacteria, preventing them from immune defense in the host’s body and antimicrobial treatments, which results in complex eradication and perpetuates chronicity (Papadopoulou et al., 2023; Ferraz, 2026). While most of the mechanistic evidence linking biomaterials-based infection control to improved healing outcomes, including biofilm-disruption and immune modulation mechanics described, derives from in vitro and animal models rather than controlled human trials; this distinction is expanded in the discussion. In addition, the longer the microbes/bacteria are colonized in the damaged tissue area, the longer they can sustain a prolonged immune response that accelerates inflammatory cytokines and proteases, leading to ECM degradation and inhibiting fibroblast activity. Ultimately, the imbalance of re-epithelialization and regeneration can lead to recurrent or spreading infection, escalating to systemic complications such as sepsis (an overactive response to an infection that leads to organ failure or tissue damage). The complicated nature of chronic wound infections, compounded by a high prevalence of antibiotic-resistant organisms, highlights the need for advanced treatment approaches, including biomaterial-based strategies, to control infection better and support wound healing (S.-J. Zhang et al., 2025; Ferraz, 2026).

Wound care has evolved from passive covering such as gauze and bandages to more advanced biomaterial-based systems that can actively mimic the wound microenvironment. Biomaterials have various roles in chronic wound healing, including providing a physical barrier against the external environment, force, and contamination; maintaining an optimal environment for the healing process;

delivering therapeutic agents to accelerate wound healing; and interacting with biological systems to activate tissue regeneration. This versatility makes biomaterials especially useful for addressing many interconnected barriers to healing seen in chronic wounds, including infection, impaired blood vessel formation, and persistent inflammation (Ferraz, 2026). On a basic level, biomaterials function as a protective scaffold that guards wounds against external pathogens and limits excessive fluid loss. Compared to connective dressing, many contemporary biomaterials, including hydrogels, hydrocolloids, and nanofiber mats, are designed to replicate components of the ECM. This structural similarity improves cell adhesion, migration, and proliferation, supporting the overall wound healing process. In addition, their adjustable porosity allows gases and nutrients to pass through, helping create a more physiologically appropriate healing environment (Nguyen et al., 2023; Ferraz, 2026).

Biomaterials have several advantages demonstrated primarily in preclinical models, such as their use as delivery systems for therapeutic agents. In these studies, hydrogels, liposomes, and polymeric nanoparticles have been shown to allow antibiotics and anti-inflammatory agents to be released and localized at the wound site over a sustained period. This controlled release decreases the frequency of dressing needed, limits systemic side effects, and keeps drug concentration focused at the wound site. Because chronic wounds are often associated with a deficiency in growth factor signaling, delivering these molecules through biomaterials can help restore the signaling pathways needed for angiogenesis and tissue repair (Ferraz, 2026). Another proposed benefit, based largely on in vitro and animal-model evidence, is that biomaterials can be designed to mimic immune defenses by releasing anti-inflammatory agents or introducing surface cues intended to encourage macrophages shift toward a pro-healing (M2) phenotype. In addition, biomaterials that are designed to release oxygen directly help counteract the hypoxia commonly seen in ischemic wounds. This not only cures infection but also addresses dysregulated immune and metabolic environments (Sousa et al., 2022; Ferraz, 2026). A key advantage attributed to biomaterials in the literature is their capacity to help combat infection, a major obstacle in chronic wound healing (Pereira et al., 2025; Pereira, Terroso, Gonçalves, Catita, Santos, Baptista, Monteiro, Lúcio, et al., 2025; Ferraz, 2026). These systems can be functionalized with antimicrobial agents, such as metal nanoparticles or antimicrobial peptides, to provide sustained local delivery. In contrast, certain natural polymers, such as chitosan, offer intrinsic antibacterial activity (Ribeiro et al., 2017; Grenho et al., 2014). Moreover, advanced biomaterials are fabricated to break down biofilm through physical, enzymatic, or stimulus-responsive mechanisms to reduce bacterial burden and resume the normal healing process (Barros et al., 2022; Kasapgil et al., 2024; Landa et al., 2025).

Despite their considerable promise for chronic wound management, biomaterial-based strategies still face real obstacles to clinical translation, including variability in patient wound presentations, high production costs, and substantial regulatory hurdles. Ensuring biocompatibility and minimizing the cytotoxicity of embedded antimicrobials or nanoparticles remain important scientific and safety concerns. Nevertheless, some biomaterial-based dressings, including silver-impregnated hydrogels and collagen scaffolds, have already reached clinical use and shown both safety and effectiveness in fighting infection and supporting healing in human patients. Continued progress in materials science, alongside growing integration with personalized medicine, is expected further to expand the clinical usefulness and adaptability of these dressings (Fadilah et al., 2022; Alberts, Tudorache, et al., 2025; Tian & Bian, 2025).

4. BIOMATERIALS FOR WOUND HEALING

4.1 Properties of an Ideal Wound Dressing/Gel

The properties of an ideal wound dressing should be evaluated based on its ability to sustain most environments, ameliorate epidermal migration, and support angiogenesis and connective tissue. It should also allow gas exchange between the damaged tissue and environment, and help maintain an appropriate wound-bed temperature to support blood flow and further aid epidermal migration. Protection against bacterial infection is essential, as is non-adherence to the wound bed to allow easy, painless removal once the healing process is complete. The dressing should additionally support debridement by promoting leukocyte migration and enzyme accumulation at the wound site, while remaining sterile, non-toxic, and non-allergenic (Dhivya et al., 2015).

4.2 Hydrogel as a Delivery Platform

A hydrogel is structured as a three-dimensional network of hydrophilic polymer chains, enabling rapid response by absorbing and retaining water to form a solid material that protects the wound or damaged tissues and supports the wound-healing process. Hydrogels have numerous advantages during the wound-healing process, such as adaptability and tuneability that allow them to interact with and incorporate agents such as antibacterial that build a shield against bacterial infection, antimicrobial cells, biomolecules, and growth factors (Gounden & Singh, 2024). It has superior biodegradability, biocompatibility, and adhesion, and it provides air permeability and a moist environment for cell migration, enhancing cell proliferation and accelerating tissue healing. In addition, preclinical studies indicate that antioxidant hydrogels may enhance the healing process by reducing excessive reactive oxygen species in chronic wounds, thereby reducing oxidative stress; improving the wound microenvironment; promoting collagen synthesis and re-epithelialization; and lowering wound pH to reduce infection. Clinical confirmation of these specific mechanistic benefits in human chronic wounds remains limited. Hydrogels fall into two categories: chemical and physical. Nevertheless, hydrogels can be derived from either natural materials, such as alginate, chitosan, and hyaluronic acid, or synthetic materials, such as polyvinyl alcohol, polyacrylamide, and polyethylene glycol (Gounden & Singh, 2024).

One of the key traits of hydrogels is their ability to replicate the extracellular matrix (ECM), which normally facilitates cellular adhesion, tissue anchorage, cellular signaling, and cell recruitment. The major elements that structure the ECM include polysaccharides, proteins, and water (Potekaev et al., 2021; Gounden & Singh, 2024). In conditions such as acute or chronic injuries, the ECM might be damaged. A hydrogel can mimic the mechanical rigidity of an ECM because its major components are water and polymers. At the same time, it can also imitate the function that incorporates cells and other ECM-associated macromolecules, allowing them to replicate ECM function as well. When applied to a wound, a hydrogel can theoretically act as a dermal matrix that mimics the structure and function of intact skin, potentially reducing scar formation by matching the tensile strength and elastic recoil of undamaged dermis. This ECM-like environment is thought to support cell growth, ECM deposition, and new tissue formation, thereby improving wound healing outcomes. Among available options, hydrogels made from hyaluronic acid, collagen, and alginate have proven especially effective at forming these ECM-mimicking matrices (Sivaraj et al., 2021; Ho et al., 2022; Gounden & Singh, 2024).

In the first 15 minutes of thermal burn, heat absorbed by the epidermis continues to transfer into deeper tissue layers, and applying a cooling agent during this state can reduce injury severity and limit scarring (Wright et al., 2019; Gounden & Singh, 2024). Hydrogel plays a key role in major dressing for first aid during burn therapy, since its high water content helps cool the burn site and stabilize wound temperature. It also helps to ease and protect the wound from infection, making it well suited for use during patient transport, such as in an ambulance. Compared to paraffin-based dressings, sterile, non-adherent cotton gauze mesh impregnated with soft white paraffin is used. Hydrogels have been associated with faster recovery and offer a safer first aid option for pediatric (such as adolescent) patients. Many ambulance services now carry hydrogel sheets, often around 96% of water, for emergency burn care. One widely used and cost-effective option is a Carbomer 940-based hydrogel that has been shown to improve tissue blood flow and reduce the extent of necrotic tissue (dead or dying tissue) (Shu et al., 2021; Surowiecka et al., 2022; Gounden & Singh, 2024).

4.3 Natural vs. Synthetic vs. Hybrid Biomaterials

Biomaterials for wound-healing hydrogels can be categorized as natural, synthetic, or hybrid materials; each offers unique biological performance and mechanical reliability. Natural polymers, including collagen, chitosan, alginate, and hyaluronic acid, have strong biological traits, including biocompatibility, intrinsic bioactivity, and structural similarity to the ECM. In vitro and preclinical studies indicate these traits support cell adhesion, proliferation, and tissue regeneration. However, natural biomaterials have limitations such as weak mechanical strength, batch-to-batch variability, and limited long-term stability (Ferraz, 2026). Synthetic polymers, including polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, polyurethane, and poly (ε-caprolactone), have better mechanical strength, are easier to shape into different configurations, and are cost-effective in manufacturing at industrial scale (Gounden & Singh, 2024). Their degradation abilities and reproducibility make them a suitable biomaterial when the application requires structural integrity. Its precise control over their hydrophilic and hydrophobic regions allows a more homogeneous framework with improved water retention (Gounden & Singh, 2024; Ferraz, 2026). A limitation of synthetic materials is the lack of inherent bioactivity, which often requires additional functionalization to support cell interaction and antimicrobial performance(Ferraz, 2026). To address the mechanical limitation of natural polymers and the low bioactivity of synthetic materials, hybrid and composite biomaterials were introduced by combining both approaches. This pairs the biofunctionality of natural polymers with the mechanical structural and design flexibility of synthetic materials (Ferraz, 2026). Hybrid biomaterials enhance the bioactivity of natural compounds. They are considered a promising direction for future wound treatment (Gounden & Singh, 2024), though the added complexity introduces greater challenges in manufacturing, cost, and regulatory approval (Ferraz, 2026).

These biomaterials are fabricated through different production processes that directly shape their mechanical behavior, degradation kinetics, and biological activity. Natural polymers are produced through extraction, purification, and chemical or enzymatic crosslinking to gain stability, moisture retention, and bioactivity. Synthetic materials are usually composed through solvent casting, electrospinning, or controlled polymerization. This allows better control of porosity, fiber diameter, and mechanical strength. Hybrid biomaterials are typically produced through blending, co-electrospinning, nanoprinting, incorporation, or in situ mineralization, yielding multifunctional scaffolds with combined structural and

biological properties (Ferraz, 2026). As polymer engineering advanced, newer hydrogel formats, including sprayable hydrogels, stimuli-responsive "smart" hydrogels, nanogels, aerogels, and cryogels, have emerged, reflecting continuous efforts to enhance both natural and synthetic biomaterials (Gounden & Singh, 2024).

5. POLYMER-SPECIFIC BIOMATERIALS USED IN CHRONIC WOUND HEALING GELS

5.1 Alginate

Alginate is a biodegradable, natural polysaccharide classified as a biomaterial; it is commonly used in medical applications. Alginate dressings have gained significant recognition in the wound-healing gel market since the 1980s due to alginate's safety, biodegradability, and biocompatibility. These properties make alginate an ideal candidate in numerous applications, including food processing, drug delivery systems, cosmetics (body care products), tissue engineering, and wound healing (Froelich et al., 2023). It is mainly composed of β-D-mannuronic acid and α-L-guluronic acid to form a flexible polymer whose structure closely resembles glycosaminoglycans (GAGs), which are an important element of the ECM, and it has great biocompatibility, low toxicity, and the ability to form a hydrogel under moderate conditions (Wierzbicka et al., 2024; Varaprasad & Jayaramudu, 2025).

Alginate has various benefits as a biomaterial in wound-healing gels, such as being one of the most promising candidate materials suitable for in vivo application, with its non-toxic, non-immunogenic properties and ability to support cell viability without invoking an inflammatory response. While its structure is similar to GAGs, it helps with binding host tissues, prompting cell adhesion, and proliferation. Its biocompatibility makes it degrade slowly, and it provides cost-effective gelation, though it requires functionalization to enhance cell attachment (Wierzbicka et al., 2024; Varaprasad & Jayaramudu, 2025). Its hydrophilic and biocompatible profile, mild gelation conditions, and structural versatility make it a preferred platform for composite development. However, its limited inherent cell adhesion, limited degradation control, and lack of mechanical strength mean that hybrid or composite strategies are often needed to optimize outcomes (Varaprasad & Jayaramudu, 2025).

In chronic wound application, alginate-based materials have become a promising material in managing chronic wound healing challenges, with their biocompatibility, biodegradability, and ability to maintain a moist wound environment. In preclinical and small-scale clinical studies, alginate has shown its ability in supporting wound closure, reducing inflammation, and promoting angiogenesis and collagen deposition, with newer formulations incorporating antimicrobial agents, growth factors, or natural compounds showing benefit in chronic wounds. However, its limitations include a lack of mechanical stability and reduced effectiveness in low-exudate or dry wounds, and it still needs to confirm long-term efficacy, cost-effectiveness, and suitability for personalized wound care in large-scale clinical trials (Mazurek et al., 2025).

5.2 Chitosan

Chitosan is classified as an alkaline polysaccharide with excellent moisturizing and adsorption properties, without the toxicity or adverse effects associated with other materials. Chitosan contains amino groups (-NH2) in its molecules, which result in a cationic nature. The positive charge promotes extracellular matrix formation and attracts negatively charged molecules. It dissolves in acidic solutions and reacts with other materials to form composites, and it can be used to easily create scaffolds, membranes, gels, nanofibers, microparticles, and sponges. In addition, it exhibits a broad range of biological actions and health benefits, such as reducing gastric ulcers (anti-inflammatory), protecting against genotoxic effects, combating cancer, and promoting faster wound healing across various stages, including fibroplasia and collagen synthesis (B et al., 2024; Varaprasad & Jayaramudu, 2025). Chitosan is a cationic natural polysaccharide that offers antimicrobial properties and biodegradability, yet it is less soluble at neutral pH, which complicates the process relative to alginate's straightforward gelation(Niculescu & Grumezescu, 2022; Varaprasad & Jayaramudu, 2025). Despite this difference, alginate and chitosan form a polyelectrolyte complex together, which makes them complementary rather than purely competing materials in medical applications (Varaprasad & Jayaramudu, 2025).

Chitosan is valued for being a biodegradable, biocompatible, bioabsorbable, and non-toxic biomaterial. It can be used in drug delivery, infusion films, scaffolds, membranes, and nanoparticles, and it is hemocompatible and non-irritating to skin. It supports wound healing through several distinct mechanisms, such as promoting hemostasis by encouraging platelet and fibrinogen aggregation at the wound site, and its cationic nature provides antimicrobial activity by disrupting bacterial membranes. In vitro and animal studies indicate it also supports wound regeneration by modulating the inflammatory response through interaction with immune cell receptors, influencing the expression of key inflammatory mediators. Despite its broad feasibility in biomedical applications, chitosan faces several limitations, such as poor solubility and limited mechanical strength in certain applications, as well as scalability difficulties for large-scale production. Its toxicity profile and the byproducts generated during biodegradation also contribute to concerns in clinical use(Heru Agung Saputra & Andreas, 2025). In chronic wound applications, chitosan, primarily in preclinical models, has been shown to enhance the process of wound healing by creating a moist environment for the injuries, facilitating cell migration, and tissue regeneration. It can help hinder bacteria at the wound site (B et al., 2024).

5.3 Collagen

Collagen can be found in a wide variety of sources, including animals and plants. Most collagen products are extracted from raw materials such as bovine and porcine skin and various fragments. In the four stages of wound healing, largely through in vitro and animal-model research, collagen plays significant roles, including controlling initial bleeding, enhancing phagocytosis and immune responses (the process by which immune cells eat and destroy pathogens), influencing gene expression, and acting as a mediator of inflammation. In addition, preclinical studies suggest collagen can activate microRNA signaling to promote the development of a macrophage phenotype (Zhang et al., 2023). Collagen offers excellent cell adhesion due to its RGD motifs, but they lack mechanical tunability and stability in an aqueous environment. Compared to collagen, alginate offers better cell adhesion, but collagen is more

cost-effective and easier to gel (Wierzbicka et al., 2024; Varaprasad & Jayaramudu, 2025). Collagen is the most abundant structural protein in mammalian connective tissues; it can be found in skin, tendon, bone, and cartilage. It has drawn considerable research due to its properties, including low immunogenicity, biodegradability, biocompatibility, hydrophilicity, and ease of processing. However, its limitations include weaker physical and chemical properties, such as limited mechanical strength, poor thermostability, and low resistance to enzymatic degradation, making crosslinking necessary for its preparation for biomedical applications (Liu et al., 2019).

5.4 Hyaluronic Acid

Hyaluronic acid (HA) plays an important role in wound healing and tissue repair due to its distinct properties. HA is a polymer containing a polyanionic disaccharide and is produced in the human body as the main component of the extracellular matrix. Preclinical and mechanistic studies indicate that HA helps moisturize the environment, promoting healing and stimulating tissue growth, fibroblast proliferation, and keratinocyte proliferation. It absorbs exudate and promotes cell migration, and its effects on wound healing include decreased inflammation, regulated tissue remodeling, and improved angiogenesis (Antoszewska et al., 2024). Even though it has an ECM-like structure and biocompatibility, it degrades much faster and is more costly than alginate, which limits its use in applications requiring prolonged structural support. Relative to alginate, these two are similar in structure and biocompatibility, but alginate offers better cost and degradation control (Varaprasad & Jayaramudu, 2025).

HA is one of the materials widely used to repair soft tissues and promote chronic wound healing due to its great biological activity, physicochemical properties, and safety profile. HA can also influence the inflammatory response during healing due to its molecular weight, while its interaction with the receptor enhances cell regeneration. Advances in materials science have enabled researchers to chemically modify HA and combine it with other biomaterials to overcome its natural limitations such as weak mechanical strength and rapid degradation. Other limitations also include a lack of large-scale randomized controlled trials with consistent outcome measures, variation in infection control, material degradation, and individual patient response, highlighting the need for larger and carefully controlled clinical studies (Măciuceanu Zărnescu et al., 2026).

5.5. Comparing the Materials

To compare the effectiveness of each biomaterial mentioned in this research, we defined the key benefits, limitations, and complications in chronic wound application and compiled them into a chart. Each benefit and limitation is taken from sources that mention each biomaterial's ability and the challenges it faces.

Table 1: Comparison of the Biomaterials

Material	Key Benefit	Key Limitation	Chronic Wound Application
Alginate	Non-toxic, non-immunogenic, cost-effective gelation, supports cell adhesion via GAG-like structure. (Wierzbicka et al., 2024; Varaprasad & Jayaramudu, 2025)	Requires functionalization for cell attachment; lacks mechanical strength; reduced effectiveness in dry/low-exudate wounds (Varaprasad & Jayaramudu, 2025)	Supports wound closure, reduces inflammation, promotes angiogenesis and collagen deposition (Mazurek et al., 2025)
Chitosan	Antimicrobial (disrupts bacterial membranes); promotes hemostasis; biodegradable, biocompatible, non-toxic (Heru Agung Saputra & Andreas, 2025)	Poor solubility at neutral pH; limited mechanical strength; scalability and biodegradation byproduct concerns (Heru Agung Saputra & Andreas, 2025)	Maintains moist environment, facilitates cell migration/tissue regeneration, hinders bacteria at wound site (B et al., 2024b)
Collagen	Excellent cell adhesion (RGD motifs); supports phagocytosis/immune response; low immunogenicity (Zhang et al., 2023; Wierzbicka et al., 2024; Liu et al., 2019)	Weak mechanical strength, poor thermostability, low enzymatic resistance; requires crosslinking(Liu et al., 2019)	Controls initial bleeding, mediates inflammation, promotes macrophage phenotype development (Zhang et al., 2023)
Hyaluronic Acid	Stimulates fibroblast/keratinocyte proliferation; promotes angiogenesis; strong safety profile (Antoszewska et al., 2024)	Degrades faster and costs more than alginate; weak mechanical strength; lacks large-scale RCTs (Varaprasad & Jayaramudu, 2025; Măciuceanu Zărnescu et al., 2026)	Moisturizes wound environment, reduces inflammation, regulates tissue remodeling (Antoszewska et al., 2024; Măciuceanu Zărnescu et al., 2026)

Table 1: This table compares four major types of biomaterial such as benefit, limitation, and application in chronic wound discussed in this review.

6. DISCUSSION

There is no single biomaterial that is universally considered superior for chronic wound healing; rather, each material's suitability depends heavily on the wound injury, type of chronic wound, and the patient's situation. With each biomaterial having its own benefits and limitations, some biomaterials share common traits; however, each biomaterial can be determined to be the better candidate used under certain conditions. Based on each material's individual physicochemical and biological properties, rather than head-to-head comparative trials which do not currently exist for these four materials, alginate appears mechanistically well-suited to chronic wounds such as diabetic foot ulcers or venous leg ulcers with moderate to heavy drainage, given its fluid-absorption capacity and anti-inflammatory effects. Chitosan's intrinsic antimicrobial properties and moisture-retention capacity suggest a mechanistic rationale for its use in infection-prone wounds such as diabetic ulcers. Collagen's cell-adhesion properties suggest it may be suited to structurally demanding, slow-healing wounds such as pressure ulcers. Hyaluronic acid's moisture-retention and cell-migration properties suggest a mechanistic rationale for wounds requiring sustained moisture and active tissue regeneration. These associations reflect plausible mechanistic fit rather than comparative clinical evidence establishing one material's superiority over another for a given wound type; no included study directly compared these four materials within the same wound population.

The strength of evidence supporting each biomaterial's use varies considerably, which limits how confidently comparative claims can be made. Alginate benefits from an established commercial history dating to the 1980s and a substantial preclinical evidence base, though confirmation of long-term efficacy, cost-effectiveness, and suitability for personalized wound care in large-scale clinical trials remains an acknowledged gap. Hyaluronic acid faces a similar issue despite its strong biological rationale and safety data; the literature notes a lack of large-scale randomized controlled trials with consistent outcome measures and variation in infection control, degradation behavior, and individual patient response across existing studies. This unevenness is not unique to any material. Across the field, much of the evidence for composite and functionalized systems is derived from animal models rather than human trials, meaning findings demonstrating benefits such as enhanced angiogenesis or reduced inflammation should be regarded as an indication of therapeutic potential rather than confirmed clinical efficacy.

The evidence review points toward several priorities for future research. First, large-scale, standardized randomized controlled trials are needed across all four materials, not only to confirm efficacy but to enable direct, head-to-head comparison that the current literature lacks. Second, greater attention should be paid to bridging the gap between complex, multifunctional preclinical systems and the practical requirement of clinical translation, including manufacturing reproducibility and regulatory feasibility. Third, future research would benefit from wound-type-specific trial design rather than a generalized approach, leading to outcome measures that reflect how strongly wound type appears to influence which material performs the best. Finally, continued development of composite systems that combine complementary material properties, such as alginate-chitosan or alginate-hyaluronic acid formulation, may prove more clinically valuable than the effort to optimize any single material in isolation.

This review is subject to several limitations. First, the strength of evidence supporting the four biomaterials is uneven. Alginate and hyaluronic acid both lack large-scale randomized controlled trials with consistent outcome measures. Second, the evidence for composite and functionalized systems across the biomaterials is derived from animal models rather than human clinical trials, so reported benefits such as enhanced angiogenesis or reduced inflammation should be interpreted as indicative of therapeutic potential rather than confirmed clinical efficacy. Third, this review does not include a formal risk-of-bias assessment or meta-analytic synthesis of quantitative outcomes, given the heterogeneity of study designs and outcome measures across the included literature. Fourth, the wound-type-to-biomaterial recommendations offered in this review are less applicable to arterial leg ulcers specifically, since arterial ulcers result primarily from inadequate arterial blood supply, and no biomaterial dressing can resolve the wound without the underlying vascular insufficiency being addressed first. Fifth, there are several sections of this review, particularly the discussion of chronic wound classification and the natural-versus-synthetic-versus-hybrid biomaterial comparison, that draw substantially on a small number of sources, which may limit the independence of the evidence synthesized in those sections. Finally, this review was restricted to English-language, peer-reviewed publications, which may have excluded relevant findings published in other languages or in non-indexed sources. As a consequence, the comparative statements made throughout this review represent a qualitatively weighted or bias-adjusted comparison. Individual included studies were not systematically evaluated for methodological quality, sample size adequacy, or risk of bias, meaning that a study's inclusion in this review does not imply equivalent methodological rigor to studies excluded or weighted differently in a systematic review. Readers should therefore interpret the comparative claims in this review as hypothesis-generating and indicative of current thinking in the field, rather than as conclusions with a quantified strength of evidence

7. CONCLUSION

None of the biomaterials examined in this article is generally the best choice for the healing of chronic wounds; rather, the appropriate material depends on the particular requirements of the wound condition. Based on mechanistic rationale drawn from each material's individual properties, rather than direct comparative clinical trials, alginate appears best suited for wounds that exude a lot of fluid, for example diabetic foot ulcers and venous leg ulcers, given its fluid-absorption capacity. Chitosan's inherent antimicrobial properties suggest particular usefulness for wounds prone to infection. Collagen's cell-adhesion properties suggest suitability for structurally demanding, slow-healing wounds such as pressure ulcers, and hyaluronic acid's moisture-retention and cell-migration characteristics suggest suitability for wounds requiring sustained moisture and active tissue regeneration. These wound-type pairings should be understood as hypotheses generated from material properties rather than conclusions supported by comparative clinical trials, which remain absent from the current literature. In the case of arterial leg ulcers, however, the choice of biomaterial is less important than addressing the underlying problem of arterial insufficiency, as no dressing can cure the wound unless blood flow is restored.

For all four materials, the supporting evidence remains uneven, since both alginate and hyaluronic acid lack large-scale randomized controlled trials, and much of the evidence for composite and functionalized systems is still based only on animal studies rather than human trials. The discrepancy between the

promise shown in preclinical studies and actual clinical validation is the main challenge confronting the field. Future research should focus on conducting standardized, direct-comparison clinical trials for different materials, on designing trials that are specific to the type of wound, and on carrying out further development of composite systems that combine complementary material properties, for example alginate-chitosan or alginate-hyaluronic acid formulations, because these combined approaches could eventually provide more clinically useful solutions than attempts to improve any single material on its own. As the fields of biomaterials and wound healing continue to progress together, it will be essential to eliminate this gap in the evidence if promising preclinical results are to be translated into reliable, evidence-based care for chronic wounds.

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9. DECLARATION

I, Cing Wun Yang, corresponding author of the manuscript titled "Biomaterial-Based Hydrogels for Chronic Wound Healing: A Comparative Review of Natural Polymers", hereby declare that the manuscript, being a review article, contains a substantial number of cross-references, both to external literature and to different sections within the paper itself. These cross-references were included solely for scholarly purposes, to help readers navigate related concepts and sections discussed elsewhere in the manuscript, and to synthesize prior findings across a broad body of literature without unnecessary redundancy. Given the wide scope of this review, extensive cross-referencing is consistent with standard practice for articles of this nature and is proportionate to the depth and length of the manuscript. I confirm that none of the references, including any self-citations, were included to inflate citation counts artificially, and that this declaration is accurate to the best of my knowledge.

Signed,
Cing Wun Yang
8/9/2026

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