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ORIGINAL PAPER

A Review Exploring the Wound-Healing Activity of Self-Healing Hydrogels: Fabrication, Characterization, Mechanism, and Biomedical Applications

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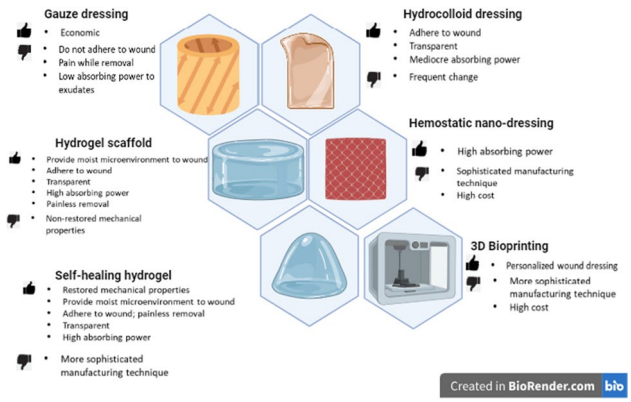
Abstract

The natural physiological response to skin injury is wound healing. However, to restore skin continuity, wound healing is a complicated process that involves the collaboration of a variety of cell types and other mediators. This process ultimately results in tissue regeneration and the restoration of skin barrier function. Hydrogels are appealing dosage forms for biomedical regenerative medicine since they are composed of 3D networks with high water content and flexible rheological features. Hydrogels that can self-heal are particularly interesting for wound treatment because they can autonomously restore their original functionalities and repair structural damage. Recently, the use of self-healing hydrogels as biomedical materials has attracted increased interest. In this review, the self-healing systems used in tissue regeneration, especially wound healing, will be explored. A focus on the fabrication methods, characterization tests, and mechanism of self-healing will be introduced, along with the biomedical applications of self-healing hydrogels loaded with conventional and therapeutic biomaterials. In addition, the differences between hydrogels and self-healing hydrogels will be discussed.

Graphical Abstract



Keywords Wound · Healing · Hydrogels · Self-healing hydrogels · Biomaterial · Skin regeneration

Abbreviations

AD	Adamantyl
Ag NPs	Silver nanoparticles
BBBGN	Borate-based bioactive glass nanofiber
CQDs	Carbon quantum dots
CMC	Carboxymethyl cellulose
CMC-A	Carboxymethyl-aldehyde
CMCS-Hep	Carboxymethyl chitosan-heparin
CMN	Cuttlefish melanin nanoparticles
CMCS	Carboxymethyl chitosan
DDS	Drug delivery system
DFU	Diabetic foot ulcer
DG	Dipotassium glycyrrhizinate

Extended author information available on the last page of the article

DM	Diabetes mellitus
DPPH	1,1-Diphenyl-2-picrylhydrazyl
ECM	Extracellular matrix
FTIR	Fourier transform infrared spectroscopy
GRAS	Generally, recognized as safe
GFs	Exogenous growth factors
GT	Gelatin
HA	Hyaluronic acid
HA-PBA	Phenylboronic acid-modified hyaluronic acid
HE	Healing efficiency
OHA	Oxidized hyaluronic acid
MRSA	Methicillin-resistant *Staphylococcus aureus*
NMR	Nuclear magnetic resonance spectroscopy
NWs	Nanowires
PA	Protocatechualdehyde
PNIPAM	Poly(N-isopropylacrylamide)
1H NMR	Proton nuclear magnetic resonance spectroscopy
rhEGF	Recombinant human epithelial growth factor
ROS	Reactive oxygen species
SA	Sodium alginate
SF	Silk fibroin
SCs	Stem cells
SEM	Scanning electron microscopy
SOD	Superoxide dismutase
3D	Three-dimensional
VEGF	Vascular endothelial growth factor

Introduction

Wound healing is a natural physiological response to tissue damage. Nevertheless, wound healing is not a simple phenomenon. Multiple steps occur between many types of cells and tissues [1]. Wound healing is a complicated and dynamic procedure in which devitalized and missing cellular structures and tissue layers are substituted. Notably, wounds impose great stress on the healthcare system due to the significantly high cost of medical treatment, the pain that patients experience, the possibility of bacterial and viral infections and the physiological and psychological costs of dealing with scars [1]. Wounds may be acute or chronic. An acute wound can be cured in approximately 3 months, depending on its depth and size. Acute wounds can be healed simply by covering the wound and depending on the self-healing mechanism of the body [2]. Nevertheless, chronic wounds can cause severe problems, such as ache, tenderness, fluid drainage and bad odours, and may progress to sepsis and amputation [3]. Chronic wounds include burns, infections, leg ulcers, pressure ulcers (bed sores), diabetic foot ulcers, venous or arterial ulcers and others. They are life-threatening because they do not heal spontaneously or rapidly [2]. In addition, surgical site wound infections are considered one of the significant reasons for illness and mortality in adult and pediatric patients. Surgical site wound infections occur after surgery and can occur at the incision or deep, counting other tissues, organs, or inside the body. By 2022, in inpatient surgery, surgical site wound infections reach 5% and 5.4% in adult and pediatric patients, respectively [4].

Globally, chronic nonhealing wounds influence approximately 8.2 million Medicare recipients. The Medicare cost estimates for all wounds ranged from 28.1 to 96.8 billion USD. In addition, outpatient care costs were 9.9-35.8 billion USD, and inpatient care costs were 5.0-24.3 billion USD [3, 5, 6]. For infection control, surgical wounds and diabetic ulcers are the most expensive to treat [5, 6]. Patients suffering from diabetes and obesity are at high risk of developing chronic wounds. Approximately 33% of the 0.5 billion people with diabetes worldwide will develop diabetic foot ulcers, and half of these individuals will develop an infection. Of these, 17% will require amputation, which is the most destructive and invasive procedure for these people. For patients who do not undergo amputation and who experience graft healing, 40% will experience recurrence within 1 year, 65% within 5 years, and more than 90% within 10 years [3, 6, 7].

For a wound to successfully heal, four extremely involuntary automated overlapping stages must occur. These stages include hemostasis, the inflammatory phase, proliferation, and remodelling, as shown in Figure 1. These stages are essential in this order and within a precise time, and any interference in one or more stages will negatively impact the healing mechanism [2, 8]. Stage (1) is hemostasis, during which the body's natural response to an injury occurs, stopping the bleeding and repairing the damage. Stage (2) is known as the inflammatory phase, and throughout this stage, damaged cells, pathogens and bacteria escape from the injured area. White blood cells, growth factors (GFs), nutrients and enzymes cause swelling, heat, pain and redness to commonly occur during this phase. In stage (3), the temporary wound matrix formed during hemostasis is replaced by granulation tissue, which consists of a large quantity of fibroblasts and other components in complex with collagen bundles and incompletely recovers the wounded skin. Finally, in stage (4), the remodelling stage, in which granulation tissue is converted to a scar, increases the tissue tensile strength [2, 8].

Chronic wounds are challenging to treat due to impaired healing and a tendency to be infected with bacteria. This is especially true if the aforementioned

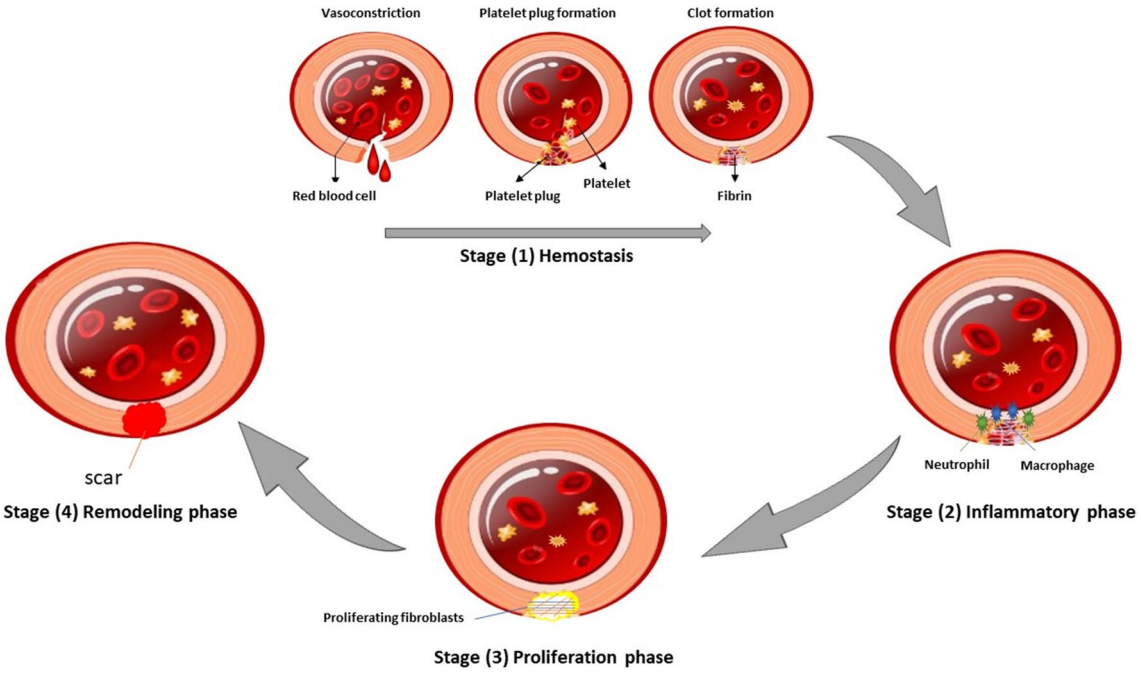


Fig. 1 A schematic illustration showing different stages of wound healing

bacteria are antibiotic resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA). With the increasing incidence of diabetes mellitus (DM) at the global level, chronic diseases and their complications have recently attracted increased amounts of attention; however, one of the most concerning complications, diabetic foot ulcer (DFU), remains a difficult problem to overcome. Studies conducted at the pathophysiological level have concluded that the healing of DFUs is impeded mainly by peripheral vascular disease and diabetic neuropathy. These factors also contribute to chronic inflammation, the prevention of growth factor secretion, and impaired neovascularization. Moreover, severe surgical and traumatic wounds, in addition to complications of DFU, have attracted the attention of researchers seeking to develop several different drug delivery systems (DDSs) to address these different wound types. In this study, we provide an overview of various types of wound dressings, ranging from simple gauze dressings and hydrocolloid dressings to hydrogel scaffolds, self-healing hydrogels, novel resorbable hemostatic nanowound dressings and three-dimensional (3D) bioprinting and soft robots. The materials used to fabricate the dressing, the advantages, the drawbacks and examples of research topics covering the dressing types will be fully discussed. The focus of this review will be on self-healing hydrogels, their advantages over hydrogels, the polymers used, the bonds involved in their formation, the drugs used to promote wound healing and characterization tests supporting their self-healing ability.

Wound dressings

Gauze dressings

The gold standard for minor wound treatment is the application of soft paraffin as an occlusive layer and the use of a frequently changed sterile nonadherent dressing pad or cloth according to the American Academy of Dermatology Association [9]. The choice of the type of dressing depends on various factors, such as the cause, size and depth of the wound; whether the wound is exuding/contaminated; and availability and economic factors [10]. A recent report compared several marketed gauze dressings (Johnson & Johnson, 3 M or Medtronic) in terms of market share and future estimation https://www.alliedmarketresearch.com/gauze-bandages-market [11]. Gauze dressing pads suffer from two main disadvantages: inability to absorb wound exudates and thus inability to adhere properly to the wound tissues and pain during dressing changes.

Hydrocolloid Dressings

These are transparent films formed by the solvent casting technique of hydrophilic polymer solutions such as gelatin, pectin, alginates, or carboxymethyl cellulose. Interestingly, the polymer used for film formation has adhesive power, so it can adhere well to tissues. The advantages of these types of dressings are that they are waterproof and clear, so healing progress can be easily monitored without

removal of the dressing; moreover, the absorbing power of the polymers sets them optimal for mildly oozing wounds [12]. Hydrocolloid dressings are available from several manufacturers, such as Johnson & Johnson and 3 M. However, hydrocolloid dressings cannot handle large-volume exudating wounds, so due to the frequent exchange rate of the dressing, the cost-effectiveness of these products has decreased.

Hydrogel Scaffolds

Hydrogels are 3D networks of hydrophilic polymers that swell but do not dissolve in water. Like hydrocolloid dressings, they are clear, but they have more flexible and malleable structures, enabling them to fill the wound space. Hydrogels are crosslinked polymer chains with 3D structures that can absorb large volumes of fluid. They are similar to living tissue due to their high water content, soft structure, and porosity [13].

Natural polymers (chitosan–alginate–hyaluronic acid (HA)–collagen) [14], semisynthetic materials (hydroxypropyl methyl cellulose) or even synthetic materials (polyvinyl alcohol–polyethylene glycol–carbomer) are used to formulate hydrogels [15]. Hydrogels have many advantages, such as painless removal, absorption of wound exudates and preservation of the moist microenvironment provided by the hydrogel, which accelerates the healing of normal wounds, chronic wounds, and even burns. In addition, the polymeric strands of the hydrogel serve as a scaffold structure, thus promoting cell division and adhesion.

Several studies have used hydrogels as DDSs for wound treatment. Wang, H. et al. loaded 3 essential oils (eucalyptus, ginger and cumin) as antibacterial agents in a physically cross-linked hybrid hydrogel constructed of carboxymethyl chitosan and carbomer 940. In a mouse burn model, these hydrogel systems accelerated wound healing by promoting transforming growth factor-β, vascular endothelial growth factor (VEGF), and epidermal growth factor while diminishing interleukin-6 and tumor necrosis factor-α levels. They concluded that this polysaccharide hydrogel loaded with essential oils has potential for use as a promising dressing for skin burns with excellent antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [16].

Diabetic wounds exhibit a slow healing pattern because the immune system is impaired. This necessitates the use of advanced drug delivery systems as 3D bioprinting materials. Although the cost of stem cells and bioengineering skin substitutes is high, their use is limited to treating large full-thickness skin defects and chronic wounds. Xia, S. et al. fabricated a 3D-printed scaffold using bioink, gelatin methacryloyl and stem cells because of their rapid proliferation rate. Curcumin was incorporated into the system because it has antioxidant activity to mitigate the generation of reactive oxidative species in the diabetic wound milieu and to decrease the apoptosis of stem cells, thus enhancing the survival of stem cells. Gelatin was chosen for the fabrication of the dressing because it comprises amino acids (aspartate, arginine and glycine) that exist in an arrangement that enhances both cell proliferation and attachment. The circular scaffold mesh showed appropriate mechanical properties and was biocompatible, and when tested in an *in vivo* diabetic wound model in mice, it was shown that it had significant healing ability [17].

Hydrogels, however, have some fundamental limitations, such as, low mechanical strength and poor stimulus resistance, "smart self-healing hydrogels", which can mechanically repair themselves when they are ruptured or traumatized, have been developed. Since it may restore its previous mechanical properties through stretchability, injectability, and shape-reformation, it is superior in terms of stability and durability [18].

Self-Healing Hydrogels

Hydrogels that can self-heal are particularly interesting for wound treatment because they can autonomously restore their original functionalities and repair structural damage. Recently, the use of smart self-healing hydrogels as biomedical materials has attracted increased interest, especially those imbedded by natural phytochemicals with antioxidant, antimicrobial and anti-inflammatory activities [19–21]. In addition, they are considered optimum dressings for chronic wounds and immunocompromised patients. This is attributed to the autonomous healing power of the dressing, which prevents the wound from contracting, forms a flexible barrier that fills the wound space and is stretchable and adaptable to any applied mechanical stress. The biomedical applications of self-healing hydrogels loaded with conventional and therapeutic biomaterials are discussed in the following section. Table 1 summarizes the differences between regular and smart self-healing hydrogels [18].

The choice of polymers or crosslinkers used to formulate self-healing hydrogels is undoubtedly one of utmost importance, as not only do they create 3D networks and scaffolds that form the backbone and basis of the formulation, but they also exhibit certain essential properties to which self-healing mechanisms are involved. Furthermore, in some peculiar cases, polymers exhibit desirable effects that can amplify the beneficial effects of added drugs or even endow

new properties, eliminating the need to add certain classes of drugs. The following section discusses various systems that enjoy self-healing power, the polymers used, the cross-linking agent, and the generated bonds. Table 2 summarizes the data of the systems used to fabricate self-healing hydrogels.

Systems Used (Polymers and Cross-Linkers) to Fabricate Self-Healing Hydrogels

Gelatin Methacrylate/Adenine Acrylate/$CuCl_2$

This system was designed by Chen, J. et al. [22]. These authors opted to use gelatin as the backbone of their self-healing gel, as it is a natural, abundant and biocompatible polymer that can be physically and chemically tailored for its intended purpose. Here, gelatin was modified with methacrylic anhydride to gelatin methacrylate to form hydrogels with improved mechanical properties and long-term stability. Adenine and copper chloride ($CuCl_2$) were added to convert this system into a self-healing system, as adenine forms coordinate bonds with Cu^{2+} and carboxylic groups on gelatin and hydrogen bonds with carboxyl groups on gelatin. The hydrogen bonds improved the bioadhesive properties of the formulation as well, thus increasing the overall residence time of the formulation while also better protecting the wound.

Thiol-Modified Poly γ-Glutamic Acid/Oxidized Hyaluronic Acid

Yang, R. et al. [23] proposed a simple yet intriguing hydrogel system with enhanced wound healing activity. The natural polymer thiol-modified poly γ-glutamic acid was chosen for its biocompatibility, biodegradability, and close resemblance to the native extracellular matrix (ECM). Thiol modification was intended to alleviate oxidative stress in the wound microenvironment to further accelerate the wound healing activity of the hydrogel. HA, which is already a component of the ECM, was added to this system to form dynamic covalent cross-links, which amplify the injectability of this formulation to effectively fill and cover deep and irregularly shaped wounds and improve its self-healing ability to autonomously repair any damage to the integrity of the gel protective barrier.

Carboxymethyl Chitosan/Oxidized Dextran

A more specialized self-healing hydrogel system was designed by Li, P. et al. [24] to combat bacterial infections of full-thickness skin wounds, especially those caused by multidrug resistant bacteria where conventional wound dressings are useless. In their study, nanosystems based on biocompatible carbon quantum dots (CQDs) were tested for their outstanding antibacterial activity and ability to combat biofilms. The CQD hydrogel network carrier was synthesized from carboxymethyl chitosan and oxidized dextran via Schiff's base linkage. CQDs augmented the mechanical resistance of the chitosan hydrogels. The overall hydrogel yield was self-healing, and the hydrogel was injectable and had adequate stretchability and compressibility, as well as anti-inflammatory and antibacterial properties.

Catechol-Modified Oxidized Hyaluronic Acid/Aminated Gelatin/Fe^{3+}

This system is quite peculiar in the sense that it does not only utilize reversible physical noncovalent interactions or chemical covalent interactions, to which the self-healing mechanisms of self-healing hydrogels can be attributed; considering that both of these interactions have their own strengths and weaknesses, Yuan, Y. et al. [25] instead opted to merge the two to take advantage of their combined strengths to yield a self-healing hydrogel with superior characteristics by utilizing the quicker bond formation, gelation, and repair speed acquired from physical cross-linking along with the improved mechanical strength and adhesion properties

Table 1: Comparisons between regular hydrogels and self-healing hydrogels [18]

Points of comparison	"Smart" self-healing hydrogels	Regular hydrogels
Resistance to wear and tear	Higher resistance	Lower resistance
Lifespan/longevity	Higher longevity	Lower longevity
Cost	More economic (less frequently replaced)	Less economic (more frequently replaced)
Performance on extremities (Knee, wrist, ankle, etc.…)	More comfortable and flexible	Less comfortable and flexible
Mechanical properties and strength	Restores mechanical properties and exhibits stronger mechanical strength	Nonrestored mechanical properties
Injectability	Good (Due to shear thinning property)	Poor
Drug release	More controlled drug release pattern	Less controlled drug release pattern
Drug leakage	No drug leakage issue	Drug leakage issue (might lead to tissue toxicity)

Table 2: Examples of systems used to fabricate self-healing hydrogels

	Polymer	Cross-linker	Self-healing mechanism	Time for hydrogel to self-heal	Wound healing activity (*in vitro* or *in vivo*)	References
1	Gelatin methacrylate	Adenine acrylate	Covalent bonding/hydrogen bonds/coordination bonds	-	*In vivo* (diabetic mice with full-thickness skin defects)	[22]
2	Thiol-modified poly (γ-glutamic acid)	Oxidized hyaluronic acid	Dynamic covalent cross-linking	1-8 hours	*In vivo* (full-thickness Sprague Dawley rat skin defect model)	[23]
3	Carboxymethyl chitosan	Oxidized dextran	Schiff base linkage	3 hours	*In vivo* (full-thickness rat back wound model)	[24]
4	Aminated gelatin	Catechol-modified oxidized hyaluronic acid/ Fe^{3+}	Schiff base cross-linking/coordination crosslinking	-	*In vivo* (Dorsum female Kunming mice skin wound model)	[25]
5	Adipic dihydrazide modified hyaluronic acid	Benzaldehyde group functionalized poly (ethylene glycol)-co-poly (glycerol sebacate)	Schiff base cross-linking	2 hours	*In vivo* (full-thickness mouse skin defect normal and motion hip joint wound)	[26]
6	Phenylboronic acid modified- hyaluronic acid	Plant derived polyphenol tannic acid	Boronic ester dynamic covalent bond	10-60 minutes	*In vitro* (mouse fibroblast line-L929)	[27]
7	Poly (N-isopropyl acrylamide)/β-cyclodextrin	Hydroxypropyl chitosan/ adamantyl	Reversible cross-linking/ host-guest interactions	-	*In vivo* (mouse full-thickness skin defect model)	[28]
8	Carboxymethyl chitosan-heparin	Carboxymethyl cellulose-aldehyde	Schiff base reaction	-	*In vivo* (Diabetic Sprague Dawley rat model by streptozocin)	[29]
9	Sodium alginate	Gelatin /protocatechualdehyde/ Fe^{3+}	Schiff base or Michael addition/coordination cross-linking/hydrogen bonding	3 hours	*In vivo* (full-thickness skin incision mouse model)	[30]
10	Silk fibroin	Acryloyl-β-cyclodextrin/2-hydroxyethyl acrylate	Host-guest interactions/β-sheet conformation	-	*In vivo* (Female Kunming mice full-thickness skin defect model)	[31]
11	Carboxymethyl chitosan	konjac glucomannan	Schiff base reaction	4 hours	*In vitro* (human umbilical vein endothelial cells) *In vivo* rat-infected wound model	[19]
12	carboxymethylated chitosan	oxidized sodium alginate	Schiff base reaction	10 minutes	*In vivo* full-thickness skin defect model in Sprague Dawley rats	[20]
13	Carboxymethyl chitosan	Oxidized laminarin	Schiff base reaction	1 hour	*In vivo* (Sprague Dawley rats skin flap)	[21]

emerging from chemical cross-linking, which they called physicochemical double-linking. This hydrogel was prepared using catechol-modified OHA, aminated gelatin and Fe^{3+}. Dynamic covalent bonds in the form of imine bonds, which are also referred to as Schiff bases, represent chemical cross-linking, while coordination bonds between Fe^{3+} and catechol, which are a type of noncovalent bond, represent physical cross-linking. This system has also demonstrated integrated antibacterial properties. The end result is a system that is injectable, self-healing, adaptable, combines the strengths of both physical and chemical cross-linking, and biocompatible and has been proven to be a competitive wound-healing formulation.

Benzaldehyde Group-Functionalized Poly(ethylene Glycol)-Co-Poly(Glycerol Sebacate)/Adipic Dihydrazide-Modified Hyaluronic Acid/Cuttlefish Melanin Nanoparticles

It can be argued that wounds situated around areas of the body with frequent movements, such as joints, are much more difficult to heal using traditional methods due to the constant motion causing stress upon the wound dressing, which leads to loss of integrity, compromising the protective barrier and desirable microenvironment. These special conditions require certain features to be present in the wound dressing. The system designed by Li, M. et al. [26] is an

approach for tackling this issue. The main component of this system is adipic dihydrazide-modified hyaluronic acid (HA). A benzaldehyde group-functionalized poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGSB) was chosen for addition to HA. This system is biocompatible and undergoes Schiff base reactions with HA, which converts this formulation into a self-healing formulation that significantly extends the service life of the formulation. The aldehyde group of PEGSB also undergoes Schiff base reactions with the chemical groups of wound tissue, yielding a hydrogel that is self-healing, stretchable, and bioadhesive, making it an attractive choice for wounds with frequent motion. To combat possible bacterial invasions, they opted to incorporate cuttlefish melanin nanoparticles (CMNs) to apply broad-spectrum highly effective photothermal antibacterial agents into their formulation, which causes minimal collateral damage. CMNs also contain catechol groups that endow the hydrogel with antioxidant properties and further improve the adhesiveness of the hydrogel to wound tissue. This makes it a potent and advanced system for healing wounds with frequent motion.

Plant-Derived Polyphenol Tannic Acid/Phenylboronic Acid-Modified Hyaluronic Acid

The system designed by Shi, W. et al. [27] for the management of various types of wounds is unique in that it incorporates phenylboronic acid-modified hyaluronic acid (HA-PBA), which forms a type of dynamic covalent bond known as a boronic ester bond that is not commonly observed in self-healing hydrogel systems. The interest in this specific bond is attributed to its peculiar properties, such as rapid formation without the need for a catalyst, biocompatibility and response to more than one stimulus. These authors reinforced this core by adding tannic acid, which is generally recognized as safe (GRAS) by the FDA and was described as having anti-inflammatory, antibacterial and antioxidant effects in addition to bond formation with HA-PBA, which changes this formulation from a standard hydrogel to a self-healing hydrogel. Silver nanoparticles were added as potent and broad-spectrum antibacterial agents that are released at a sustained and steady rate from the core hydrogel network, and this rate increases in response to increased bacterial activity. This system has proven to be an effective multirole wound dressing that is suitable for a variety of wound types.

Hydroxypropylchitosan/Poly(N-Isopropylacrylamide)/β-Cyclodextrin/Adamantyl

The designers of this system wanted to accommodate special features in their formulation while retaining the required cytocompatibility and biodegradability. Dong Zhu, Y. et al. [28] prepared self-healing hydrogel networks using an intriguing material, namely, poly(N-isopropylacrylamide) (PNIPAM), which is a thermosensitive material that is relevant because the wound temperature is an obvious *in situ* stimulus. By adding hydroxypropyl chitosan, PNIPAM reversibly cross-links with adamantyl acrylate to form a 3D hydrogel network that is thermosensitive and can autonomously heal large cracks that are up to several millimeters wide. The physical cross-linking between β-cyclodextrin and adamantyl (AD) further improves upon this core by increasing the injectability and flexibility of the formulation. The performance of the hydrogel can also be tailored by altering the quantity of AD. Dipotassium glycyrrhizinate was added to augment the antibacterial and anti-inflammatory properties of the formulation. The end result is a wound dressing that is injectable, stretchable and capable of self-healing small cracks as well as large cracks and is adjustable, antimicrobial and anti-inflammatory.

Carboxymethyl Chitosan-Heparin/Carboxymethyl Cellulose-Aldehyde

This system was proposed by Chang, G. et al. [29] for the purpose of assisting with the impeded and delayed healing of diabetic wounds. The purpose of their work was to perform multistep systematic improvement of hostile and inhospitable diabetic wound conditions to render the wound microenvironment more favourable and subsequently allow the release of exogenous growth factors (GFs) from the hydrogel network to function at a controlled steady rate and accelerate wound healing. This was achieved by using carboxymethyl chitosan-heparin (CMCS-Hep). This derivative of chitosan was chosen due to the ability of heparin to bind with GFs and stabilize them against proteolysis. Carboxymethyl cellulose (CMC), which is oxidized into carboxymethyl-aldehyde (CMC-A), was selected for crosslinking with CMCS-Hep via a Schiff base reaction to form the CMC-Hep/CMC-A hydrogel (CMCSH), which mimics native ECM and is also self-healing and injectable. The resemblance of this hydrogel network to the ECM allows it to accommodate the loaded superoxide dismutase and recombinant human epithelial growth factor (rhEGF), retain them and release them at a steady rate. SOD improves the severity of the wound, suggesting that rhEGF induces healing via an injectable, self-healing, biocompatible and safe dosage form.

Sodium Alginate/Gelatin/Protocatechualdehyde/Fe^{3+} Ions

In their work, Liang, Y. et al. [30] investigated polysaccharide systems secreted by marine organisms, such as brown algae, due to their biocompatibility, biodegradability, safety, and adhesiveness and subsequently decided to improve upon these foundations by fixing all of the flaws of these natural systems. The core component of the algae adhesive, sodium alginate (SA), was used in combination with gelatin (GT)

due to the significant interactions between the amino groups and carboxylic groups of SA and GT, which induce a level of cohesion between the two polymers to form the core of the system. GT was specifically chosen due to its special scarcely utilized feature, the phase transition caused by a change in temperature. Aldehyde and catechol containing protocatechualdehyde (PA) and Fe^{3+} ions were added to this core for various reasons: the aldehyde group of PA interacts with the amino groups of GT through either Schiff base reactions or Michael addition interactions, which further improve the mechanical properties and adhesiveness of the preparation and the cohesion between its components. This dual-dynamic crosslinking endows the hydrogel network with injectability, self-healing ability and adhesiveness. The coordination bonds formed between Fe^{3+} and PA support preparation with photothermal antibacterial effects, which allows the exploitation of near-infrared-assisted photothermal antibacterial activity for the elimination of persistent bacteria. The reversibility of adhesiveness due to the aforementioned temperature-dependent adhesion and phase transformation facilitates the removal and repositioning of the preparation when it is improperly administered so that it can correctly seal and cover the wound to accelerate the healing process.

Silk Fibroin/Acryloyl-β-Cyclodextrin/2-Hydroxyethyl Acrylate

In this study, Yu, R. et al. [31] noted the excellent properties of silk fibroin (SF)-based hydrogels and their potential for use as wound dressings. They were interested in properties such as nonimmunogenicity, biocompatibility, long-term stability and biodegradability, and the outstanding mechanical strength of the base-unaltered SF-based hydrogel; however, this material was not without flaws, and its usefulness as an effective wound dressing was limited by its long gelation time, high-temperature-assisted treatment, poor injectability, and absence of self-healing ability. To overcome these drawbacks, they added acryloyl-β-cyclodextrin (Ac-CD) and 2-hydroxyethyl acrylate to form host-guest interactions and β-sheet conformations with SF, affording this system self-healing capability and injectability and enhancing its stability and mechanical performance. Curcumin is certainly a very beneficial drug in wound healing because it has antioxidant and anti-inflammatory effects and induces the healing process through multiple mechanisms; however, it has been described as difficult to treat due to its hydrophobic nature and low stability under physiological conditions. The ability of Ac-CDs to bind and form complexes with hydrophobic compounds allows them to act as drug carriers, which results in the retention and sustained release of curcumin and its proper exploitation for wound healing. The healing power of the preparation was potentiated, and the healing process was accelerated through the use of a versatile self-healing package.

Characterization Tests of Gels

Self-healing hydrogels are an emerging class of polymeric materials capable of autonomously repairing damage through dynamic reversible bonds and interactions. When subjected to external stresses, the crosslinks within the hydrogel network can break and reform, enabling the material to recover its original mechanical properties and structural integrity. Proper characterization of self-healing hydrogels is critical for understanding their healing mechanism and optimizing their design. In addition, the physical properties of the hydrogels affect the release pattern of the loaded drugs within the 3D gel network. These common characterization tests of hydrogels will be discussed briefly in the following section. Special tests to prove self-healability are mentioned below.

Microstructure of the Hydrogels

The detailed 3D structure of the matrix and the surface of the polymeric hydrogels can be visualized using scanning electron microscopy (SEM) after freezing the hydrogel sample. SEM imaging was conducted using a vacuum to prevent scattering of the electron beams. SEM microphotographs can be used to detect the physical properties of hydrogels, such as pore size and distribution, gel porosity, polymeric strand thickness and orientation of the gel matrix [32].

Scanning electron microscopy was utilized by Yang, P. et al. [19] to visualize the pore size of the cross-linked hydrogel system they formulated using carboxymethyl chitosan and oxidized konjac glucomannan. They concluded that loose pores with even and relatively large sizes represent an ideal scaffold network for enhancing cell proliferation and migration.

Mechanical Testing

The mechanical properties of hydrogels are commonly evaluated using a universal testing machine. The mechanical properties can be expressed as the tensile strength, fracture energy and elastic modulus, which determine the recovery of fracture energy for hydrogels according to the ASTM D638 standard [33].

The mechanical response of a hydrogel to applied stress is a good indication of how the hydrogel system will behave in the body and is also reflected in its tissue regeneration performance. Yang, R. et al. [23] concluded that the type of polymer and its concentration affect the mechanical properties of the produced hydrogel system. They deduced a direct relationship between the polymer concentration and

the compressive modulus of the hydrogel. They used an HA polymer cross-linked with poly γ-glutamic acid. Their results showed that when the polymer weight percentage increased from 5 to 15%, the hydrogel compression strength increased from 0 to 0.11 ± 0.034 MPa. They reported that this mechanical strength value was suitable for wound healing applications. Moreover, the cross-linking of HA by poly γ-glutamic acid via H-bonding enhances the mechanical properties of the hydrogel system.

Rheological Analysis

Rheological measurements are widely employed to investigate the viscoelastic characteristics and gelation behavior of hydrogels using different types of rheometers: Couette type, cone-and-plate type, Poiseuille type, or plate-and-plate type [34].

In their study, Yang, R. et al. [23] analysed the rheological behaviour of a hydrogel system of HA cross-linked by poly γ-glutamic acid by measuring the energy storage modulus (G') and the loss modulus (G'') to deduce the critical point of sol-gel transformation. The strain amplitude sweeps curves exhibited a plateau for (G') and (G'') at all polymer concentrations, and the linear viscoelastic domain calculated by the ratio of (G')/(G'') >10 confirmed the stability of the 3D hydrogel network. The increase in the shear storage modulus and the shear loss modulus with increasing frequency verified the reversible cross-linking of the hydrogel polymer strands.

Swelling Index

The swelling index of a hydrogel is an important criterion because it measures the ability of the hydrogel to absorb wound exudates before it disintegrates or loses its matrix. Briefly, the weight of the freshly prepared hydrogel sample was measured (W_1), after which the hydrogel was immersed in distilled water for a certain time. Throughout the experiment, the hydrogel was removed and dried, after which the new weight was recorded (W_2). The swelling index was calculated as follows in equation (1) [34]:

$$Swelling\ index = \frac{(w_2 - w_1)}{w_1} \tag{1}$$

In a study performed by Yang, P. et al. [19], the authors used konjac glucomannan, which has high hydrophilicity, and confirmed that the hydrogels developed favourable water absorption characteristics. The hydrophilicity and swelling properties of the formulated hydrogels were assessed by examining the swelling rate of the hydrogels in phosphate-buffered saline. The results of the experiment showed good swelling performance of the hydrogel system. As the concentration of the gelator forming the hydrogel increases, the swelling rate of the hydrogels decreases, which is connected to the decrease in the number of hydrogel pores after intensive cross-linking of the hydrogel 3D network at high gelator concentrations. In addition, a study designed by the authors on the hydrogels with different polmer concentrations revealed that hydrogels degraded faster at low polymer concentration that reached 80% after 16 hours.

Moisture Content

Hydrogels provide a suitable moist microenvironment for trauma healing; hence, the water content of hydrogels is an important parameter for the tissue regeneration process. The mass of the freshly prepared hydrogel was recorded as m_1 using an electric balance. After freeze-drying (to remove all water), the gel sample was reweighed m_2, and the water content was calculated as follows in equation (2): [35]

$$C = \frac{(m_1 - m_2)}{m_1} \times 100\% \tag{2}$$

Together, the swelling index and water content of a hydrogel system are correlated with the type and concentration of the polymer used, in addition to the degree of cross-linking of the polymer strands. Hydrogel systems of HA cross-linked by poly γ-glutamic acid swiftly swelled during the first 5 minutes, attaining equilibrium in terms of water content afterwards. Similar to the swelling index, the water content of the hydrogels decreased with increasing polymer concentration [23].

Special Characterization Tests to Ensure Self-Healability

The healing power of self-healing hydrogels must be evaluated by determining their ability to autonomously repair themselves via reversible chemical or physical bonds. This approach is crucial for ensuring the suitability of the system for use as an effective dressing for wound healing purposes. The ability of a polymer system to form reversible chemical bonds can be assessed through spectroscopic and X-ray methods [36].

Spectroscopy Methods

Spectroscopic analysis techniques, such as Fourier transform infrared (FTIR), Raman and nuclear magnetic resonance (NMR) spectroscopy, can validate the presence of reversible bonds and the type of interactions in self-healing hydrogels [36]. FTIR spectroscopy involves a wide range of analyses, ranging from small molecules to more complex structures, such as cells and tissues. FTIR spectroscopy is a fast, sensitive and nondestructive method for analysis. In infrared

tests of molecular vibrations, each functional group has a significant absorption band that corresponds to the nature of the functional group. This approach is helpful for determining the formation of reversible bonds after the incision and healing of the hydrogel by comparing the IR spectra of the hydrogel before and after the incision test. In the case of supramolecular hydrogels, FTIR can be utilized to study the noncovalent bonds responsible for hydrogel gelation, which can be achieved by repeating the experiment at different time intervals [36].

Yang, P. and coauthors [19] utilized FTIR analysis to verify the cross-linking between carboxymethyl chitosan and oxidized konjac glucomannan. The oxidation of konjac glucomannan ensures successful cross-linking and thus the formation of self-healing hydrogels. When the authors compared a lyophilized sample of konjac glucomannan and its oxidized form, the deduced FTIR spectrum of konjac glucomannan showed a peak at 1745 cm^{-1} corresponding to the C–O stretching vibration of the acetyl group, whereas the spectrum of the oxidized form displayed a peak at 1730 cm^{-1} corresponding to the available aldehyde group and another peak at 890 cm^{-1} corresponding to the oxidation of konjac glucomannan.

In their study, Shi, W. and coauthors, [27] synthesized a hyaluronic acid-phenylboronic acid polymer conjugate by attaching the phenylboronic acid polymer to HA via an amide bond using 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydroxybenzotriazole as the coupling agent. They proposed this system with or without encapsulated silver nanoparticles. The authors analysed their proposed system by proton nuclear magnetic resonance (1H NMR), and the results showed more than 95% conjugation. The results showed that rapid gelation occurred between the proposed system and tannic acid solution when mixed due to complexation between the phenylboronic acid group of the system and the catechol and gallate groups of tannic acid. The addition of tannic acid provided green synthesis of silver nanoparticles due to the reducing power of tannic acid [27].

In this study, Chen, J., et al., suggested the use of different models of gelatin-based self-healing hydrogels complexed with Cu^{2+} ions for antibacterial effects as wound dressings for diabetic wound healing. Gelatin (enzymatically degraded natural protein and absorbed by the body) was modified by the addition of methacrylic anhydride, and upon the application of 1H NMR for analysis, the modified gelatin methacrylate exhibited two characteristic peaks at 5.3 ppm and 5.6 ppm, corresponding to acrylamide double bonds, indicating that the double bond was successfully attached to the gelatin molecule. Adenine (an adhesion molecule that enhances long-term adhesion of the wound dressing and long-lasting protection of the wound) was modified by acryloyl chloride, which resulted in a new absorption band in the FTIR spectrum of acrylated adenine at 1660 cm^{-1} assigned to double bonds and was absent in the FTIR spectrum of adenine only [22].

Yang, R. and coworkers [23] designed a system of γ-poly(glutamic acid)/cysteine/oxidized hyaluronic acid (OHA). The synthesis depends on a dynamic covalent cross-linking hydrogel dressing based on joining γ-poly(glutamic acid) polypeptide with cysteine. This reaction involved carbodiimide coupling between the carboxyl group of γ-poly (glutamic acid) and the amino group of cysteine. The reaction was assessed with 1H NMR and FTIR, which revealed two peaks at 2.8 ppm and 3.4 ppm and a new -SH stretching peak at 2562 cm^{-1}, respectively. In addition, the peaks at 1560 cm^{-1} and 1670 cm^{-1} are attributed to amide II and amide I bonds, respectively, which indicate γ-poly(glutamic acid) and cysteine bonding. The OHA was evaluated by the appearance of a specific peak at 1730 cm^{-1} in the FTIR spectrum representing the aldehyde group formed by oxidation of the proximal hydroxyl group in HA, in addition to an additional chemical shift at 4.8–5.4 ppm in the 1H NMR spectrum of hemiacetals from aldehyde groups [23].

Mechanical Healability

Self-healing properties can also be ensured by mechanical testing to ensure durability and how well mechanical properties can be restored after exposure to damage. There are many factors to consider in terms of time dependency and healing efficiency, such as the polymer type, the polymer concentration, the type of cross-linker, the concentration of the cross-linker and the nature of the formed bond. This can be tested by tension and compression tests to determine the macrolevel self-healing properties, where the hydrogel system can be sliced in half and these 2 halves of the hydrogel are positioned in close contact. After a certain period of time and under ambient conditions, the two hydrogels were examined to monitor their healing into a complete hydrogel. The extent of healing and the restored mechanical properties can be calculated as described in equation (3) by the healing efficiency equation, which compares the properties of the gel before and after damage repair: [36]

$$Healing\ efficiency\ (HE) = \frac{Mechanical\ value\ healed}{Mechanical\ value\ initial} \times 100\% \quad (3)$$

An interesting study to detect the self-healability of hydrogel systems of HA (10%) cross-linked by poly γ-glutamic acid after cutting by visual means. Briefly, two samples of the hydrogel, one sample coloured with Brilliant Blue and the other with Allura Red, were cut into two halves, and the two dissimilar coloured parts were placed alongside the cut-line under ambient conditions. The results of the study showed that the different coloured hydrogel samples completely healed into one mass after 1 hour. The authors

attributed this autonomous healing process to the dynamic covalent cross-linking of the thiol-aldehyde groups in the 3D polymeric network of the hydrogel. Interestingly, as the number of cuts increased in the hydrogel sample, the self-healability extended to 3 and even 8 hours. In the end, researchers utilized tensile strength testing to validate the restored mechanical properties of the reformed hydrogel sample to confidently propose this hydrogel system as a superior wound dressing [23].

Figure 2 shows the results of the experiments confirming the self-healing and mechanical characterization of the hydrogels with the appropriate devices.

Loaded Drug Molecules

The role of the loaded therapeutic molecules in the process of wound healing is as important as the role of the hydrogel systems discussed earlier. Therefore, this section will focus on the drugs loaded in various self-healing hydrogels, the natural source, the therapeutic dose, the mechanism by which they promote tissue regeneration and the experimental confirmation of their healing ability. Table 3 lists the therapeutic molecules loaded in various self-healing hydrogels, the natural source, the therapeutic dose, the mechanism by which they promote tissue regeneration and the experimental results confirming the healing power of the hydrogels.

Taurine

In their study, Zhou, Z. et al. [37] incorporated taurine, which has strong anti-inflammatory properties, into a novel *in situ* self-healing hydrogel. Standard hydrogels, such as gauze, replace traditional diabetic wound dressings due to their ability to absorb wound exudates while maintaining their integrity. This difference is ascribed to the complex cross-linked polymer scaffold structure of these materials. Moreover, the excellent moist environment provided by these materials supports the wet healing theory, where a moist environment surrounding the wound helps in cell migration and blood vessel regeneration. The authors also opted to augment their hydrogel by adding carboxymethyl chitosan (CMCS) and OHA to promote wound healing in diabetic wounds. In addition to its self-healing property, this formed hydrogel is also pH responsive, indicating that the increased acidity of the diabetic wound enhances taurine

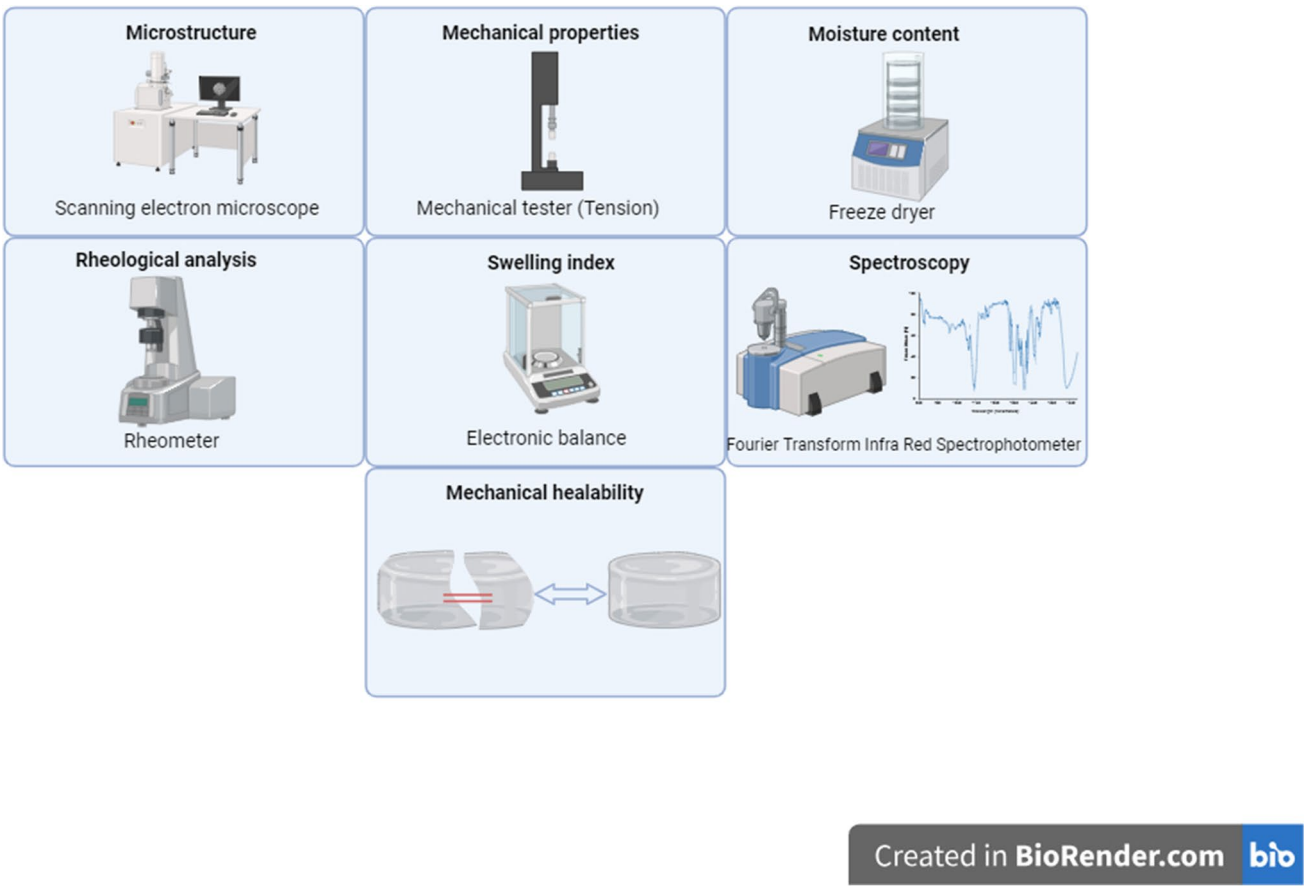


Fig. 2 Diagram of characterization experiments confirming the self-healing and mechanical properties of hydrogels with the appropriate devices

Table 3: Collective table of therapeutic molecules loaded in various self-healing hydrogels; the source if natural; the therapeutic dose; the mechanism by which they promote tissue regeneration; and the experimental results confirming the healing power of the hydrogels

	Drugs	Origin if natural	Dose in wound healing	Mechanism of wound healing	Wound healing activity	References
1	Taurine	bile of ox	8 mg	Anti-inflammatory properties	*In vivo*	[37]
2	Tobramycin	Streptomyces tenebarius	-	Broad spectrum bactericidal activity	*In vitro*	[38]
3	Silver nanoparticles	-	1 mg/mL	Broad spectrum bactericidal activity	*In vitro*	[27]
4	Insulin	Animal pancreas	1 U	Re-epithelialization Pro-angiogenesis Collagen deposition	Both *in vitro* and *in vivo*	[39]
5	Bone marrow mesenchymal stem cells	1-week-old Sprague−Dawley rats	3 or 4 passages	Secretion of growth factors Vascularization Re-epithelialization	*In vivo*	[40]
6	Dipotassium glycyrrhizinate	Licorice root	-	Antibacterial Anti-inflammatory	*In vivo*	[28]
7	Super oxide dismutase\ recombinant human EGF	-	-	ROS scavenging Vascularization	Both *in vitro* and *in vivo*	[29]
8	Metformin/ curcumin	Curcuma longa (for curcumin)	25 mg of curcumin 2 mg/mL metformin	ROS scavenging Pro-angiogenesis Anti-inflammatory	*In vivo*	[41]
9	Berberine/exosomes	Berberis, phellodendron (for berberine)	1.0 mg/mL of berberine	Antibacterial Angiogenesis Anti-inflammatory	*In vivo* and *in vitro*	[19]
10	Curcumin/tannic acid/ zinc ion	Curcuma longa (for curcumin)	-	Antibacterial Angiogenesis Anti-inflammatory	*In vivo* and *in vitro*	[20]
11	Laminarin/chitosan/ Ceria nanozymes	-	-	Angiogenesis Anti-inflammatory	*In vivo*	[21]

release from the hydrogel. Zhou, Z. et al. demonstrated that the anti-inflammatory properties of taurine led to the suppression of cytokine production, thus increasing the favourability of the wound microenvironment for fresh tissue generation and promoting cell migration and accelerating wound healing in diabetic rats.

Tobramycin

Huang, Y. et al. [38] loaded tobramycin into a self-healing hydrogel composed of quaternized chitosan, oxidized dextran and polydopamine-coated polypyrrole nanowires (NWs) for use as a novel dressing for burns. Oxidized dextran forms a Schiff base, which cross-links with tobramycin, allowing its pH dependent, slow release. The acidic medium in the tissue milieu provided by the bacterial exudates controls the release of tobramycin, thus preventing the overconsumption of antibiotics. The results of the *in vitro* experiment obtained from this study demonstrated that this tobramycin dressing was effective against *Staphylococcus aureus*, *Escherichia coli,* and *Pseudomonas aeruginosa* for more than 11 days, making it an attractive choice even for the most heavily contaminated wounds. In addition, the use of photothermally activated NWs enhances the antibacterial activity of the dressing, especially against drug-resistant bacteria. In addition, quaternized chitosan and oxidized dextran showed antioxidant properties, thus leading to a reduction in tissue inflammation, the induction of collagen deposition, vascular regeneration and more rapid wound closure.

Tannic Acid-Silver Nanoparticles (Ag NPs)

Although many types of hydrogels that carry a wide range of antibacterial agents can effectively combat infections caused by normal bacteria, they are ineffective against drug-resistant strains of MRSA. For this reason, Shi, W. et al. [27] formulated injectable, self-healing hydrogels fortified with Ag NPs. Their reported results demonstrated outstanding antibacterial activity against both gram-positive and gram-negative bacteria and even MRSA. Despite the promising results demonstrated by the Ag NPs, the healing of chronic

wounds was still hampered. The explanation for this difference was the elevated levels of reactive oxygen species (ROS), which rendered the microenvironment of the wound hostile and unsuitable for cell migration and proliferation. To overcome this, the authors introduced tannic acid, which is an antioxidant and ROS scavenger, into their formulation, consequently improving the rate of wound healing. Another advantage of the designed system is its pH dependence and ROS responsiveness, which means that increased bacterial proliferation leads to increased release of Ag NPs.

Insulin

The current treatment strategy for DFU involves protecting wounds against bacterial infection and providing a moist environment [39]. Recently, insulin was shown to play a role in wound healing, as it not only induces re-epithelialization by promoting the migration and multiplication of keratinocytes but also accelerates angiogenesis, suggesting that insulin is a good choice for treating DFU. However, the topical application of insulin faces many challenges, such as a cut-off molecular weight for the stratum corneum, a short half-life and quick loss of activity due to the acidity of the wound microenvironment and increased prevalence of peptidases. Li, Z. et al. [39] loaded insulin into a novel self-healing gel composed of N-carboxyethyl chitosan, hyaluronic acid–aldehyde, and adipic acid dihydrazide. These findings support the advantages of conventional hydrogels in addition to the improved mechanical properties achieved by repairing the hydrogel itself following the application of any external stimulus. This property allows the hydrogel to be injectable and pH responsive while sustaining insulin release.

Bone Marrow-Mesenchymal Stem Cells

Bai, H. et al. [40] designed a novel delivery system to treat DFUs enclosing bone marrow mesenchymal stem cells (SCs). SCs enjoy valuable wound-healing properties, as they differentiate into various types of cells and secrete growth factors vital for wound healing, hence inducing vascularization and re-epithelialization. However, protease-rich and chronically inflamed conditions in the wound environment can lead to the formation of a hostile milieu for SCs. To overcome this problem, Bai, H. et al. [40] incorporated SCs into the same self-healing hydrogel system previously described [39] as a new type of therapy called combination therapy. This designed treatment led to a significant reduction in inflammatory mediators released extensively by macrophages in the wound microenvironment. This anti-inflammatory effect renders the wound microenvironment more favourable and less hostile to SCs, allowing them to proliferate and differentiate into new blood vessels and deposit collagen. These findings were supported by *in vivo* experiments conducted on a diabetic rat model.

Dipotassium Glycyrrhizinate

Dipotassium glycyrrhizinate (DG) was incorporated into self-healing hydrogels designed by Zhu, D. et al [28]. DG has dual-action, anti-inflammatory and antimicrobial properties, especially against antibiotic-resistant bacteria. Zhu, D. et al. used derivatives of both acrylamide and chitosan to form self-healing hydrogels with excellent *in situ* injectable features, making them the system of choice for wound dressings for various types of skin injuries. *In vivo* studies conducted on a mouse full-thickness skin defect model proved the superiority of this designed system to traditional marketed wound dressings and that this system is considered a promising candidate for wound dressings in the future.

Superoxide Dismutase/Recombinant Human Epidermal Growth Factor (EGF)

The impeded healing process of diabetic wounds can be attributed to two main factors: inadequate regeneration of new blood vessels and insufficient levels of GFs. This occurs due to oxidative stress resulting from the reduced expression of the metalloenzyme superoxide dismutase (SOD), which scavenges ROS. Decreased expression of the SOD enzyme leads to an increase in O^{2-} and subsequent apoptosis of migrating cells and destruction of epithelial growth factor, which is vital for wound healing. The previously discussed conditions necessitate the use of exogenous GFs. The dual inclusion of both SOD and recombinant human epidermal growth factor (rhEGF) by Chang, G. et al. [29] in an injectable, self-healing hydrogel system enhanced the healing of chronic wounds. The uncontrollable release of EGF, together with the short half-life of EGF, causes frequent changes in the dressing. To solve this problem, Chang, G. et al. incorporated heparin, which moderately binds to rhEGF, into their system to not only protect rhEGF against proteolysis but also control its release at a desirable sustained rate. The self-healing hydrogel system provides a moist environment, absorbs exudates and protects against bacterial contamination. This property makes the injectable, self-healing hydrogel system suitable for wound healing in diabetic patients.

Metformin/Curcumin

In their work, Tan, W. et al. [41] incorporated both metformin and curcumin into mesoporous polydopamine NPs (MPDA NPs) in a self-healing hydrogel system for the treatment of diabetic wounds. The accumulation of ROS, the prevention of migrating cells from preforming their functions, and the destruction and alteration of vital GFs disrupt

angiogenesis and delay the healing of diabetic wounds. Strong antioxidants, such as metformin and curcumin, which are loaded in nanosystems, help to restore the balance between O^{2-} formation and scavenging. Moreover, both metformin and curcumin have anti-inflammatory effects. In addition, metformin, along with the enhanced utilization of glucose in the wound microenvironment, led to the induction of angiogenesis, which provided the migrating cells with oxygen and nutrients to proliferate and differentiate. However, dual loading of these two drugs does not protect wounds against the most severe threat to diabetic wounds, which can be bacterial infections; this protection might become more complicated if the aforementioned bacteria are multidrug resistant. This could lead to limb amputation or even mortality. The incorporation of chitosan into self-healing gels provides them with integrated antibacterial properties. To summarize, this self-healing preparation not only protects against wounds and eliminates bacterial infections but also improves the condition of the wound and accelerates the process of wound healing, as proven by an *in vivo* study conducted on a streptozotocin-induced diabetic rat model.

Antioxidant Activity

The antioxidant power of the biomaterials components of self-healing hydrogels enables them to scavenge the overexpressed ROS in the trauma microenvironment and hence protect the damaged tissue from the deleterious effect of the oxidants that hinder the wound healing process. Conventionally, antioxidant activity is determined using 1,1-diphenyl-2-picrylhydrazyl (DPPH), which is known for its powerful free radical scavenging ability, as a reference. Briefly, the absorbance of the methanolic DPPH solution was initially measured using a UV−VIS spectrophotometer at 517 nm, the absorbance of DPPH was then redetermined after the hydrogel sample was added, and finally, the DPPH scavenging ability was calculated using the following equation [23]:

$$\text{DPPH scavenging } \% = (\text{A0} - \text{A1})/\text{A1} \times 100 \quad (4)$$

where A_0 is the absorbance of the blank (methanolic DPPH solution) and A_1 is the absorbance of the sample (methanolic DPPH solution + hydrogel sample).

Ju, Y. et al. [20] used another experimental model to assess the antioxidant activity of their hydrogel system. The cells were incubated in 48-well plates with 2 types of cells—human umbilical vein endothelial cells and human skin fibroblasts—with a nanohydrogel system composed of carboxymethyl chitosan/oxidized SA cross-linked via Schiff base reactions and loaded with curcumin-tannic acid-zinc ion nanospheres for 8 hours. Then, hydrogen peroxide was introduced for oxidative stress induction in the aforementioned cells. Afterwards, a fluorescent dye (dichlorodihydrofluorescein) was added, and fluorescence images were captured using a fluorescence microscope. Initially, dichlorodihydrofluorescein is nonfluorescent by itself, but upon generation of ROS, green fluorescence is produced within the cells. The results of the study highlighted the superior antioxidant power of this system and ascribed this to the presence of curcumin and tannic acid, which are rich in polyphenols with antioxidant activity.

Antibacterial Activity

Upon wound infection, the subsequent inflammation of the tissues around the wound and the release of inflammatory mediators may either interrupt proper healing or worsen, possibly leading to severe systemic bacterial infection. Recent research has concluded that wound dressings that exert antibacterial effects appear to be valuable. A self-healing hydrogel system of carboxymethyl chitosan crosslinked with Konjac glucomannan and loaded with berberine and exosomes was shown to be effective against *Escherichia coli* and *Staphylococcus aureus*. This was attributed to the carboxymethyl chitosan polymer and the loaded berberine [19].

Biocompatibility Experiment

It is desirable to fabricate wound dressings with high biocompatibility and low cytotoxicity; thus, the choice of hydrogel components should be highly important. The use of natural biomaterials, whether polymers are used to form hydrogels or loaded drugs, ensures the formation of safe and biocompatible wound dressings. In a recent study, hydrogels of two crosslinked natural polysaccharides, carboxymethyl chitosan and oxidized konjac glucomannan, were loaded with two biomaterials, berberine and exosomes, to guarantee good biocompatibility of the hydrogel system with wound tissue. The high percentage of cell viability in the cytotoxicity assay using human umbilical vein endothelial cells following incubation with the hydrogels via the cell counting method proves the safety and biocompatibility of the hydrogel system [19].

Wound Healing Activity (in vitro and in vivo models)

The performance of self-healing hydrogels as promising wound dressing treatments should be assessed. The wound healing activity of these hydrogels can be validated either *in vitro* or *in vivo* using suitable animal species. The different cell culture methods, the induced wound models and the mechanism of action of tissue regeneration are discussed in the following section.

Li, P. et al. [24] used the nanoform CQDs of gentamicin sulfate in a polymeric (CMCS and dextran) self-healing

hydrogel system for treating an infected wound model. The anti-inflammatory and antibacterial activities of this system were assessed in male rats with induced wounds 1.0 cm in diameter on their backs that were infected with *S. aureus*. The rats were randomly divided into 3 groups: a control group (nonmedicated hydrogel), a commercial hydrogel dressing group, and a designed medicated hydrogel group. The results showed that the medicated hydrogel group was superior among all the treatments and exhibited the fastest healing rate (98% after 10 days). Histopathological examination of the tissues around the wounds in the medicated hydrogel group revealed high regularity of the epithelium and connective tissues, increased fibroblast and collagen content, decreased inflammatory cells, and increased blood vessel and hair follicle counts. The indicated hydrogels promoted wound healing by increasing the thickness of the granulation tissue and increasing collagen deposition. Moreover, when the bacterial count decreased to a minimum, biofilm formation was prohibited by 93.6% around the wound tissue treated with the medicated hydrogels. The authors attributed this boosted antibacterial and antibiofilm activity to the cationic charge of the polymeric hydrogel, which neutralized the negative charge and the subsequent acidic microenvironment of the bacterial membrane.

Li, L. et al. [42] examined the wound healing power of a fabricated hydrogel system composed of CMC, an adipic dihydrazide, and a poly(ethylene glycol) derivative loaded with ciprofloxacin in both a hemorrhaging liver model and a full-thickness skin defect model in male Sprague–Dawley rats. The liver-hemorrhage model was generated by an abdominal incision via a 10 G needle, whereas a 6-mm-diameter full-thickness skin lesion was introduced on the shaved back of the rats. The results of the liver-hemorrhage model demonstrated the excellent hemostatic power of the ciprofloxacin hydrogel system, as indicated by the 5.6-fold decrease in the amount of bleeding compared to that in the control group (wounds treated with commercial dressing). The researchers explained that the adhesion strength (24 kPa) of the hydrogel to the skin was sufficient to hold the gel solution to the wound tissues, allowing the hydrogel to flow and fill the irregular cavities of the wound, which, after a few seconds, changed to a sol-to-gel process. Together with the hydrophilic nature of the hydrogel, which maintained a continuous moist environment to encourage wound healing, the rapid release of ciprofloxacin, which has antibacterial effects, provided excellent conditions for wound healing without infection. Histomorphological analysis of skin wound tissues from the ciprofloxacin-treated group revealed significantly fewer inflammatory cells, new thicker granulation tissue, new epidermis, and a few new blood vessels than did those from the control group.

As mentioned before in section "Loaded drugs; self-healing hydrogel with metformin and curcumin", Weiwei et al. [41] designed dual curcumin- and metformin-loaded nanocomposite polysaccharide-based self-healing hydrogels and assessed their wound healing ability using a streptozotocin-induced diabetic rat model. Briefly, the authors first induced a type I diabetes model in male Sprague−Dawley rats via the use of streptozotocin. Then, 4 cuts were made on the dorsal skin of the rats, each measuring 1 cm. Afterwards, the rats were divided into 4 groups: one group was treated with changeable sterile gauze, 3 M Tegaderm™ dressing, nonmedicated hydrogel, and medicated hydrogel. In the other negative control group, the wounds were wrapped with sterile gauze. Finally, the regeneration power was assessed by analysing the wound images over 2 weeks. After 14 days, histomorphological and immunohistochemical assessments of the fresh wound tissues proved that the designed curcumin and metformin hydrogel system enhanced re-epithelization, granulation, collagen deposition and angiogenesis during diabetic wound healing. In addition, the *in vitro* cytotoxicity of these hydrogels was evaluated by a CCK-8 assay, which confirmed their biocompatibility.

Figure 3 summarizes the hurdles at which the wound can heal.

Resorbable Hemostatic Nanowound Dressings

The shift to the use of resorbable nanowound dressings with hemostatic properties is gaining interest. Nanosystems have a high surface-to-volume ratio and thus display unique physicochemical properties that are useful in the field of reconstructive medicine, especially when scaffolds are used as cell carriers.

Using a spray-drying technique, Szymonowicz, M. et al. [43] designed a complex dressing based on nanofibers of chitosan, SA and CMCSs. The ability of this multiresorbable wound dressing model to rapidly activate the clotting process and enhance hemostatic properties enables this system to be used in cases of deep or severe bleeding wounds. This system enjoys the unique feature that when in contact with whole blood/plasma, it rapidly absorbs fluids and changes from powder to an amorphous gel form [43].

Another study was conducted by Armstrong, D. et al. [44], who noted the superiority of a cost-effective resorbable borate-based bioactive glass nanofiber (BBBGN) matrix for treating DFUs within 12 weeks; these ulcers failed to heal properly while using other conventional medicaments. The results obtained in this study demonstrated that a faster wound closure rate was attained even after the very first week of treatment using the BBBGN matrix. The authors even suggested that the BBBGN dressing might also reduce the incidence of wound infections, including MRSA

Fig. 3 Hurdles to the wound healing process

infection. In addition, it improved neurosensation in approximately 40% of the 40 patients were included in the study [44].

Recently, the ability of nanomembranes fabricated using the natural and biodegradable polymer polyhydroxyalkanoate, ranging from 2-8 w%, to regenerate tissue by electrospinning has been proven. The physical and mechanical properties of these nanomembranes even resonate with the characteristics of human tendons in terms of Young's modulus. In addition, these nanomembranes exhibited high biocompatibility and good adhesion to mouse fibroblasts from the NIH 3T3 line and diploid human embryonic cells from the M22 line. Electrospun polyhydroxyalkanoate nanomembranes showed positive proliferative power when evaluated as experimental wound dressings in experiments on a female BALB/c mouse surgical skin lesion model and thus were proposed as wound dressings for the healing of skin defects [45].

A recent review highlighted the merits of curcumin in the wound healing process, especially when it is used in nanodelivery systems such as nanohydrogels, nanoparticles and nanofibers [2]. Another study proposed the use of a curcumin-loaded bilosomal hydrogel fabricated from dual alginate dialdehyde/chitosan natural, bioactive and biodegradable polymers cross-linked via Schiff's base together with calcium chloride as a robust, efficient, and user-friendly dressing for wound healing in a male Albino rat wound model [46].

3D Bioprinting and Soft Robots

The novel use of 3D printing technology to fabricate wound dressings that meet specific patient requirements is gaining interest [47]. This necessitates the use of a certain type of polymer system to form a dressing with a predetermined thickness, leading to the use of the term "personalized" wound dressing according to the patient and wound conditions [48].

Many recent studies have highlighted the advantages of using 3D printing technology to fabricate wound dressings. Kim, S. et al. [49] focused on the advantages of biocompatibility and its usefulness in providing a suitable environment for the growth of natural cells, as well as the ease of loading cells into self-healing hydrogels due to their unique rheological properties. They even projected that in the near future, bioprinted self-healing hydrogels will be used to fabricate organs in the laboratory.

Another approach for using 3D modular bioprinting to develop injectable hydrogels was described by Liu, Y. [50] and coworkers. They were able to first fabricate separate self-healing hydrogel modules of chitosan hydrogels using phenol-functionalized chitosan and polyethylene glycol derivatives as printing bioinks, which were subsequently assembled into integrated cross-linked self-healing hydrogel systems using visible light. This hydrogel system could be directly injected into damaged tissues, which were subsequently subjected to visible light energy to initiate modular integration. This modular integrated system had an excellent tissue-like structure and served as a scaffold with enhanced tissue regeneration power.

A novel study focused on the biomedical application of self-healing hydrogels in promoting spherical tissue fusion by encapsulating molecules/stem cells and thus facilitating cell fusion. The spaces between the spherical bodies were securely filled with the flow of the autonomously healing hydrogels to ensure physical contact between the bioprinted treatment and the surrounding tissues. Consequently, the fusion of spheroids together into larger tissue strands is enhanced. This developed self-healing hydrogel system is useful for building models that are used to conduct *in vitro* tissue culture experiments that mimic diseases such as myocardial infarction. These bioprinted models can be used for screening drugs, particularly when high cell densities and heterogeneity are important [51].

Wang, W. et al. [52] studied various factors: 1) printing speed, 2) printing resolution, 3) maximum self-healing efficiency, 4) time required to achieve self-healing, 5) conductivity, and 6) Young's modulus. These factors affect the performance of 3D-printed photopolymerizable polyvinyl alcohol and chemically/ionically cross-linked poly(acrylic acid) resins prepared via the micro continuous liquid interface production (μCLIP) technique. The scientists used variable concentrations of ferric chloride (0.75–1.25 wt.%) as an external stimulus to activate the self-healing power of the meshed network of the μCLIP-produced SH hydrogel. This system could be used to design ionotronic devices for health monitoring systems and soft robots with the ability to repair damage autonomously. The authors studied the use of this self-healing hydrogel system as a knuckle

sensor to detect the motion of a finger during folding and unfolding.

Conclusion

This review outlines the current practices and novel approaches for the fabrication of wound dressings. The core stone of designing a successful wound dressing is to fabricate a dosage form that mimics the tissue microenvironment. A "smart" dressing should overcome two challenges: pain during application and dressing-change frequency. An overview of various wound dressings, ranging from simple gauze dressings to sophisticated 3D-printed systems, is provided. In this work, treatments comprising self-healing polymeric hydrogels were highlighted, with a special focus on the added advantages, polymers used and drugs loaded. Self-healing hydrogels enjoy tunable mechanical characteristics by controlling external stimuli (e.g., temperature, pH, stress) to match the targeted wound tissue. The autonomous restoration of the self-healing hydrogels gives them the advantage of rebuilding their 3D scaffold matrix after any damage, which allows them to serve as valuable wound dressings capable of preventing microbial contamination of the wounds they cover, especially in immunocompromised patients. Moreover, as hydrogels, they have the advantages of mechanical flexibility and the ability to promote hydration of the wound microenvironment. However, self-healing hydrogel systems involve the use of polymers of variable sources and crosslinkers that match the nature of the polymers used, together with the formation of new covalent/noncovalent bonds. Hence, in-depth studies to confirm the biocompatibility, toxicity and safety of self-healing hydrogel systems are needed to ensure smooth transfer from bench to market.

Future Perspectives

The current practice of treating wounds is shifting to the use of hydrogel systems that mimic the biological properties of human tissues. Advances in materials science help in designing tailored or "personalized" wound dressings to match patient conditions. However, further studies to determine the biocompatibility of these hydrogel systems are needed. In addition, further research is required to monitor the stability of self-healing hydrogels under physiological conditions. Recently, bioprinted self-healing hydrogels have gained attention because of their unique characteristics of flowing and filling the wound space well, high absorption of exudates, and good bioadhesion to wound tissues. In the near future, bioprinted self-healing hydrogels will be used to fabricate organs in the laboratory.

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Declarations

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