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Review Article

# Recent Advances in Bioactive Hydrogel Composites for Wound Healing: Mechanisms, Materials and Clinical Prospects

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## ABSTRACT

Wound healing is a complex and dynamic biological process that can be significantly impaired by infection, chronic inflammation, and underlying systemic conditions such as diabetes and vascular disorders. Conventional wound dressings primarily provide physical protection and often fail to actively support tissue regeneration or regulate the wound microenvironment, leading to delayed healing and increased complications. In this context, bioactive hydrogel composites have emerged as promising advanced wound care materials due to their ability to mimic the extracellular matrix, maintain a moist environment, and deliver therapeutic agents in a controlled manner. This review summarizes recent advances in the design and application of bioactive hydrogel composites for wound healing and tissue regeneration. Emphasis is placed on the classification of hydrogels based on natural, synthetic, composite, and hybrid polymers, as well as their unique physicochemical and biological properties. The mechanisms by which these hydrogels promote healing-such as enhanced cell adhesion, proliferation, migration, angiogenesis, and modulation of inflammation-are discussed in detail. In addition, advances in fabrication strategies, including physical and chemical crosslinking, injectable systems, stimuli-responsive hydrogels, and 3D-printable bioinks, are highlighted. Key *in vitro* and *in vivo* evaluation parameters relevant to wound healing applications are also reviewed. Finally, current clinical prospects, translational challenges, and future directions-including personalized and theranostic hydrogel systems are outlined. Overall, bioactive hydrogel composites represent versatile and multifunctional platforms with significant potential to overcome the limitations of conventional wound care and improve clinical outcomes.

**Keywords:** Bioactive hydrogels, Drug delivery, Stimuli-responsive hydrogels, Wound healing.

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## INTRODUCTION

Bioactive hydrogel composites are increasingly used in wound care due to their ability to mimic the extracellular matrix, deliver therapeutic agents in a sustained manner, maintain moisture and promote cell activity for tissue repair. Their tunable and multifunctional properties make them more effective than traditional dressings, especially for complex or hard to heal wounds (Cao *et al.*, 2023).

Wound healing occurs in four stages-haemostasis, inflammation, proliferation and remodelling-to restore damaged tissue. However, chronic wounds, diabetes, vascular disorders and infections can disrupt this process. Modern wound dressings go beyond simple protection by offering antimicrobial action, regulating inflammation, promoting angiogenesis and delivering therapeutic agents in a controlled manner to support effective healing (Sanpinit *et al.*, 2025). Among these advanced materials, bioactive hydrogels stand out for their adaptable physical,

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chemical and biological properties. When used as composites, they can be tailored to meet the specific needs of different wound environments and healing stages (Cao *et al.*, 2023). Bioactive hydrogel composites are advanced biomaterials that closely mimic the extracellular matrix, providing a moist, supportive 3D environment that promotes cell growth, nutrient transport and tissue repair. Their hydrophilic structure enhances healing, while incorporation of antimicrobial agents, growth factors, or natural bioactive helps control inflammation, prevent infection and stimulate regeneration. By combining natural and synthetic polymers, these composites achieve better mechanical strength, tunable degradation and controlled drug release overcoming many limitations of traditional dressings. Their adaptable nature allows use as injectable gels, membranes, or scaffolds in wound care, drug delivery and regenerative medicine. Additionally, their responsiveness to pH or temperature enables more precise, personalized therapeutic approaches (Hui *et al.*, 2024).

This review presents a comprehensive overview of recent advances in bioactive hydrogel composites for wound healing, tissue regeneration and antimicrobial applications. It highlights key mechanisms of biological modulation, the role of natural, synthetic and hybrid polymers and current clinical relevance. By integrating insights from materials science, pharmacology and medicine, the review examines innovative design strategies, functionalization approaches and translational challenges. Essential issues such as biocompatibility, sustained drug release and large-scale production are critically discussed, along with emerging technologies that are shaping the future of next-generation hydrogels (Gounden and Singh, 2024).

## Search strategy

In this review, relevant literature was collected through a systematic search of electronic databases including PubMed, Scopus, Web of Science and Google Scholar. Keywords such as bioactive hydrogels, hydrogel composites, wound healing, natural and synthetic polymers, drug delivery, stimuli-responsive hydrogels and tissue regeneration were used individually and in combination. Peer-reviewed research articles, review papers and selected clinical studies published in English were screened and analysed, with emphasis on hydrogel materials, formulation strategies, biological mechanisms, evaluation methods and clinical relevance in wound healing applications.

## Discussion / Review of Literature

The literature reviewed confirms that bioactive hydrogel composites constitute a clear advancement over conventional wound dressings by actively regulating the wound microenvironment rather than providing passive coverage. Unlike traditional materials that inadequately manage moisture, infection and tissue regeneration, hydrogel composites form an ECM-like hydrated matrix that supports cell adhesion, migration and proliferation. This functional advantage explains their reported effectiveness in chronic, infected and delayed-healing wounds, where conventional dressings often fail (Frykberg and Banks, 2015; Fan *et al.*, 2021).

Comparative evaluation of material systems identifies polymer selection as a decisive factor influencing hydrogel performance. Natural polymers such as alginate, chitosan, collagen and hyaluronic acid consistently exhibit excellent biocompatibility and intrinsic bioactivity but suffer from limited mechanical strength, rapid degradation and variability. In contrast, synthetic polymers including PVA, PEG and PAAm provide reproducible mechanical stability and tunable degradation but lack biological cues. The literature therefore strongly supports composite and hybrid hydrogels, which integrate the bioactivity of natural polymers with the structural reliability of synthetic systems, resulting in superior and more clinically relevant wound-healing platforms (Cao *et al.*, 2021; Hui *et al.*, 2024).

Mechanistically, bioactive hydrogel composites promote wound repair through coordinated modulation of inflammation, angiogenesis and extracellular matrix remodelling. Sustained and localized delivery of antimicrobial agents, growth factors and antioxidants has been shown to reduce infection, limit prolonged inflammation and accelerate progression to the proliferative phase-an outcome particularly critical in diabetic and chronic wounds. These multifunctional effects distinguish hydrogel composites from single-function dressings and highlight their therapeutic relevance in complex wound environments (Qi *et al.*, 2022; Liang *et al.*, 2021).

Advances in fabrication strategies further enhance the clinical promise of hydrogel composites. Smart and stimuli-responsive hydrogels enable environment-triggered drug release, while injectable and 3D-printable systems allow minimally invasive administration and patient-specific scaffold design. Despite strong preclinical evidence, translation is limited by challenges such as lack of standardized evaluation methods, scalability issues and regulatory complexity. Overall, the literature supports bioactive hydrogel composites as versatile and effective wound-care systems, with future success dependent on standardization, scalable manufacturing and integration of multifunctional, personalized designs consistent with the conclusions outlined in this review.

## WOUND

A wound is defined as a break or disruption in the normal anatomical structure and functional continuity of the skin or underlying tissues resulting from external or internal injury. Such damage compromises the protective barrier function of the skin, making the affected site vulnerable to microbial invasion, fluid loss, and impaired tissue function. Wounds represent a significant clinical concern because they can negatively impact patient quality of life and, if not managed appropriately, may lead to complications such as infection and delayed tissue restoration.

Effective wound management therefore focuses on protecting the injured site, preventing contamination, and supporting the body's natural repair mechanisms. A clear understanding of the basic nature of wounds is fundamental for the development of advanced wound care materials and therapeutic strategies (Gounden and Singh, 2024; Almadani *et al.*, 2021).

### Common Wound Types

Acute wounds are skin or tissue injuries that typically heal within four weeks with proper care, caused by surgery, trauma, burns, chemicals, or radiation. They can be superficial, partial-, or full-thickness, with deeper wounds prone to scarring. Healing follows haemostasis, inflammation, proliferation and remodelling. Management aims to prevent infection, maintain moisture, control pain and ensure timely closure, using sutures, debridement and appropriate dressings-such as non-adherent, hydrogel, alginate, or negative pressure therapy-based on wound depth, exudate and patient needs (Olutove *et al.*, 2024).

Chronic wounds including arterial, diabetic, venous and pressure ulcers, stall in the inflammatory phase due to persistent inflammation, cytokines, biofilms and senescent cells. Assessment involves wound documentation and vascular evaluation, while management follows the TIME framework-debridement, infection control, moisture balance and edge care-along with addressing underlying causes. Successful healing requires a personalized, multidisciplinary approach (Bowers and franco, 2020).

Diabetic wounds especially foot ulcers, affect up to 25% of patients and pose major medical and economic burdens. Poor blood flow, neuropathy and vascular damage from chronic hyperglycaemia delay healing, prolong inflammation, reduce angiogenesis and disrupt ECM remodelling, leading to fragile tissue and high risk of infection. Management focuses on glycaemic control, debridement, infection prevention and advanced therapies like negative pressure therapy, growth factors, stem cells and nutritional support (Dasari *et al.*, 2021).

Burn wounds differ in depth and severity, with Jackson's model defining zones of necrosis, stasis and hyperaemia. They range from superficial to full-thickness, with deeper injuries causing heightened inflammation, slower healing and increased infection and scarring risks. Management centres on stabilization, infection control and early closure using excision, grafts, or skin substitutes. Healing follows normal phases but is complicated by hypermetabolism and immunosuppression. Despite advances in engineered skin and modern dressings, infection control and functional recovery remain major challenges (Rowan *et al.*, 2015).

## WOUND HEALING: BIOLOGICAL BACKGROUND AND CLINICAL NEED

Wound healing is a coordinated biological process essential for restoring skin structure and function after injury. It progresses through four overlapping stages: haemostasis (clot formation), inflammation (removal of debris and pathogens), proliferation (collagen formation, angiogenesis and re-epithelialization) and remodelling (tissue maturation and strengthening). These phases are governed by complex interactions among fibroblasts, keratinocytes, endothelial cells, immune cells, signalling molecules and the extracellular matrix (Almadani *et al.*, 2021).

In clinical practice, wound healing can be impaired by factors such as diabetes, vascular diseases, infections, aging and chronic wounds like diabetic foot ulcers or pressure sores. These conditions often disrupt the normal repair process, resulting in delayed healing, higher infection risk, tissue damage and even increased mortality. This underscores the need for advanced wound care approaches that not only protect the wound but also promote tissue regeneration, regulate the wound environment and minimize complications (Mamun *et al.*, 2024).

### Phases of wound healing

#### *Haemostasis Phase*

The haemostasis phase starts immediately after injury to stop bleeding and lay the groundwork for healing. Blood vessels constrict and platelets adhere and aggregate to form a temporary plug while releasing growth factors such as PDGF, TGF-β and VEGF. At the same time, the coagulation cascade forms a fibrin mesh that stabilizes the clot and creates a provisional extracellular matrix. This structure not only seals the wound but also releases chemotactic signals that attract neutrophils and macrophages, effectively transitioning the process into the inflammatory phase (Zhang *et al.*, 2024; Qi *et al.*, 2022).

### Inflammatory phase

The inflammatory phase follows haemostasis and clears debris, pathogens and damaged tissue to prepare the wound for repair. Neutrophils arrive first, releasing ROS, proteases and cytokines to control infection. Mast cells release histamine, increasing vascular permeability and forming nutrient-rich exudate. Monocytes then differentiate into macrophages, shifting from an M1 pro-inflammatory role to an M2 reparative role that promotes regeneration. While necessary, prolonged inflammation can damage tissue and delay healing, so a timely transition to the proliferative phase is essential (Das *et al.*, 2015; Landen *et al.*, 2016).

### Proliferative phase

The proliferative phase begins a few days after injury and is characterized by granulation tissue formation and new ECM deposition, including collagen, hyaluronic acid, proteoglycans

and elastin. Fibroblasts drive this phase by producing ECM and becoming myofibroblasts that contract the wound. Keratinocytes migrate to restore the epidermis, while endothelial cells form new blood vessels in response to hypoxia-driven signals such as HIFs and VEGF. Macrophages further support angiogenesis and fibroblast activity. These coordinated events create a vascular, collagen-rich matrix that enables re-epithelialization and transitions the wound into the remodelling phase (Zhang *et al.*, 2024; Shaw and Martin, 2016).

### Remodelling phase

The remodelling (maturation) phase is the final and longest stage of wound healing, lasting months to over a year. In this phase, type III collagen is replaced by stronger, crosslinked type I collagen, increasing tensile strength and reducing scar thickness. Excess vessels regress and unneeded cells undergo apoptosis, leaving a stable but weaker-than-normal scar. Any imbalance in ECM synthesis and degradation can slow healing or cause abnormal scarring, including hypertrophic scars or keloids (Qi *et al.*, 2022; Walsh *et al.*, 2000).

### Challenges in Conventional Wound care

Conventional wound care has several limitations that can slow healing and worsen clinical outcomes. Traditional dressings such as gauze, cotton and povidone-iodine provide basic coverage but exhibit short residence time, cause wound desiccation, adhere painfully to newly formed tissue and inadequately manage exudate-often leading to either excessive dryness or maceration. Many topical agents, including silver sulfadiazine, rapidly lose their therapeutic effectiveness in the presence of wound fluids. Additional challenges include rising antimicrobial resistance, limited tools for real-time wound monitoring and insufficient clinical evidence supporting many conventional practices. As illustrated in Figure 1, these limitations translate into poor performance in key wound-care parameters such as infection control, moisture retention and drug-delivery capability when compared with bioactive hydrogel systems. Collectively, these shortcomings increase infection risk, delay tissue regeneration and contribute to the development of chronic wounds, highlighting the urgent need for more effective and accessible advanced wound-care solutions (Frykberg and Banks, 2015).

## BIOACTIVE HYDROGEL COMPOSITES

Bioactive hydrogel composites are polymer-based networks designed to mimic natural tissue, enhanced with bioactive molecules that stimulate cell activity, support tissue regeneration and allow controlled release of therapeutic agents (Fiorati *et al.*, 2021). Bioactive hydrogel composites combine hydrophilic polymers with bioactive molecules, fillers, or stimuli-responsive elements to boost mechanical strength and therapeutic function. Mimicking the extracellular matrix, they support cell adhesion, proliferation and tissue regeneration while enabling controlled drug or growth factor release. Their multifunctional properties, including antibacterial and osteoconductive effects, overcome conventional hydrogel limitations, making them ideal scaffolds for regenerative medicine, minimally invasive therapies and enhanced wound healing (Omidian *et al.*, 2024).

Three-dimensional, water-swollen crosslinked hydrophilic networks-often called "super-absorbent hydrogels"-can absorb 10-20 times their dry weight in water. Their key features include high swelling capacity, excellent oxygen permeability, strong biocompatibility and effective drug loading and release, making them well suited for mimicking natural tissue environments (Raina *et al.*, 2022).

### Classification of Bioactive Hydrogels

Bioactive hydrogels are generally classified into four main types based on origin, composition and function: natural, synthetic, composite and hybrid hydrogels. Natural hydrogels are derived from biopolymers such as polysaccharides (alginate, chitosan, hyaluronic acid) and proteins (collagen, gelatin). They offer excellent biocompatibility, biodegradability and strong ECM-like support for cell adhesion, growth and differentiation. Although naturally bioactive, they often face limitations like low mechanical strength and batch-to-batch variability (Cao *et al.*, 2021).

Synthetic hydrogels, made from polymers like Polyethylene Glycol (PEG), Polyvinyl Alcohol (PVA) and Polyacrylamide (PAAm), offer precise control over mechanical properties, degradation rates and chemical functionality. Because they lack natural bioactivity, they are often modified or combined with bioactive agents to improve biological performance. Their high tunability makes them ideal for customizable drug delivery systems and tissue-engineering scaffolds (Ho *et al.*, 2022).

Composite hydrogels combine polymer networks with reinforcing materials-such as nanoparticles, ceramics, or fibres-to improve mechanical strength and biological function. Additives like hydroxyapatite or graphene oxide can provide osteoconductive or antimicrobial properties while maintaining flexibility. These polymer-filler interactions create multifunctional hydrogels with performance superior to conventional systems, especially for applications like bone tissue engineering (Hui *et al.*, 2024).

Hybrid hydrogels are created by blending natural and synthetic polymers through physical or chemical crosslinking to combine natural polymers' biocompatibility with the strength and stability of synthetic materials. They can be further enhanced with nanofillers or bioactive groups to adjust degradation and therapeutic performance. Thanks to this versatility, hybrid hydrogels are highly promising for customized biomedical uses, including regenerative therapies and controlled drug delivery (Rana and Siegler, 2024). The distinct advantages and limitations

of natural, synthetic and composite hydrogels used in wound healing are summarized in Table 1.

### Features and Benefits for Wound Healing

Biocompatibility is a key attribute of bioactive hydrogels, allowing them to integrate safely with the body, minimize immune reactions and create a supportive environment for tissue repair (Chelu *et al.*, 2024). By mimicking the Extracellular Matrix (ECM) with their hydrated, three-dimensional polymer network, these hydrogels offer an ideal scaffold that supports cell adhesion, migration and proliferation, ultimately enhancing tissue regeneration (Fan *et al.*, 2021). Another major advantage is their bioactivity, as they can incorporate and release agents like growth factors, antimicrobials and antioxidants. These help regulate the wound environment by preventing infection, reducing inflammation and promoting angiogenesis and collagen formation (Chelu *et al.*, 2024). Their strong moisture-retention ability keeps the wound bed hydrated, prevents scab formation, supports autolytic debridement, allows oxygen flow and helps reduce pain and scarring. Together, these features make bioactive hydrogels multifunctional systems that address the complex needs of wound healing and promote faster, more effective recovery (Fan *et al.*, 2021).

## MATERIALS USED IN HYDROGEL FORMULATION

### Natural Polymers Used in Hydrogel Formulation

Natural polymers from plant, animal, or microbial sources are widely used in hydrogels because of their biocompatibility, biodegradability and close resemblance to native tissues. Classified mainly into polysaccharides and proteins, they offer structural support and essential bio-functionality for biomedical applications (Varghese *et al.*, 2020).

### Polysaccharides of Plant and Animal Origin

Plant-based polysaccharides like cellulose, starch, alginate, guar gum and inu lin are abundant, affordable and eco-friendly. Cellulose provides strong mechanical support and can be modified for biomedical use, while alginate and guar gum form biocompatible gels ideal for wound care and drug delivery. Animal-derived polysaccharides such as chitosan and Hyaluronic Acid (HA) add further functionality-chitosan offers antimicrobial and adhesive properties and HA enhances hydration, ECM mimicry and tissue repair (Hu and Xu, 2020; Gyles *et al.*, 2017).

### Protein-Based Polymers

Proteins like collagen, gelatin, silk fibroin and fibrin are widely used in hydrogels due to their biocompatibility and bioactivity. Collagen supports cell adhesion and tissue regeneration, while gelatin-its thermoresponsive derivative-is ideal for injectable hydrogels and wound dressings. Silk fibroin offers high mechanical strength for scaffolds and drug delivery systems and fibrin provides a natural matrix that promotes cell migration and wound healing, though it degrades quickly (Hu and Xu, 2020).

Natural polymer-based hydrogels are widely used in tissue engineering, wound healing, drug delivery and regenerative medicine because they offer excellent biocompatibility, biodegrade into non-toxic products and mimic the natural cellular environment. However, their drawbacks-such as low mechanical strength and batch-to-batch variability-often necessitate blending them with synthetic polymers or inorganic fillers to create hybrid or composite hydrogels with improved performance (Varghese *et al.*, 2020).

### Synthetic Polymer-Based Hydrogels

Synthetic polymer-based hydrogels are broadly used in biomedical applications because they offer high mechanical strength, chemical stability and slower degradation than natural polymers. Their durability makes them suitable for long-term use and they are often combined with other polymers to tailor specific properties. Commonly used synthetic polymers include Polyacrylamide (PAAm) and its derivatives, Polyvinyl Alcohol (PVA) and Polyethylene Glycol (PEG) (Garnica-Palafox and Sanchez-Arevalo, 2016).

### Common synthetic polymers used in hydrogels include

Polyacrylamide (PAAm) and its derivatives are hydrophilic synthetic polymers capable of forming stable hydrogel networks with tunable physicochemical properties. Through functional modification, PAAm-based hydrogels can exhibit pH- and temperature-responsive behaviour, enabling controlled and stimuli-responsive drug release. Their mechanical stability makes them suitable for smart biomedical and drug delivery applications.

Polyvinyl Alcohol (PVA) is a biocompatible and hydrophilic polymer widely used in hydrogel formulations due to its mechanical strength and flexibility. PVA hydrogels possess interconnected porous structures and can be physically crosslinked without toxic agents, supporting their application in tissue engineering and wound dressings (Taheri *et al.*, 2011).

Polyethylene Glycol (PEG) and Polyethylene Oxide (PEO) are biocompatible, hydrophilic polymers widely used in hydrogel systems and approved for biomedical applications. These polymers form stable hydrogel networks that can be easily functionalized to enhance crosslinking density, mechanical strength, and controlled degradability. Owing to their low immunogenicity and tunable properties, PEG/PEO-based hydrogels are extensively employed in drug delivery and tissue engineering applications (Akhtar *et al.*, 2016; Jung *et al.*, 2007).

**Table 1: Comparative properties of natural and synthetic hydrogel materials used in wound healing studies.**

| Type of Hydrogel | Examples | Reported Advantages | Key Limitations | Reference |
|---|---|---|---|---|
| Natural hydrogel | Alginate, Chitosan, Collagen, Gelatin, Hyaluronic Acid, etc. | Good biocompatibility; mimic ECM; support cell adhesion, proliferation, moisture retention | Variable mechanical strength; fast degradation; batch-to-batch variability | (Cao *et al.*, 2021) |
| Synthetic hydrogel | PEG, PVA, PLGA, synthetic polymers | Tunable mechanical properties; reproducible; stable | Less bioactive cues; may require functionalization for cell interactions | (Ho *et al.*, 2022) |
| Composite / hybrid hydrogel | Blend of natural + synthetic polymers + bio-actives | Combines bioactivity with tunability; can deliver drugs/ agents; controlled degradation | More complex fabrication; potential for phase separation or stability issues | (Hui *et al.*, 2024) |

ECM = Extracellular Matrix; PEG = Polyethylene Glycol; PVA = Polyvinyl Alcohol; PLGA = Poly (Lactic-Co-Glycolic Acid)

## Hybrid hydrogels

Hybrid hydrogels are multifunctional materials that integrate polymers, nanoparticles, or biological components to enhance mechanical strength, functionality and biomimicry. They can be polymeric (improved strength and responsiveness), nanocomposite (added functionality via nanoparticles), or biological (proteins, peptides, or cells for ECM-like behaviour), making them versatile for medical and advanced materials applications (Olteanu *et al.*, 2024).

Hybrid hydrogels are advanced biomaterials combining polymers with nanostructures or bioactive molecules to boost strength, bioactivity and controlled drug release. Nanoparticles like carbon nanotubes or gold enhance stiffness, responsiveness and sustained therapeutic delivery, supporting cell growth and tissue engineering (Palmese *et al.*, 2019).

Hybrid hydrogels' multifunctional, ECM-mimicking structure and tunable, responsive drug release support cell adhesion, migration and growth, making them ideal for targeted therapies, regenerative medicine and disease modelling in conditions like cancer, cardiovascular disease and chronic wounds (Ren *et al.*, 2019).

## Smart and stimuli responsive hydrogels

Self-healing, a key property of natural materials like skin, bone and wood, inspires hydrogels that can repair themselves, expanding their potential in biomedical applications (Wu *et al.*, 2008). Self-healing hydrogels are promising for biomedical applications. Although synthetic hydrogels mimic tissue properties, they often lack natural repair ability. Introducing dynamic reversible interactions allows self-repair via sacrificial bonds that break and reform, using both covalent and non-covalent strategies to enhance mechanical strength and resilience (Bode *et al.*, 2013).

Hydrogels can achieve self-healing via dynamic oxime bonds, reversible hydrophobic interactions, or ionic intercalation, enabling gel-sol transitions, enhanced toughness and strong adhesion (Mukherjee *et al.*, 2015). Stimuli-Responsive ("Smart") Hydrogels respond to environmental cues-temperature, pH, light, or chemicals-by swelling, shrinking, or undergoing phase changes, enabling controlled drug release and dynamic tissue interaction. Thermo-responsive hydrogels (e.g., PNIPAM) gel at body temperature, pH-sensitive hydrogels adjust release based on wound acidity and light-responsive systems allow precise spatiotemporal control. Such multifunctional hydrogels are promising for advanced wound care, tissue engineering and on-demand drug delivery (Chai *et al.*, 2017; Liang *et al.*, 2021).

## Injectable and printable hydrogels (3D, *In situ* forming)

Injectable Hydrogels are delivered as liquids, these hydrogels gel *in situ* via physical or chemical crosslinking, filling irregular defects and providing a hydrated matrix for cell adhesion, migration and tissue repair. They enable controlled release of drugs, growth factors, or cells and their shear-thinning and self-healing properties allow easy injection and structural stability. 3D-printable versions further enhance precision for tissue regeneration applications (Sarvepalli and Kandagatla, 2025; Kondiah *et al.*, 2016).

Printable Hydrogels (Bioinks) are designed for 3D bioprinting, bioinks create tissue-like scaffolds with controlled architecture and cellular organization. They balance printability, mechanical stability and biocompatibility, supporting cell viability during fabrication. Natural, synthetic and composite hydrogels are tailored for extrusion, inkjet, or light-based printing. Layer-by-layer assembly replicates native microenvironments, while stimuli-responsive and self-healing features enhance their functionality in regenerative medicine and tissue engineering (Fang *et al.*, 2023). The major differences between injectable hydrogels and 3D-printable hydrogels (bioinks) are summarized in Table 2.

## CROSS LINKING STRATEGIES

Modern hydrogel fabrication, including chemical/physical crosslinking and 3D bioprinting, allows precise control over porosity, mechanics and degradation for tailored therapies. Functionalization with bioactive molecules or nanoparticles enhances cell interactions, while biomimetic and nanocomposite designs improve strength, bioactivity and antimicrobial function. Multi-stimuli-responsive systems enable on-demand, adaptable therapeutic responses (Karchoubi *et al.*, 2024; Zhang *et al.*, 2021).

Physical crosslinking creates reversible hydrogel networks through non-covalent interactions such as hydrogen bonds, ionic interactions, crystallization, hydrophobic associations and host-guest complexes. Methods like freeze-thaw cycles, pH, or temperature changes enable safe, dynamic gels-e.g., PVA forms elastic networks via crystallization, hydrophobic polymers self-assemble into micelles and cyclodextrin-PEG systems yield stimuli-responsive materials (Liang *et al.*, 2024).

Hydrogen bonding, though weak, is key for hydrogel formation and responds to pH, solvent and temperature changes. Reversible bonds, such as protonated carboxylic acids, create dynamic, self-healing networks, exemplified by poly(N-vinylpyrrolidone)/gallic acid hydrogels in biosensing applications (Zhao *et al.*, 2020).

**Ionic Interaction:** Polyelectrolyte hydrogels form via ionic bonds between multivalent ions (e.g., $Ca^{2+}$, $Fe^{3+}$) and polymers or through electrostatic attraction between oppositely charged chains. These reversible bonds enhance mechanical strength, toughness and self-healing. Chitosan-based hydrogels are a common example, combining structural stability with biological functionality (Yuan *et al.*, 2018).

**Crystallization-based Hydrogels:** Freeze-thaw cycles create crystalline regions in polymer chains that serve as physical crosslinks. In Polyvinyl Alcohol (PVA) hydrogels, repeated cycles strengthen the network and mechanical properties and porosity can be tuned by varying the number of cycles and polymer concentration (Wu *et al.*, 2011).

**Hydrophobic Interactions:** Amphiphilic polymers self-assemble in water, with hydrophobic segments forming micelles that act as physical crosslinks. These hydrogels are ideal for delivering hydrophobic drugs and can respond to environmental stimuli (Lim *et al.*, 2019).

Ex**:** Hydrophobically modified gelatin hydrogels efficiently deliver fibroblast growth factor, enhancing neovascularization (Takei *et al.*, 2020).

### Host-guest interactions

These rely on reversible inclusion complexes between host molecules like cyclodextrins and guest polymers, stabilized by hydrophobic forces, hydrogen bonding, or van der Waals interactions (Ma and Zhao *et al.*, 2015). Their reversible nature provides stimuli-responsive and tunable behaviour, enabling easy functionalization. These hydrogels are well suited for controlled drug delivery, tissue engineering and self-healing systems, offering on-demand release and adaptable mechanics (Mantooth *et al.*, 2019).

**Chemical Crosslinking:** This method forms covalent bonds between polymer chains, creating permanent, mechanically robust hydrogels.

Click chemistry is a common approach, using highly selective reactions-such as Diels-Alder cycloaddition between electron-rich dienes and dienophiles (e.g., furan-based compounds)-to couple

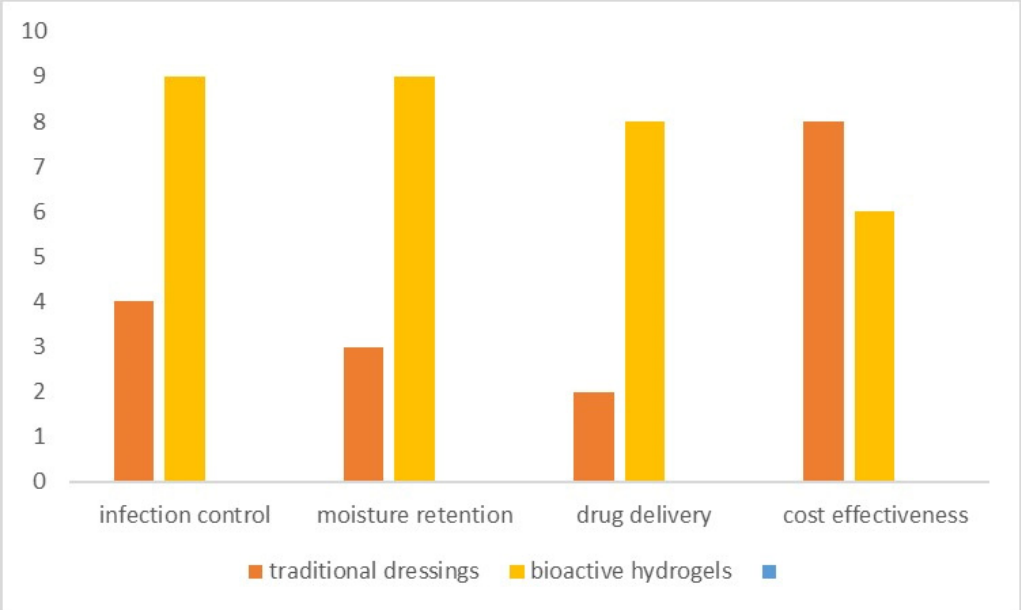



**Figure 1:** Comparison of traditional wound dressings and bioactive hydrogels across key wound-care parameters.

biomolecules and form crosslinked networks. These reactions proceed efficiently under mild conditions and produce minimal byproducts, making them ideal for versatile hydrogel fabrication (Yu *et al.*, 2015).

Schiff base reactions form dynamic imine bonds between aldehyde and amino groups, giving hydrogels reversible crosslinking and self-healing. For instance, alginate dialdehyde crosslinked with acrylamide-modified chitin shows self-repair efficiency depends on substrate ratio and pH (Ding *et al.*, 2015). Injectable hydrogels using Schiff base linkages, like HA-CHO with hydrazide-functionalized poly (γ-glutamic acid), provide good mechanical strength, biocompatibility and adaptability for biomedical use (Ma *et al.*, 2018).

### Oxime Crosslinking

Oxime bonds form when aminooxy groups (e.g., hydroxylamine) react with aldehydes or ketones, creating hydrolytically stable, chemo-selective crosslinks. These dynamic bonds enable reversible gel-sol transitions and self-healing under mild acidic conditions. For example, hydrogels from keto-functional copolymers (P(DMA-stat-AA)) crosslinked with difunctional alkoxyamines produce stable yet reversible networks suitable for biomedical use (Kalia and Raines, 2008).

### Enzymatic Crosslinking

This method forms hydrogels under mild, biocompatible conditions, avoiding side reactions from solvents or photo-initiators. Limitations include high cost and substrate specificity. A common example is the microbial transglutaminase-catalysed acyl-transfer reaction between glutamine and lysine residues (Bhattarai *et al.*, 2010). Enzyme-mediated crosslinking of tyramine-modified polymers like silk fibroin and gelatin accelerates gelation, enhances tensile strength and improves degradation control, making these hydrogels well-suited for cell delivery and tissue engineering (Guo *et al.*, 2012).

## EVALUATION PARAMETERS

### *In vitro* Evaluation Methods

*In vitro* Evaluation of Hydrogels are assessed through physicochemical and biological assays to determine their biomedical suitability. Common methods include:

### Swelling studies

Dried hydrogels were first immersed in pH 1.2 HCl for 2 hr, then transferred to pH 7.4 phosphate buffer for 8 hr. At set intervals, samples were removed, blotted to remove surface water, weighed and returned to the medium until equilibrium swelling was achieved (Lin *et al.*, 2005). The degree of swelling (wt.) at each interval was calculated using the following equation:

$$S = \frac{\text{weight of swollen hydrogel} - \text{weight of dry hydrogel} \times 100}{\text{weight of swollen hydrogel}}$$

### Stability studies

The optimized hydrogel was evaluated per ICH Q1A (R2) guidelines. Samples were stored at 25 °C/60% RH and 30 °C/65% RH for six months and assessed for changes in appearance, drug content, swelling behaviour and drug release profile (Kumar Singh Yadav and Shivakumar, 2012).

### Mechanical testing

Rheological and Mechanical Evaluation of hydrogels are assessed for viscoelasticity, shear-thinning and gelation kinetics, essential for injectable and printable systems. Mechanical strength and elasticity are measured via tensile and compression tests. Dynamic Mechanical Analysis (DMA) evaluates stiffness, toughness and fatigue resistance, while oscillatory shear tests assess network stability under physiological conditions (Chen *et al.*, 2017).

### Microscopic and structural characterization

Hydrogels are analysed using SEM for surface morphology and pore structure, XRD for crystallinity and FTIR for chemical bonds and crosslinking. SEM reveals features affecting swelling, mechanical strength and nutrient diffusion, while XRD and FTIR shifts confirm crosslinker incorporation, polymer network formation and drug-polymer interactions (Ashames *et al.*, 2022).

### Drug loading and Release

Drug encapsulation is quantified using HPLC or UV-Vis to determine the amount incorporated into the hydrogel. Release kinetics are evaluated under controlled conditions (pH, temperature, ionic strength) and modelled (e.g., Higuchi, Korsmeyer-Peppas) to understand diffusion and degradation. Release profiles reflect hydrogel porosity, crosslinking density and drug interactions, guiding optimization of therapeutic performance (Bibire *et al.*, 2024).

### Cell-based assays

Hydrogel cytotoxicity is assessed using live/dead assays with calcian-AM and propidium iodide. Cell proliferation, adhesion and migration studies evaluate biocompatibility and tissue integration potential. MTT, Alamar Blue and BrdU assays quantify metabolic activity and proliferation, while immunostaining and confocal microscopy examine cytoskeletal organization and cell spreading on hydrogel matrices (Canciani *et al.*, 2023).

### *In vivo* evaluation studies

These studies assess hydrogel biocompatibility, biodegradability and therapeutic efficacy under physiological conditions.

### Animal models

Hydrogels are implanted in models like rats, rabbits, or mice at sites such as skin wounds, bone defects, or subcutaneous tissue

**Table 2: Comparison of key characteristics of injectable hydrogels and 3D-printable hydrogels (bioinks).**

| Key Properties | Injectable Hydrogels | 3D Printable Hydrogels (Bioinks) | References |
|---|---|---|---|
| Physical State | Liquid (sol) before injection; gels *in situ*. | High-viscosity liquid or gel (bioink) for extrusion. | (Sarvepalli and Kandagatla, 2025; Kondiah *et al.*, 2016; Fang *et al.*, 2023) |
| Viscosity and Flow | Shear-thinning; becomes less viscous under shear stress (e.g., during injection) and quickly re-gels once stress is removed. | Shear-thinning and thixotropic; must hold its shape after extrusion but flow easily through the nozzle. | |
| Gelation Time | Fast; must solidify quickly in the body to maintain its shape at the target site. | Tunable; must gel fast enough to support subsequent layers but slow enough to allow for continuous printing. | |
| Structural Fidelity | Conforms to irregular defects; suitable for non-uniform geometries. | Enables layer-by-layer fabrication with predefined shapes; less ideal for complex internal geometries. | |
| Cell Viability | High, as cells experience minimal shear stress during injection. | May be affected by extrusion-related shear stress but generally remains acceptable. | |
| Mechanical Strength | Low to moderate, suitable for soft tissue filling. | Can be designed with higher mechanical strength for load-bearing applications. | |
| Key Advantage | Minimally invasive delivery, conforming to irregular tissue defects. | High-precision fabrication of complex, patient-specific scaffolds. | |
| Applications | Localized drug delivery, soft-tissue fillers, cell delivery and regenerative medicine. | Fabrication of tissue scaffolds (bone, cartilage, skin), organ-on-chip models and customized biomedical devices. | |

Gelation time and viscosity are critical determinants of printability and injectability.

to assess tissue response, degradation and regenerative potential (Vo *et al.*, 2015).

### Functional assessments

Hydrogels are assessed via behavioural tests (Ex: motor function in nerve regeneration), wound closure monitoring and biomarker analysis (inflammatory markers, growth factors). Imaging techniques like histology, immunohistochemistry and micro-CT confirm tissue regeneration and integration, while angiogenesis and collagen deposition studies evaluate repair quality and long-term outcomes (Gorenkova *et al.*, 2018).

### Imaging and histological analysis

Techniques like micro-CT, MRI and fluorescence imaging track hydrogel distribution, degradation and effects on tissue morphology. Histology evaluates cell infiltration, inflammation, angiogenesis and tissue remodelling, while confocal/multiphoton microscopy enables real-time hydrogel-cell interaction tracking. Immunohistochemistry identifies specific regeneration and integration markers (Shazeeb *et al.*, 2018).

## FUTURE DIRECTIONS / RESEARCH GAPS

Next-generation hydrogels feature programmable responsiveness, cell encapsulation, immune modulation and infection sensing, expanding applications from wound healing to oncology, orthopaedics, cardiovascular repair and tissue engineering. Clinical trials in cancer, chronic wounds and organ regeneration, together with better regulatory alignment and increased RandD, are accelerating their clinical adoption.

A major challenge in hydrogel research is the lack of standardized testing, making it difficult to compare studies or predict *in vivo* performance from *in vitro* data. Patient variability-differences in immune response, age, comorbidities and wound environment-limits the effectiveness of universal formulations, emphasizing the need for personalized approaches. Additional barriers include complex hydrogel composition, batch-to-batch variability and strict regulatory requirements, all slowing clinical translation.

Personalized and theranostic hydrogels are emerging as next-generation platforms designed for patient-specific, on-demand and real-time therapeutic and diagnostic functions. By combining drug delivery with imaging, biosensing, or immune modulation, these hydrogels enable adaptive, precision therapies for cancer, infections and tissue repair. Similarly, combination therapy hydrogels that co-deliver multiple drugs or integrate cell-based therapies with controlled release provide new strategies to overcome tumour microenvironment barriers




**Figure 2:** Current limitations in hydrogel development and emerging future prospects driven by research and innovation.

and improve outcomes in difficult-to-treat conditions. Despite these advances, several challenges remain in translating hydrogel technologies to clinical practice. Figure 2 highlights the major limitations in hydrogel development, including standardization issues, regulatory barriers and scalability concerns, while also illustrating emerging opportunities such as personalized and theranostic hydrogel platforms. Addressing these gaps is essential for future clinical success.

## CONCLUSION

Bioactive hydrogel composites represent a promising advancement in modern wound management because they address the major limitations of conventional dressings by providing moisture balance, controlled drug release, antibacterial protection and support for cell growth. Their ability to mimic the extracellular matrix, promote angiogenesis, modulate inflammation and deliver therapeutic agents makes them highly effective for acute, chronic and infected wounds. Although challenges remain-including scalability, regulatory requirements and patient-specific variability-ongoing innovations in smart, stimuli-responsive and multifunctional hydrogels are paving the way for their broader clinical translation. Continued research integrating materials science, biotechnology and clinical evaluation will be essential for developing next-generation hydrogels capable of personalized and precision wound therapy.

## SUMMARY

This review highlights recent advances in bioactive hydrogel composites for wound healing, focusing on materials, fabrication strategies and biological mechanisms that promote tissue regeneration. Current evaluation approaches, clinical potential and translational challenges of advanced and smart hydrogel systems are also discussed.

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## ABBREVIATIONS

**ECM:** Extracellular matrix; **PEG:** polyethylene glycol; **PVA:** Polyvinyl alcohol; **PAAm:** polyacrylamide; **PLGA:** Poly(lactic-co-glycolic acid); **HA:** Hyaluronic acid; **PEO:** Polyethylene oxide; **PNIPAM:** Poly(N-isopropylacrylamide); **PDGF:** Platelet-derived growth factor; **TGF-β:** Transforming growth factor-beta; **VEGF:** Vascular endothelial growth factor; **ROS:** Reactive oxygen species; **HIFs:** Hypoxia-inducible factors; **SEM:** Scanning electron microscopy; **XRD:** X-ray diffraction;

**FTIR:** Fourier transform infrared spectroscopy; **HPLC:** High-performance liquid chromatography; **DMA:** Dynamic mechanical analysis; **MRI:** Magnetic resonance imaging; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **ICH:** International Council for Harmonisation; **RH:** Relative humidity; **UV-Vis:** Ultraviolet-Visible spectroscopy; **BrdU:** 5-bromo-2'-deoxyuridine; **micro-CT:** Micro-computed tomography; **RandD:** Research and Development; **TIME:** Tissue, Inflammation/Infection, Moisture balance, and Edge of wound; **PNIPAAm:** Poly(N-isopropylacrylamide).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

S.K.M. and F.S.D. conceptualized and designed the review framework. S.K.M., M.M.Y., H.N.S., A.S., and R.N.H. conducted the literature search and contributed to data compilation and interpretation. P.A., A.G.R., and M.A.U. provided critical inputs on material design, fabrication strategies, and translational perspectives. S.K.M. and M.M.Y. prepared the initial draft of the manuscript. F.S.D. supervised the work, critically edited the manuscript, and acted as the guarantor. All authors reviewed and approved the final manuscript.

## CONSENT FOR PUBLICATION

All authors have read the content of the manuscript and agreed on its submission for publication.

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