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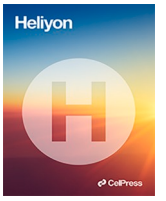

Review article

Advancing diabetic wound care: The role of copper-containing hydrogels

Mohammad Ebrahim Astaneh [a,b,c], Narges Fereydouni [b,c,d,*]

[a] Department of Anatomical Sciences, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran
[b] Department of Tissue Engineering, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran
[c] Student Research Committee, Fasa University of Medical Sciences, Fasa, Iran
[d] Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran

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ABSTRACT

Diabetic wounds pose a significant challenge in healthcare due to their complex nature and the difficulties they present in treatment and healing. Impaired healing processes in individuals with diabetes can lead to complications and prolonged recovery times. However, recent advancements in wound healing provide reasons for optimism. Researchers are actively developing innovative strategies and therapies specifically tailored to address the unique challenges of diabetic wounds. One focus area is biomimetic hydrogel scaffolds that mimic the natural extracellular matrix, promoting angiogenesis, collagen deposition, and the healing process while also reducing infection risk. Copper nanoparticles and copper compounds incorporated into hydrogels release copper ions with antimicrobial, anti-inflammatory, and angiogenic properties. Copper reduces infection risk, modulates inflammatory response, and promotes tissue regeneration through cell adhesion, proliferation, and differentiation. Utilizing copper nanoparticles has transformative potential for expediting diabetic wound healing and improving patient outcomes while enhancing overall well-being by preventing severe complications associated with untreated wounds. It is crucial to write a review highlighting the importance of investigating the use of copper nanoparticles and compounds in diabetic wound healing and tissue engineering. These groundbreaking strategies hold the potential to transform the treatment of diabetic wounds, accelerating the healing process and enhancing patient outcomes.

1. Introduction

Diabetic wound care has traditionally relied on a combination of standard wound management techniques, including debridement, infection control, and the use of dressings to maintain a moist wound environment [1–3]. The gold standard for diabetic wound treatment has been the use of advanced dressings such as foam, hydrocolloid, and alginate dressings, combined with offloading techniques to reduce pressure on the wound site [4–7]. Additionally, negative pressure wound therapy (NPWT) has emerged as a benchmark treatment, significantly enhancing wound healing by promoting granulation tissue formation and reducing edema [8,9]. Despite these advancements, the chronic nature of diabetic wounds often leads to prolonged healing times, frequent infections, and a high risk of complications such as amputation [3,7,10]. Therefore, while these conventional methods are essential, they often fall short

* Corresponding author. Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran.
E-mail addresses: Narges.fereydouni2020@gmail.com, n.fereydouni@fums.ac.ir (N. Fereydouni).

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in addressing the multifaceted challenges posed by diabetic wounds. They are a puzzle of complexity, entailing numerous obstacles in the realms of treatment and recovery. People living with diabetes often find themselves grappling with impaired wound healing, a predicament that leads to a myriad of complications and protracted recuperation. These complications run the gamut from infections and delayed wound closure to tissue necrosis and, in dire circumstances, even necessitating amputation [10,11]. Yet, a ray of hope shines through recent innovations in the sphere of wound healing. Devoted researchers and diligent healthcare professionals have been toiling tirelessly to concoct ingenious methodologies and therapeutic strategies that are precisely honed to combat diabetic wounds head-on. Their overarching aim is to expedite the healing journey and elevate patient outcomes. A focal point in these advancements revolves around the creation of avant-garde materials and methodologies meticulously tailored to tackle the distinctive challenges presented by diabetic wounds. These challenges include impaired blood circulation, compromised immune responses, and persistent inflammation [12–17,252–256].

Within the tapestry of these innovations, the field has witnessed the emergence of biomimetic hydrogel scaffolds as a beacon of promise in the battle against diabetic wound healing complexities (Fig. 1A–F). These hydrogels emulate the natural extracellular matrix with a flair and possess properties that actively foster angiogenesis and the formation of novel blood vessels. They actively encourage collagen deposition and trigger the intricate machinery of the healing process [18,19]. In their quest to promote angiogenesis, these biomimetic hydrogel scaffolds not only flaunt biocompatibility but also boast antibacterial attributes, significantly mitigating the risk of infection and creating a hospitable ambiance for the process of healing. On another front, researchers have made remarkable strides in the development of injectable hydrogel composites that act as catalysts in the wound-healing narrative. They efficaciously curtail infections, nurture tissue regeneration, and expedite the intricate dance of wound healing. These precisely calibrated hydrogel composites establish an optimal ecosystem for healing, triggering cell growth and tissue regeneration by dispatching therapeutic agents directly to the site of the wound. This groundbreaking achievement carries within it the seeds of a potential revolution in the domain of diabetic wound treatment [18,20–27]. Another noteworthy leap involves the crafting of bioactive self-rejuvenating hydrogel scaffolds characterized by the inclusion of silica-based nanocomposites. These scaffolds, with their awe-inspiring ability, breathe new life into blood vessels, accelerate collagen deposition, and orchestrate the dance of tissue remodeling. By fostering angiogenesis and easing the formation of fresh blood vessels, these self-rejuvenating hydrogel scaffolds are

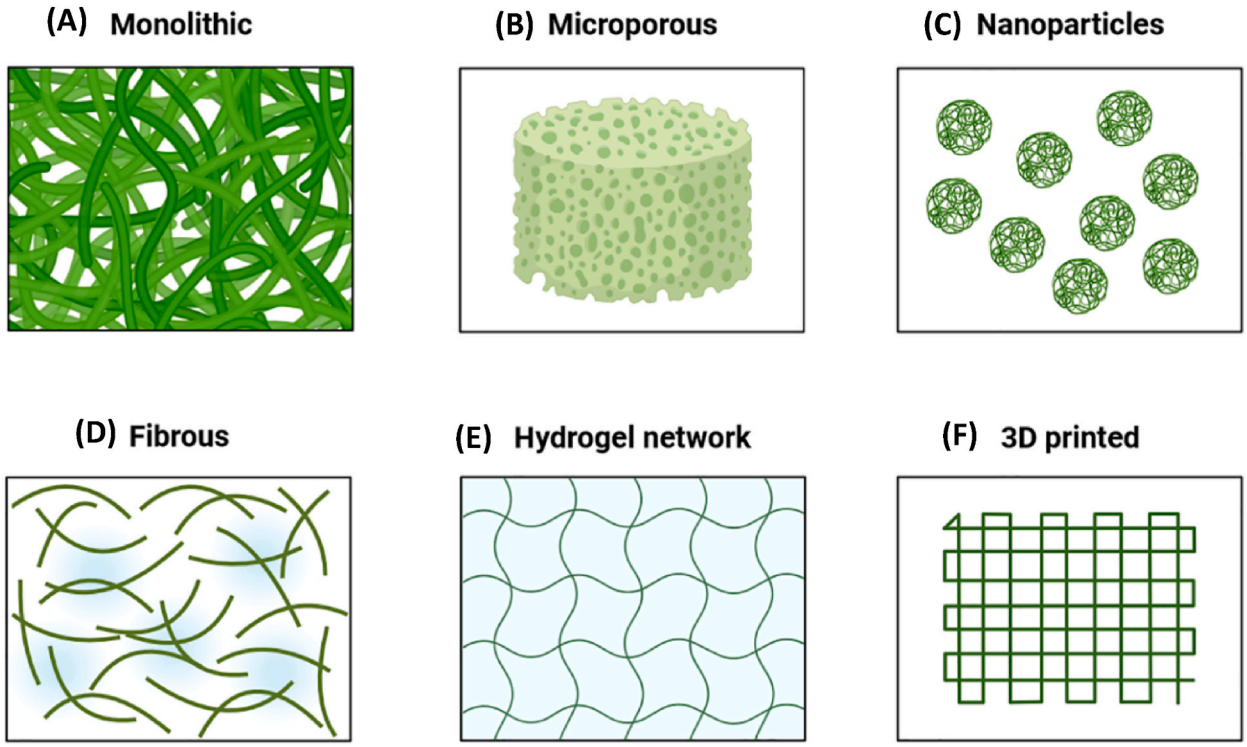

Fig. 1. Scaffold Types for In Situ Tissue Regeneration: (A) Monolithic Scaffold: Solid structure formed from a single material, providing mechanical support and potential tissue mimicry. Limited porosity may affect nutrient and oxygen diffusion. (B) Microporous Scaffold: Scaffold with small pores enabling nutrient and waste exchange, promoting cell infiltration and tissue integration. Made from polymers or ceramics. (C) Nanoparticles: Tiny particles functionalized with bioactive molecules, offering a large surface area for cell attachment. Can release growth factors or drugs to enhance tissue regeneration. (D) Fibrous Scaffold: Interconnected fibers resembling the extracellular matrix, facilitating cell attachment, migration, and tissue formation. Can be made from natural or synthetic polymers. (E) Hydrogel Network: Three-dimensional network of hydrophilic polymers with high water content, creating a hydrated environment for cell growth. Can be chemically modified to enhance cell adhesion. (F) 3D Printed Scaffold: Customizable scaffold fabricated using additive manufacturing techniques, allowing precise matching to target tissue structure. Can incorporate multiple materials and complex architectures, enabling patient-specific scaffolds.

midwives to enhanced wound healing and the birth of healthy skin tissue [22,28–32]. As if that weren't enough, the application of 3D-printed dermal scaffolds has emerged as a bespoke solution to the conundrum of diabetic wounds. These scaffolds are meticulously designed to quell pathological scarring, nurture the healing process, and guide macrophage polarization toward an anti-inflammatory demeanor [24,33]. By delivering a structured framework for tissue regeneration, these 3D-printed dermal scaffolds present a holistic approach to the treatment of diabetic wounds, addressing multiple facets of the healing journey.

Now, let's turn our gaze toward copper, a trace element that plays an indispensable role in various biological machinations. In recent years, copper has attracted considerable attention for its prospective therapeutic applications in the realms of wound healing and tissue engineering [34,35]. The integration of copper nanoparticles and compounds into hydrogel-based strategies holds tremendous promise in tackling the intricate challenges associated with healing diabetic wounds (Table 1). These wounds, often inscrutable in their healing processes, stand to gain substantially from copper's multifaceted properties—its antimicrobial, anti-inflammatory, and angiogenic prowess. Copper nanoparticles, with their idiosyncratic physicochemical attributes, promise enhanced therapeutic efficacy compared to their bulk copper counterparts. By incorporating copper nanoparticles or compounds into hydrogels, researchers can forge bioactive scaffolds that perpetuate the gradual release of copper ions at the wound site. This precise, localized, and controlled release of copper facilitates its therapeutic effects while minimizing systemic toxicity [24,25,36–51].

Copper's antimicrobial attributes assume paramount importance in the realm of diabetic wound healing, given the proclivity of these wounds to succumb to infections [52–55]. Copper ions have proven their mettle by demonstrating broad-spectrum antimicrobial activity against an array of pathogens, including drug-resistant strains [56–58]. The integration of copper into hydrogels brings about a significant reduction in the infection risk, fostering an aseptic wound milieu conducive to the process of healing (Table 1). Furthermore, copper's anti-inflammatory properties orchestrate a symphony of moderation in the inflammatory response at the wound site, steering it toward a harmonious healing journey [59–62]. Copper ions meticulously regulate the expression of pro-inflammatory cytokines while stoking the production of anti-inflammatory factors, thereby dialing down excessive inflammation and facilitating the regeneration of tissue [63–65]. Copper also unfurls its influence in the arena of angiogenesis, an indispensable element in the theater of wound healing. Copper ions serve as catalysts, inspiring the production of angiogenic factors, thus nurturing the growth of blood vessels and enhancing the blood flow to the wound area. This augmented vascularization expedites the delivery of oxygen and nutrients to the wound site, thereby fast-tracking the process of tissue regeneration. But copper doesn't stop at healing wounds; it extends its benevolence to the domain of tissue engineering. When incorporated into hydrogels, copper nanoparticles, and compounds foster a conducive environment for cell adhesion, proliferation, and differentiation, creating a microcosm that is primed for tissue regeneration [24,42,44,48–51,66–70].

In harnessing the potential of copper nanoparticles and compounds, researchers have unearthed ingenious strategies that hold the promise of a paradigm shift in the treatment of diabetic wounds. One of the salient advantages of these approaches lies in their ability to expedite the healing process (Table 1). Diabetic wounds often meander through extended healing timelines due to their vexing tissue regeneration patterns. However, the integration of copper nanoparticles and compounds into hydrogels has yielded promising outcomes in hastening the wound-healing narrative (Table 1). This discovery carries significant weight, as it has the potential to truncate the healing timeline for diabetic wounds, thereby bestowing improved outcomes upon patients. Moreover, the exploration of copper-centric approaches in the realms of diabetic wound healing and tissue engineering harbors the potential to elevate the overall quality of life for individuals grappling with diabetes. Diabetic wounds are a ubiquitous byproduct of diabetes and can snowball into grave infections, necessitating amputations in the absence of judicious treatment. By pioneering effective treatments utilizing copper nanoparticles and compounds, researchers stand at the precipice of advancing healthcare by offering superior alternatives for the management and healing of diabetic wounds [18,24,37,39,40,45–49,68,71–73].

In essence, current treatment options for diabetic wounds include a range of therapies such as traditional wound dressings, negative pressure wound therapy, hyperbaric oxygen therapy, and the use of growth factors or skin substitutes [1–9]. However, these modalities have limitations, including insufficient control of infection, inadequate promotion of angiogenesis, and the inability to effectively manage chronic inflammation [3,7,10]. Hence, copper-containing hydrogels offer a promising alternative by addressing these gaps. These hydrogels combine the moisture-retentive properties of traditional dressings with the antimicrobial, anti-inflammatory, and angiogenic benefits of copper ions. Unlike other treatments, copper-containing hydrogels provide a controlled release of copper, reducing the risk of systemic toxicity while enhancing the wound-healing process (Table 1). This dual-action approach not only accelerates healing but also minimizes the risk of complications, positioning copper-containing hydrogels as a superior option in the management of diabetic wounds. Consequently, it is imperative to pen an appraisal of the pertinence of investigating copper nanoparticles and compounds in the context of diabetic wound healing and tissue engineering. These pioneering paradigms wield the potential to metamorphose the landscape of diabetic wound treatment, hasten the healing journey, and augment patient outcomes. The inexorable march of research and development in this arena is poised to catalyze enhancements in healthcare and elevate the quality of life for individuals wrestling with diabetes.

1.1. Understanding diabetic wound healing

Diabetic wound healing is a complex and intricate process, particularly for individuals grappling with diabetes. This ailment significantly hampers the wound-healing process due to a multitude of complications it introduces. One of the primary culprits is the persistent elevation of blood sugar levels, which leads to heightened oxidative stress and inflammation. These disruptive factors impede the standard wound healing mechanisms, exacerbating the already challenging task of wound recovery [74–78]. Moreover, diabetes is accompanied by peripheral neuropathy and peripheral vascular disease, which further exacerbate the situation. These additional conditions reduce blood flow and diminish sensation in the affected areas, throwing the entire wound-healing process off

Table 1
Examples associated with copper-containing hydrogels for diabetic wound healing.

Name/names	Cells	Bacteria	Animals	Inducing Diabetes	Wound Creation	Findings	Ref
pH-Responsive GOD-CP Inverse Opal Hydrogel (GOD-CP McP)		*E. coli & S. aureus*	Sprague-Dawley rats (250 g)	streptozotocin	skin circumcision procedure	PVP-coated CP nanodots were pH-responsive, changing color and generating ROS in response to pH variations; Immobilized GOD efficiently catalyzed glucose into gluconic acid and H_2O_2, leading to pH decrease and ROS production; GOD-CP McPs exhibited strong antibacterial effects against *E. coli* and *S. aureus*, disrupting bacterial colonies and biofilms.; CP nanodots also stimulated angiogenesis, facilitating tissue regeneration; GOD-CP McPs demonstrated effective wound closure, thicker regenerated tissue, and improved wound microenvironment compared to control groups; Tissue characterization confirmed reduced inflammation, increased vessel density, and aligned collagen in treated groups; The microparticles exhibited pH-responsive structural color sensing, which can be used for real-time monitoring of wound microenvironment.	[48]
gAu-CuS CSs hydrogel, and gAu-CuS HSs hydrogel	RAW 264.7 & NIH 3T3	*E. coli & S. aureus*	BALB/c male mice (20–25 g)	streptozotocin	full-thickness skin wound	gAu–CuS HSs hydrogel showed higher ROS production in bacteria compared to gAu–CuS CSs; GSH (Glutathione) levels decreased in bacterial cells treated with gAu–CuS HSs hydrogel, indicating oxidative stress; Lipid peroxidation levels (MDA) also increased in bacteria exposed to gAu–CuS HSs hydrogel; The gAu–CuS HSs hydrogel showed enhanced adhesiveness and hemostatic properties compared to controls and gAu–CuS CSs hydrogel; gAu–CuS HSs hydrogel directly polarized macrophages to the M2 state, which is associated with prohealing effects; gAu–CuS HSs hydrogel could enhance cell migration and proliferation, contributing to wound healing; Wounds treated with gAu–CuS HSs hydrogel showed significantly accelerated healing, with the best wound closure at 14 days after light exposure. Even in the absence of light, gAu–CuS HSs hydrogel exhibited better healing than control groups; Histological evaluation revealed improved tissue regeneration and collagen deposition in gAu–CuS HSs-treated wounds; Angiogenesis was enhanced, and inflammation was reduced in the gAu–CuS HSs group; Long-term systemic toxicity of gAu–CuS HSs hydrogel have shown No adverse effects on mice health or major organs (heart, liver, spleen, lung, kidney) were observed after 20 days of treatment	[49]
CS–Ag–Cu hydrogel	HUVECs & L929	*E. coli & S. aureus*	Four-week-old male Sprague-Dawley rats (160–180 g)	streptozotocin	circular full-thickness wound	The hydrogels exhibited antibacterial activity due to the release of silver ions; good hemocompatibility of the hydrogels; Cytocompatibility tests showed that the hydrogels had no significant toxic effects on cells; Live/dead staining confirmed the cellular safety of the hydrogels; The hydrogels also promoted cell migration and angiogenesis in vitro; Wound healing was significantly accelerated with the CS–Ag–Cu hydrogel treatment; Histological analysis showed improved epidermal thickness, granulation tissue formation, collagen deposition, and reduced inflammation in the hydrogel-treated wounds; CD31 staining indicated enhanced angiogenesis in the hydrogel-treated wounds; The hydrogel treatment resulted in faster wound closure compared to controls;	[40]
PABC hydrogel scaffold	BM-EPCs	*E. coli & S. aureus*	male ICR mice (30–35 g)	streptozotocin	circular full-thickness wound	copper ion release from BGNCs was sustained and controlled, enhancing antibacterial and angiogenesis properties; PABC scaffold exhibited self-healing properties, injectability, and dynamic	[68]

(*continued on next page*)

Table 1 (*continued*)

Name/names	Cells	Bacteria	Animals	Inducing Diabetes	Wound Creation	Findings	Ref
						mechanical behavior; PABC scaffold significantly promoted the proliferation and angiogenesis of endothelial cells in vitro; PABC-treated wounds were nearly covered with new epidermis; Histological analysis showed thicker granulation tissue in PABC-treated wounds, reduced scar formation, and enhanced collagen deposition and remodeling; PABC scaffold upregulated blood flow in diabetic wounds, and immunofluorescence staining revealed increased numbers of new blood vessels. It enhanced the expression of angiogenesis-related proteins (HIF-1α, VEGF-A, VEGF R2), indicating a role in promoting angiogenesis. The sustained release of copper ions from the scaffold likely contributed to this effect.	
SA-DFO/Cu hydrogels	HUVECs		male C57BL/6 aged 8 weeks	streptozotocin	full-thickness skin wound	Effective against *E. coli* and *S. aureus*; Accelerated wound closure, reduced inflammation, increased collagen deposition, promoted angiogenesis; Biocompatibility (In Vitro) showed >85 % cell viability; Increased proliferation, migration, and tube formation	[39]
H-HKUST-1	HEKa & HDF		Diabetic (db/db) mutant mice (8–10 weeks)	mutation	full-thickness skin wound	PPCN protected HKUST-1 NPs from degradation in protein-containing solutions like FBS; Cytotoxicity assays revealed that H-HKUST-1 induced significantly lower cytotoxicity compared to CuSO4 and HKUST-1 NPs; PPCN and H3BTC showed no toxicity to the tested cells; H-HKUST-1 induced minimal cell apoptosis, in contrast to CuSO4 and HKUST-1 NPs, which significantly induced apoptosis; H-HKUST-1 significantly promoted cell migration, especially in comparison to CuSO4 and HKUST-1 NPs; The sustained release of copper ions from H-HKUST-1 contributed to increased cell migration; H-HKUST-1 significantly accelerated wound healing compared to other treatments; H-HKUST-1 promoted angiogenesis, collagen deposition, and re-epithelialization, facilitating faster wound closure; H-HKUST-1 was well-tolerated by the mice and contributed to their weight maintenance; H-HKUST-1 and HKUST-1 NPs promoted neovascularization at the wound site; increased collagen deposition in wounds treated with H-HKUST-1 enhanced the wound healing process	[72]
E/C dermal scaffold	HMEC-1 & RAW264.7		male Sprague–Dawley rats (200–250 g)	streptozotocin	full-thickness skin wound	The E/C hydrogel, containing copper ions, exhibited sustained release of copper ions over time; The scaffolds exhibited good physical properties and biocompatibility; The E/C hydrogel promoted wound healing by reducing inflammation, promoting angiogenesis, and regulating macrophage polarization; The E/C hydrogel led to improved wound quality with normal skin appearance, thickness, and collagen deposition, effectively reversing scarring in diabetic wounds	[24]
Cunps@CMCS-PCA Hydrogel		*E. coli* & *S. aureus*	male Sprague–Dawley rats (220–250 g)	streptozotocin	full-thickness skin wound	Cunps@CMCS-PCA Hydrogel enhanced angiogenesis, induced the highest migration and tube formation, stimulated VEGF secretion, prevented autophagy, and increased VEGFR2; Cunps@CMCS-PCA hydrogel shifted macrophage polarization from pro-inflammatory to anti-inflammatory, reduced INOS expression and increased CD206, and suppressed inflammatory response via JAK2/STAT3 signaling pathway; Cunps@CMCS-PCA Hydrogel accelerated wound closure in diabetic rats, reduced bacterial proliferation, improved reepithelialization and wound healing quality, and enhanced collagen deposition and wound healing quality; Cunps@CMCS-PCA	[45]

(*continued on next page*)

Table 1 (*continued*)

Name/names	Cells	Bacteria	Animals	Inducing Diabetes	Wound Creation	Findings	Ref
						Hydrogel increased CD31 expression indicating vascular proliferation and promoted angiogenesis; Cunps@CMCS-PCA Hydrogel inhibited inflammation in vivo, reduced inflammatory cells infiltration, lowered the levels of IL-6 and IL-1β, and promoted macrophage polarization to an anti-inflammatory phenotype	
GelMA/AA/Cu hydrogels	L929	*E. coli & S. aureus*	male Kunming mice	streptozotocin	controlled skin wound	The GelMA/AA/Cu1.0 hydrogel showing ideal self-healing stability and efficiency due to coordination of Cu^{2+} and carboxyl ligands; the GelMA/AA/Cu1.0 hydrogel showing the highest stretchability and resilience to mechanical stress; GelMA/AA/Cu hydrogels showed efficient antibacterial activity; GelMA/AA/Cu hydrogels exhibited good cytocompatibility with L929 cells, except for the GelMA/AA/Cu1.5 hydrogel, which hindered cell proliferation to some extent; GelMA/AA/Cu hydrogels demonstrated adhesive properties, adhering well to various substrates, making them suitable as tissue adhesives; GelMA/AA/Cu hydrogels exhibited effective hemostatic ability in vivo when applied to bleeding liver wounds in mice; GelMA/AA/Cu1.0 hydrogels promoted faster wound healing in diabetic mice compared to control groups, with better epithelialization and collagen deposition; GelMA/AA/Cu1.0 hydrogels reduced inflammation (IL-6 expression) and promoted vascular regeneration (α-SMA and CD31 expression) during the wound healing process	[37]
Copper Peptide-Functionalized RADA16 Nanofiber Scaffolds (RADA16, 5%R-GHK-Cu, and10%R-GHK-Cu)	HUVECs & L929		male Sprague–Dawley rats (7 weeks)	streptozotocin	full-thickness dermal wound	R-GHK-Cu (5 %, 10 %) treatment enhanced wound healing in diabetic mice compared to PBS and RADA16. - Histological analysis showed mature tissue formation and collagen deposition. - Increased expression of angiogenesis markers (eNOS and CD31) indicated enhanced angiogenesis in R-GHK-Cu groups; R-GHK-Cu (5 %, 10 %) significantly accelerated wound closure compared to RADA16 and control groups. - Histological analysis showed improved tissue regeneration, less granulation tissue, and better-arranged collagen deposition in R-GHK-Cu groups; 5%R-GHK-Cu and 10%R-GHK-Cu promoted endothelial cell (EC) proliferation. - Fibroblast cell density was significantly higher on 5%R-GHK-Cu and 10%R-GHK-Cu; Copper release from 5%R-GHK-Cu and 10%R-GHK-Cu showed a two-stage release process	[18]
hydrogel with different additives, including TGF-β, copper peptide, stanozolol, and ascorbic acid			Female BALB-C mice (4–5 months)	streptozotocin	Laparotomy Incision Wound	Copper peptide and stanozolol treatment resulted in significantly higher scar tissue thickness compared to other groups; ascorbic acid-treated wounds showed significantly lower proliferation rates in the skin layer, suggesting faster healing and remodeling	[71]
MN hydrogel samples (PAM, PAM/Cu^{2+}, PAM-PDA, PAM-PDA/Cu^{2+})			male Sprague–Dawley rats (200–250 g)	streptozotocin	full-thickness skin wound	The hydrogel MN back patching exhibited efficient photothermal conversion properties and photothermal stability; it demonstrated antibacterial effects in vivo, especially with NIR irradiation; good cytocompatibility; MNs showed the ability to release drugs effectively into skin tissue; MN patches demonstrated accelerated wound healing in a rat model; Collagen deposition, angiogenesis, and anti-inflammatory responses were promoted by MN patches	[46]

balance. It is akin to navigating a turbulent sea with a malfunctioning compass. Consequently, wounds take an extended period to heal, become susceptible to infections, and struggle to regenerate healthy tissue [79–86]. The consequences of diabetic wounds extend beyond the immediate healing process and have a profound impact on the overall well-being and quality of life of individuals battling diabetes. Chronic wounds, which defy timely healing, are a common outcome. These persistent troublemakers are particularly vulnerable to infections, which can escalate into severe conditions such as cellulitis, osteomyelitis, and even sepsis [87–95]. However, the complications do not end there. Diabetic wounds have a propensity to evolve into ulcers, which, if left unattended, can lead to gangrene—a life-threatening condition—and the grim possibility of amputation. When individuals with diabetes already contend with health complications like obesity or cardiovascular disease, these wounds become even more menacing in their implications [96–98].

In light of these formidable challenges, there is an urgent need for innovative approaches to accelerate diabetic wound healing. Researchers and medical experts are actively exploring a plethora of strategies to address this conundrum. Imagine advanced wound dressings like hydrogels and nanofibers that create an optimal environment for wound healing. Additionally, they are investigating the potential of growth factors, stem cell therapy, and tissue engineering to stimulate tissue regeneration and expedite wound closure [18,24,37,39,40,45–49,68,71–73]. In summary, it is imperative to delve into the mechanics underlying the impaired wound-healing process in diabetes. This pursuit is the key to unlocking a treasure trove of effective strategies to accelerate diabetic wound healing. The complications associated with diabetic wounds are not trivial matters, and they compel us to venture into uncharted territory in search of innovative solutions. Through this journey of enlightenment and the implementation of novel interventions, we inch ever closer to mastering the art of managing and preventing the complications that diabetic wounds bring, thereby enhancing the quality of life for those valiantly living with diabetes.

1.2. The role of microbes in diabetic ulcers

Diabetic ulcers are particularly susceptible to microbial infections, which play a crucial role in complicating and prolonging the healing process. understanding the role of microbes in diabetic ulcers is essential for developing effective treatment strategies. Addressing these infections promptly and effectively is crucial to improving healing outcomes in diabetic patients [99–104]. The high glucose levels in diabetic patients create an environment that is conducive to the growth of various pathogenic microorganisms, including bacteria, fungi, and viruses [105–107]. These microbes can colonize the wound site, leading to infections that can result in further complications such as delayed wound healing, increased inflammation, and in severe cases, tissue necrosis [108–110].

Bacterial infections are the most common in diabetic ulcers. Common pathogens include *Staphylococcus aureus* and *Pseudomonas aeruginosa* [111–113]. These bacteria can form biofilms on the wound surface, which protect them from antibiotics and the body's immune response. This biofilm formation is a significant barrier to effective wound healing as it not only prolongs the inflammatory phase but also impairs tissue regeneration [114,115].

While less common than bacterial infections, fungi such as *Candida* species can also complicate diabetic ulcers [116–118]. Fungal infections are typically seen in chronic, non-healing wounds and can exacerbate the already impaired wound-healing processes seen in diabetic patients [109,119,120].

Therefore, the innovative strategies for combating these infections, including the use of copper-containing hydrogels which could release copper ions have shown broad-spectrum antimicrobial properties, effectively reducing the microbial load in the wound. By mitigating the risk of infection, these hydrogels create a more favorable environment for tissue repair and regeneration.

1.3. Copper as a therapeutic agent in diabetic wound healing

Copper exhibits immense potential as a therapeutic modality for the recuperation of wounds afflicting individuals with diabetes [121–124]. This is attributed to copper's remarkable attributes, rendering it efficacious in combatting infections, mitigating inflammation, and fostering the proliferation of nascent blood vessels (Table 1). Within the context of diabetic wounds, infections represent a prevalent challenge, yet the antimicrobial properties of copper can act as a formidable defense. Additionally, copper boasts anti-inflammatory prowess, thus orchestrating control over the body's inflammatory response and nurturing a more conducive milieu for the healing process [59–62]. Furthermore, copper possesses the capability to invigorate the genesis of fresh blood vessels, an especially crucial facet given the propensity for impaired blood vessel growth among individuals with diabetes. Nonetheless, the comprehensive comprehension of copper's mechanisms and the optimization of its utilization in the domain of diabetic wound convalescence necessitate further exploration via research and clinical studies. By harnessing the distinctive attributes of copper, we stand on the cusp of ameliorating wound healing outcomes and elevating the quality of life for individuals contending with diabetes [18,24,37,39,40,45–49,68,71–73].

1.3.1. Antimicrobial properties of copper

Copper possesses a remarkable talent for battling against a multitude of microscopic foes [125,126]. Its unique prowess lies in its ability to combat bacteria, fungi, and viruses, making it a highly promising candidate for treating infections in diabetic wounds (Table 1). Extensive scientific exploration has consistently affirmed copper's capacity to thwart the growth and survival of these minuscule adversaries. The mechanism at play is nothing short of fascinating. When copper comes into contact with these microorganisms, it deploys its secret weapon—copper ions. These ions engage with the cellular structures of the microorganisms, instigating chaos within their delicate membranes. The result? These pesky germs find themselves leaking their innermost secrets, a process that ultimately leads to their demise. But that's not all. Copper ions don't stop there. They wreak havoc on the enzymes inside these microorganisms, throwing a wrench into the works of their vital functions [127–129]. As if that weren't enough, they induce

substantial stress within the germs, causing havoc with their DNA, proteins, and other critical components. By eliminating these germs from the equation in diabetic wounds, copper plays a pivotal role in both infection prevention and treatment [127,130]. Infections pose significant hurdles for individuals with diabetes, substantially impeding the natural healing process. However, copper's superhero-like ability to combat germs creates a more conducive environment for wounds to mend. It significantly reduces the risk of infection-related complications, facilitating improved wound healing [39,40,44,46,131–139]. Ingenious minds have even devised special dressings and coatings infused with copper, ensuring a prolonged battle against germs at the wound site (Table 1). These copper-based treatments have demonstrated their mettle, both in controlled laboratory environments and real-life scenarios with patients. They've succeeded in diminishing the germs' presence within diabetic wounds and lowering infection rates.

Nevertheless, the judicious use of copper in diabetic wound healing is paramount. Factors like the appropriate quantity and duration of copper application must be carefully considered [34,140–142]. Excessive copper can be detrimental to our body's cells. Furthermore, further research is imperative to elucidate the optimal utilization of copper as a treatment and its potential long-term impact on wound healing [34,140,141,143]. However, with its potent ability to neutralize germs through the release of copper ions, copper undoubtedly stands as a formidable contender in the battle against infections in diabetic wounds. It disrupts the very essence of these germs, causing chaos within their cell membranes, hindering their enzymatic functions, and inducing considerable stress [39,40,46,131,134,135,138]. Collectively, these actions translate to fewer germs within wounds and improved healing prospects for individuals grappling with diabetes.

1.3.2. Anti-inflammatory effects of copper

In the realm of diabetic wound care, a vexing foe emerges: the specter of excessive inflammation that can cast a shadow over the healing process [61,144–147]. The intricate dance of healing is often disrupted by this unwelcome guest. But behold, copper emerges as a potential savior, armed with its anti-inflammatory prowess, ready to quell the tumultuous storm of inflammation that rages within diabetic wounds [61,62,148–151]. A multitude of studies now bear witness to copper's remarkable ability to influence the behavior of inflammatory foot soldiers, including the valiant neutrophils and the steadfast macrophages [152]. Neutrophils, the swift responders to wounds, play a pivotal role in the initial stages of inflammation. Copper ions wield their influence over these soldiers, orchestrating a symphony of change. They curtail the production of certain pro-inflammatory substances like interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) within neutrophils [153–155]. In doing so, copper assumes the role of a peacemaker, soothing the fiery flames of inflammation. On the flip side, the noble macrophages are tasked with clearing the battlefield of cellular debris and nurturing tissue repair [61,62,148,156]. Here, copper ions inspire these guardians to adopt an anti-inflammatory stance. This transformation leads to the release of soothing substances such as interleukin-10 (IL-10) [157,158] and transforming growth factor-beta (TGF-β) [71, 159]. These substances serve as diplomats, brokering peace and harmony within the war-torn land of inflammation while paving the way for tissue regeneration. Copper, by taming the tempest of inflammation in diabetic wounds, fosters an environment conducive to healing and the rebirth of tissue. Excessive inflammation, you see, can obstruct the formation of new blood vessels, disrupt the choreographed movements of cells essential to wound healing, and impede the production of critical components of the extracellular matrix. Copper's anti-inflammatory wizardry counters these adversities, ensuring a smoother and more efficient path to healing [24, 40,160–168]. Yet, while copper's anti-inflammatory saga in diabetic wound healing has unfolded, the full intricacies of the narrative remain veiled. Scientists continue to unravel the hidden pathways and molecular mechanisms through which copper conducts its symphony of inflammation modulation.

In summation, copper's gift of inflammation reduction bestows upon it the mantle of a promising contender in the battle against the excessive inflammatory response that plagues diabetic wounds. By orchestrating a delicate ballet with inflammatory cells and controlling the production of both pro-inflammatory and anti-inflammatory factors, copper emerges as a beacon of hope. It dims the flames of inflammation, ushering in a more hospitable environment for healing and tissue rejuvenation for those navigating the challenging terrain of diabetes.

1.3.3. Angiogenic potential of copper

In the intricate realm of diabetic wound healing, one formidable foe emerges - impaired angiogenesis, the intricate process of weaving new blood vessels [156,169–177]. This deficiency significantly contributes to the frustratingly sluggish pace of recovery in those grappling with diabetes. Yet, amid this challenge, a glimmer of hope arises: copper, a formidable ally with the power to stimulate the growth of fresh blood vessels within the recesses of diabetic wounds [160,178–181]. This revelation breathes life into the quest for effective solutions, for it strikes at the heart of the problem - insufficient blood supply to the wound's core. Copper, in its ionized form, emerges as the catalyst for this transformative journey. It orchestrates a symphony of angiogenic factors, notably the venerable vascular endothelial growth factor (VEGF) [24,39,44,139,159,160,182]. This wondrous conductor of healing orchestrates the proliferation and graceful migration of endothelial cells, the architects behind new blood vessels. As copper fosters the production and release of VEGF and its ilk, it paves a luminous path for the enigmatic dance of angiogenesis within diabetic wounds. The manifold benefits of enhancing angiogenesis through copper are a boon to the process of wound healing. Firstly, it breathes life into the dormant river of blood, channeling vital nutrients, life-giving oxygen, and vigilant immune sentinels toward the wound's epicenter. This influx of resources is the lifeblood of the healing endeavor, sustaining the metabolic demands of burgeoning tissues and ushering away the detritus of battle. But copper's benevolence doesn't end here. The emergence of new blood vessels heralds the advent of granulation tissue, a pivotal player in the healing symphony. This tissue serves as the scaffolding upon which the architects of repair, the migrating cells, weave their intricate designs. It is the cradle of new tissue, nurturing its growth with tender care. Moreover, copper's touch extends to the realm of inflammation, where neutrophils and macrophages wage their battles. With its deft hand, copper guides these warriors, ensuring a harmonious equilibrium between inflammation and angiogenesis. This delicate balance propels the course of

healing forward while heralding the resolution of inflammation's tumultuous reign [18,39,131,134,135,139,159,161,165,168,183–188].

In summation, copper's capacity to nurture angiogenesis is a treasured asset in the quest to mend diabetic wounds. Through its orchestration of angiogenic factors and the subsequent growth of new blood vessels, copper ushers in a renaissance of blood flow, nutrient bestowal, and tissue revival within the confines of the wounded terrain. This augmentation of angiogenesis nurtures a sanctuary for the sacred rite of wound healing, promising brighter tomorrows for those embattled by diabetes.

2. Engineering copper-containing hydrogels for diabetic wound care

2.1. Biomimetic hydrogel for diabetic wound care

Harnessing the power of natural processes and integrating bioactive components, hydrogels have sparked a revolution in the field of wound management, particularly when it comes to diabetic wounds (Table 1). These cutting-edge materials have emerged as a remarkable solution, offering a distinctive and highly efficient approach that mirrors the body's innate healing mechanisms. Comprising a three-dimensional network of hydrophilic polymers, hydrogels possess the remarkable capacity to absorb and retain significant amounts of water (Table 1). In the realm of wound care, hydrogels possess a distinctive ability—an ability that allows them to create a vital, moisture-rich environment precisely at the site of injury. This is a pivotal factor, essential for achieving the pinnacle of healing. Moreover, hydrogels can undergo tailoring to liberate bioactive constituents, encompassing growth factors, antimicrobial warriors, and inflammation-soothing agents. These bioactive agents assume a central role in the enhancement of the intricate healing process by rousing cell proliferation, diminishing the peril of infection, and orchestrating the symphony of the body's inflammatory response [23,189–200].

The advent of these innovative technologies has kindled fresh hope for individuals grappling with diabetes-related wounds that resist healing. Diabetic wounds, often characterized by delayed healing and heightened vulnerability to infections, present formidable challenges for both patients and healthcare providers. However, hydrogels offer a promising remedy that comprehensively addresses these challenges (Table 1). By mimicking the innate healing processes of the human body, hydrogels create an environment that fosters and expedites the wound-healing journey. They provide the essential moisture required for cell migration, angiogenesis, and the regeneration of tissue. Furthermore, the precise and controlled release of bioactive components from hydrogels catalyzes cellular activities, promoting the rejuvenation of tissues while combating microbial threats. The potential impact of hydrogels on the lives of individuals grappling with diabetes is nothing short of profound. The improved outcomes in wound healing can preempt severe complications like amputations, reduce hospital stays, and substantially enhance the overall quality of life for patients. Through the effective management of diabetic wounds, hydrogels hold the potential to alleviate the physical, emotional, and financial burdens that accompany chronic wounds (Fig. 2) [18,24,48].

With the incorporation of glucose oxidase (GOD) and copper peroxide (CP) into the hydrogel system, multifaceted coverage and monitoring capabilities can be achieved. The fundamental concept underlying the developed hydrogel pertains to the incorporation of GOD and CP into inverse opal particles characterized by structural coloration. These particles are constructed using the biocompatible hyaluronic acid methacryloyl (HAMA) and the pH-responsive acrylic acid (AA). The primary objective of the hydrogel system is to achieve multifaceted coverage and monitoring capabilities for diabetic wound healing. The hydrogels were synthesized using a reverse replication method, wherein silica colloidal crystal templates were infused with a hydrogel solution containing HAMA and AA. Subsequently, the templates were etched to yield inverse opal hydrogel particles. The immobilization of GOD onto the hydrogel particles was achieved through chemical crosslinking, while CP nanodots were incorporated into the particles via physical doping. The prepared hydrogels displayed distinct structural colors that visually indicated the pH of the wound and intelligently inferred its healing progress. These hydrogels possessed a highly ordered three-dimensional porous architecture and exhibited pH-responsive behavior. Furthermore, they showcased a wide-spectrum antibacterial efficacy and the ability to stimulate angiogenesis. Experimental findings revealed that the hydrogels exhibited remarkable antibacterial effects against *Escherichia coli (E. coli)* and *Staphylococcus aureus (S. aureus)* in vitro. Additionally, they facilitated wound closure and demonstrated superior angiogenic effects compared to control groups in a diabetic acute wound model. The hydrogels effectively lowered glucose levels and generated ROS, thus contributing to the wound-healing process. The mechanism underlying the wound-healing properties of the copper-containing hydrogels involves the cascade catalytic activity of GOD and CP. GOD catalyzes the breakdown of glucose to produce hydrogen peroxide (H_2O_2), while CP catalyzes the subsequent generation of ROS. These ROS play a pivotal role in conferring antibacterial properties and promoting neovascularization, ultimately facilitating wound healing. In summary, the prepared copper-containing hydrogels exhibit significant potential for the management of diabetic wounds. They offer multiphase coverage, real-time monitoring capabilities, antibacterial properties, and the ability to promote angiogenesis. The integration of GOD and CP within these hydrogels enhances their chemodynamic properties, rendering them suitable for wound management. The incorporation of copper compounds further augments their antibacterial and wound-healing effects [48].

To further enhance the wound healing properties of the hydrogel, it can be functionalized with copper peptides, specifically glycyl-histidyl-lysine (GHK), which have been shown to enhance angiogenesis and tissue repair. The base idea of the prepared hydrogel was to develop a biomimetic scaffold that promotes wound healing, particularly in diabetic patients. The hydrogels were designed using a self-assembling peptide called RADA16, which forms a nanofiber structure similar to the extracellular matrix (ECM). The GHK peptides were then incorporated into the RADA16 nanofibers to provide angiogenesis cues. The hydrogels were fabricated using a simple and customizable process. The prepared hydrogels exhibited favorable physicochemical properties. They formed stable hydrogel structures and had a nanofiber architecture similar to the natural ECM. The hydrogels also showed good biocompatibility and promoted the

adhesion and proliferation of endothelial cells and fibroblasts. The experimental results demonstrated the benefits of the prepared hydrogels. In in vitro studies, the hydrogels significantly increased the adhesion and proliferation of endothelial cells and fibroblasts. In in vivo studies using healthy and diabetic mice, the hydrogels accelerated wound closure and promoted collagen deposition and angiogenesis. The copper peptide-functionalized hydrogels showed superior performance compared to control groups treated with RADA16 or PBS (Phosphate-buffered saline) alone. The mechanism of action of the copper-containing hydrogels in wound healing is attributed to the properties of copper peptides. Copper ions released from the hydrogels stimulate angiogenesis by upregulating the expression of endothelial nitric-oxide synthase (eNOS) and CD31, which are involved in cell adhesion and angiogenesis. The copper peptides also synergistically promote the levels of hypoxia-inducible factor-1α (HIF-1α) and VEGF, further enhancing angiogenesis and tissue repair. It can be concluded that the copper peptide-functionalized hydrogels based on RADA16 nanofibers offer a promising approach for wound healing, particularly in diabetic patients. The hydrogels mimic the natural ECM structure and provide angiogenesis cues, leading to accelerated wound closure, enhanced collagen deposition, and improved tissue regeneration. The incorporation of copper peptides further enhances the therapeutic effects of the hydrogels by promoting angiogenesis and stimulating the expression of key molecules involved in wound healing [18]. Anther hydrogel was also specifically designed to promote wound healing in a diabetic mouse model. One of the key components of the hydrogel was copper compounds, which were dissolved in the hydrogel matrix. The design principles of the hydrogel involved incorporating not only copper compounds but also other agents such as stanozolol and ascorbic acid. Stanozolol is a synthetic anabolic steroid that has been shown to enhance wound healing, while ascorbic acid, also known as vitamin C, is known for its role in collagen synthesis and antioxidant properties. The study demonstrated that the single-dose application of ascorbic acid in the hydrogel matrix significantly improved the breaking strength of the skin in the diabetic mouse model. This suggests that topically applied ascorbic acid has a positive effect on wound healing. Copper compounds also interacted with cellular processes, such as angiogenesis and extracellular matrix synthesis, to facilitate the healing of diabetic wounds [71].

In conclusion, the development and utilization of hydrogels that harness natural processes and incorporate bioactive components represent a groundbreaking advancement in wound management, particularly for individuals with diabetes. These innovative technologies offer a unique and highly effective strategy that mimics the body's healing mechanisms. With their ability to significantly improve outcomes and enhance the overall quality of life, hydrogels bring newfound hope to individuals living with diabetes and pave the way for a brighter future in wound care.

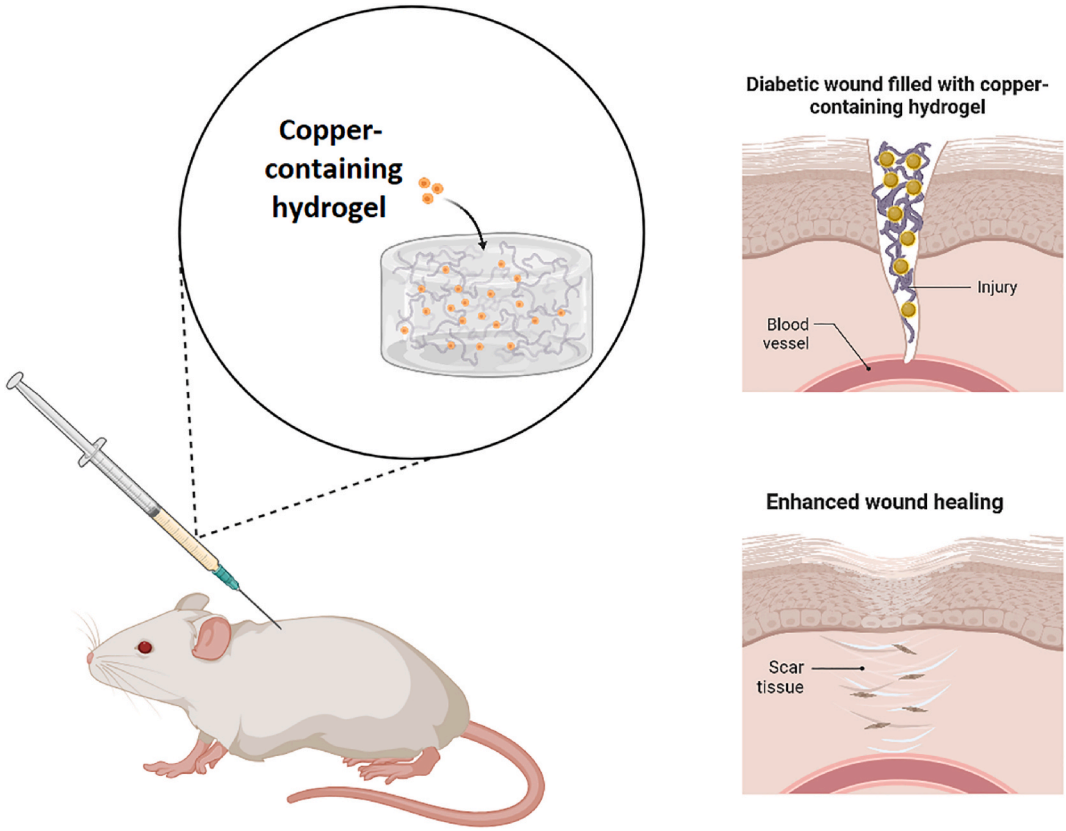

Fig. 2. Copper-containing hydrogels have the potential to enhance the healing process of diabetic wounds by providing antimicrobial activity, promoting angiogenesis, and stimulating collagen production.

2.1.1. Injectable hydrogel

Injectable hydrogels have emerged as an innovative approach within the realm of diabetic wound healing and skin repair, offering distinct properties and functionalities that effectively address the challenges intrinsic to diabetic wounds. This academic discourse explored notable advancements in this domain, encompassing the development of heterostructural enriched injectable hydrogel composites with mace-like structures, injectable and self-healing hydrogels endowed with antibacterial and angiogenic attributes, as well as bioactive antibacterial silica-based nanocomposite hydrogel scaffolds [40,46,68].

The developed hydrogel is based on the integration of mace-like Au-CuS heterostructures (abbreviated as gAu-CuS HSs) into a silk fibroin-hyaluronic acid (SF-HA) based injectable hydrogel. The primary objective is to facilitate a multistage programmed enhancement of wound healing. Copper-containing compounds, particularly the Au-CuS HSs, play a crucial role in augmenting the characteristics and functionality of the hydrogel. The composition of the hydrogel is guided by the utilization of SF-HA as the foundational scaffold material. This choice is primarily motivated by its desirable attributes, such as biocompatibility and adjustable biophysical traits. The construction of the hydrogel involves the synthesis of mace-like Au-CuS heterostructures, which are subsequently integrated into the SF-HA hydrogel, resulting in the formation of a nanostructured bridge. The resultant hydrogels exhibit physicochemical attributes that include consistent rheological properties, exceptional adhesion to diverse substrates, and the ability to generate nanostructured bridges. Furthermore, these hydrogels demonstrate antibacterial properties when exposed to near-infrared light and exhibit pronounced hemostatic efficacy. Empirical evidence unequivocally demonstrates that the gAu-CuS HSs hydrogel accelerates the wound healing process in diabetic mice. This effect is achieved through the promotion of cell proliferation, angiogenesis, and fibroblast migration to the wound site. Additionally, the hydrogel exerts regulatory influence over the wound microenvironment by mitigating inflammation and stimulating the production of anti-inflammatory factors. Importantly, the gAu-CuS HSs hydrogel exhibits significantly superior wound closure rates compared to control groups and facilitates collagen deposition. At the heart of the mechanism governing copper-infused hydrogels within the context of wound healing lies the phenomenon of macrophage polarization towards the M2 phenotype—a pivotal catalyst in expediting the intricate process of recuperation. Moreover, the hydrogel plays a crucial role in orchestrating the intricate process of cytokine expression, involving key players in the fields of inflammation and wound healing, such as IL-6, TGF-β1, and IL-10. Notably, the copper compounds embedded within the hydrogel not only contribute to its antibacterial attributes but also actively stimulate the generation of oxygen radicals. Therefore, the incorporation of copper-containing compounds, specifically the mace-like Au-CuS heterostructures, into the SF-HA hydrogel enhances its functionality and accelerates wound healing. The hydrogel exhibits commendable physicochemical properties, antibacterial characteristics, and the ability to regulate the wound microenvironment. The pivotal role played by copper compounds in enhancing the overall performance of the hydrogel in promoting wound healing is evident [49].

The focal point of the hydrogel's evolution revolves around the conceptualization of an injectable, self-healing hydrogel with the potential to significantly enhance wound healing, particularly in scenarios involving infections and diabetes. The genesis of this hydrogel entails the amalgamation of chitosan (CS) and metal ions, specifically silver (Ag) and copper (Cu) compounds. The incorporation of Ag^{+} and Cu^{2+} within the hydrogel aims to establish a synergistic wound-healing platform by combining their respective antibacterial properties and angiogenesis-promoting capabilities. The hydrogel design involves the combination of CS, Ag, and Cu compounds. The manufacturing process involves cross-linking the amino and hydroxy groups present in CS with metal ions. The resulting hydrogel is injectable, possesses suitable viscosity, and exhibits self-healing characteristics. It can form a stable matrix that aligns with the requirements of the wound-healing process. The prepared hydrogel demonstrates various physicochemical attributes. Notably, it exhibits remarkable antibacterial activity attributed to the presence of Ag^{+} ions, which possess broad-spectrum antibacterial properties. Moreover, the hydrogel fosters the process of angiogenesis via the deliberate and controlled release of Cu^{2+} ions, which are widely acknowledged for their inherent angiogenic prowess. Beyond these attributes, the hydrogel exhibits commendable biocompatibility and hemocompatibility, in addition to its capacity to effectively facilitate the migration of cells. Empirical findings highlight the advantages of the prepared hydrogel. In vitro investigations demonstrate sustained release of Ag^{+} and Cu^{2+} ions from the hydrogel, effectively inhibiting bacterial proliferation while promoting cell viability. In in vivo studies conducted on rat models with infected and diabetic wounds, the hydrogel accelerates wound healing, reduces inflammation, and enhances angiogenesis. Wounds treated with the hydrogel exhibit faster healing rates and improved tissue regeneration compared to control groups. The wound-healing properties of the copper-containing hydrogel are attributed to the synergistic interplay between its antibacterial attributes and angiogenesis-promoting qualities. The controlled release of Ag^{+} ions from the hydrogel impedes bacterial growth, preventing infection and creating a favorable environment for wound healing. Simultaneously, the release of Cu^{2+} ions stimulates angiogenesis, facilitating the formation of blood vessels and enhancing tissue regeneration. Hence, the prepared hydrogel, incorporating copper compounds (Ag^{+} and Cu^{2+}), demonstrates significant potential for enhancing wound healing, particularly in cases involving infection and diabetes. The hydrogel, in its essence, showcases a triumvirate of notable attributes: antibacterial prowess, the facilitation of angiogenesis, and an expedited progression of the wound-healing process. It is imperative to underscore that the symbiotic interplay arising from the concurrent presence of Ag^{+} and Cu^{2+} ions within the hydrogel profoundly augments its collective therapeutic efficacy. Further research efforts are warranted to explore the intricate mechanisms and metabolic pathways through which the hydrogel functions in the context of wound healing [40].

Another developed hydrogel represents a bioactive and self-healing antibacterial dressing specifically designed to enhance the wound-healing process in diabetic patients. It incorporates copper-containing bioactive glasses (BGNC) into a biocompatible macromolecular network. The hydrogel scaffold is composed of polyethylene glycol diacrylate (PEGDA) and sodium alginate (ALG), which contribute to its antibacterial properties and dynamic self-healing capabilities. The construction of the hydrogel scaffold involves UV light crosslinking, where PEGDA is crosslinked in the presence of ALG and BGNC. ALG forms initial crosslinks with BGNC, establishing the primary antibacterial network, while subsequent photocrosslinking of PEGDA forms the secondary network. This

innovative design, which was called PABC hydrogel scaffold, enables the hydrogel to effectively seal wounds, absorb wound exudate, prevent bacterial infections, stimulate angiogenesis, and expedite the healing of diabetic wounds. The hydrogel scaffold, following meticulous preparation, exhibits a range of noteworthy attributes. These encompass exceptional injectability, a remarkable capacity for self-healing, and viscoelastic mechanical properties that merit recognition. Furthermore, it demonstrates formidable antibacterial efficacy, effectively combatting both Gram-positive and Gram-negative bacterial strains. A comprehensive physicochemical analysis serves to confirm the presence of essential elements, including silicon, calcium, and copper, within the framework of the hydrogel scaffold. Empirical observations firmly substantiate that the hydrogel scaffold exerts a profound impact on the viability, proliferation, and angiogenic potential of endothelial progenitor cells (EPCs) when examined in controlled in vitro environments. In vivo investigations utilizing a diabetic mouse model provide compelling evidence that the hydrogel scaffold promotes the restoration of blood vessel networks, increases HIF-1α/VEGF expression, accelerates wound healing, and facilitates skin tissue regeneration. Wounds treated with the hydrogel exhibit increased granulation tissue thickness, enhanced collagen deposition, and improved blood vessel formation compared to control groups. The wound-healing properties of the copper-containing hydrogel scaffold are attributed to a multifaceted array of mechanisms. Copper ions released from the hydrogel stabilize HIF-1α, leading to increased VEGF secretion by cells, thereby initiating blood vessel formation and vascularization. Simultaneously, the antibacterial attributes of the hydrogel act as a protective barrier against infections, while its bioactive nature enhances early angiogenesis and promotes skin tissue development. Hence, the meticulously developed copper-containing hydrogel scaffold demonstrates multifunctional properties and exhibits a high degree of angiogenic potential. It emerges as a promising candidate in the field of regenerative medicine, particularly in contexts where angiogenesis plays a crucial role. The integration of copper compounds enhances the antibacterial attributes and therapeutic effects of the hydrogel, offering a potential solution for the complex challenges associated with diabetic wound healing and skin regeneration [68].

Collectively, these advancements in injectable hydrogel composites present auspicious solutions for the intricate realm of diabetic wound healing and skin repair. By delivering mechanical reinforcement, controlled drug dispensation, antibacterial characteristics, and stimulation of angiogenesis, these materials significantly contribute to the overarching healing process. Consequently, they hold the potential to catalyze a paradigm shift in the treatment of diabetic wounds and pave the way for groundbreaking advancements within the medical field.

2.1.2. Nanoparticle-infused hydrogels

The combination of nanotechnology and hydrogels holds great promise for diabetic wound healing. The ability to engineer nanoparticles with specific properties and incorporate them into hydrogels allows for targeted and controlled delivery of therapeutic agents, prevention of infection, and maintenance of an optimal wound healing environment. These advancements have the potential to significantly improve the treatment outcomes for diabetic patients with chronic wounds [39,72,73].

In line with this potential, a hydrogel was prepared from sodium alginate (SA) hydrogel that was cross-linked with calcium ions (Ca^{2+}), enriched with deferoxamine (DFO), and embedded with copper nanoparticles (CuNPs), which was called SA-DFO/Cu hydrogels. This hydrogel is intentionally engineered to possess dual attributes of promoting angiogenesis and exhibiting antibacterial properties, strategically tailored for the context of diabetic wound healing. The hydrogel was meticulously crafted employing a Ca^{2+} cross-linking methodology. Sodium alginate (SA) solutions, incorporating DFO and CuNPs, underwent thorough mixing, followed by cross-linking in a $CaCl_2$ solution. This precise fabrication approach facilitated the effective incorporation of DFO and CuNPs within the hydrogel matrix. A comprehensive assessment of the physicochemical properties of the prepared hydrogel revealed a gamut of advantageous features. The hydrogel demonstrated commendable biocompatibility and exhibited robust antibacterial characteristics in in vitro settings. Its surface displayed a smooth texture, while its internal structure was characterized by a multi-layered porous arrangement, culminating in impressive mechanical integrity. Notably, the hydrogel boasted a substantial water content, a pivotal attribute in sustaining a moist wound microenvironment conducive to the healing process. Empirical evidence derived from experimentation unequivocally substantiated the hydrogel's prowess in accelerating the healing of diabetic wounds. In a murine model simulating diabetic wounds, the hydrogel not only expedited wound closure but also substantially bolstered angiogenesis while concurrently mitigating persistent inflammatory responses. Amidst the domain of in vitro assessments involving the cultivation of human umbilical vein endothelial cells (HUVECs), the hydrogel's extraordinary prowess was unequivocally unveiled. This exceptional substance not only served as a potent catalyst, eliciting the proliferation, migration, and intricate orchestration of vascular structures within these cellular microcosms but also exhibited a laudable prowess in countering common microbial adversaries, including the notorious *Staphylococcus aureus* and the ubiquitous *Escherichia coli*. Delving into the intricate mechanistic facets underpinning the copper-containing hydrogel's profound efficacy in the realm of wound healing reveals a multifaceted landscape. At the heart of this phenomenon lies a meticulously orchestrated interplay between DFO and CuNPs. These dynamic components, in concert, orchestrate a significant elevation in the levels of HIF-1α and VEGF, thereby orchestrating a substantial augmentation of the complex process of angiogenesis. In parallel, the hydrogel effectively curtails protracted inflammatory responses and augments collagen deposition within the wound milieu, collectively fostering expedited and improved wound healing. To culminate, the hydrogel, adeptly formulated with DFO and CuNPs, has unequivocally exhibited immense promise in the domain of diabetic wound healing. Its multifaceted profile encompassing pro-angiogenic, antibacterial, and wound-healing attributes positions it as a potent therapeutic strategy. The integration of copper compounds, prominently CuNPs, significantly contributes to its therapeutic efficacy. This hydrogel indeed portends the potential to emerge as a superior therapeutic modality for diabetic wound healing, meriting further exploration in forthcoming clinical practice [39].

Recently, another hydrogel was formulated based on Cu/TiO_2-SiO_2 nanoparticles, which were synthesized utilizing the sol-gel method. These nanoparticles were then incorporated into a polymeric hydrogel composed of carboxymethylcellulose (CMC) and

polyacrylic acid (PAA). The hydrogel's design principles focused on creating a durable and biocompatible matrix capable of effectively delivering the Cu/TiO_2-SiO_2 nanoparticles to the wound site. Fabrication methods encompassed the sol-gel process and the integration of the nanoparticles into the hydrogel matrix. The physicochemical attributes of the resultant hydrogel underwent comprehensive characterization. The Cu/TiO_2-SiO_2 nanoparticles exhibited a dimension of 3.5 ± 0.8 nm, featuring a pristine anatase crystal structure. Meanwhile, the hydrogel, composed of CMC and PAA, exhibited stability, biocompatibility, and pertinent physicochemical traits suitable for applications in wound healing. Empirical findings underscored a substantial enhancement in the wound healing process upon the administration of the Cu/TiO_2-SiO_2 nanogel. This therapeutic intervention fostered reepithelialization and tissue regeneration, culminating in the complete resolution of diabetic foot ulcers (DFU). Furthermore, infection was effectively curtailed, obviating the necessity for amputation. These outcomes unequivocally illuminate the therapeutic merits of the prepared hydrogel, signifying its pivotal role in expediting and ensuring the comprehensive recovery of DFUs. The modus operandi of the copper-laden hydrogel in the realm of wound healing is contingent upon the catalytic attributes intrinsic to the Cu/TiO_2-SiO_2 nanoparticles. These nanoparticles, in a highly selective manner, cleave carbon-carbon, carbon-nitrogen, and carbon-oxygen bonds residing within the DNA and RNA nucleotides of bacterial entities, thus impeding the progression of infection. Furthermore, these nanoparticles instigate tissue regeneration and expedite wound healing, collectively engendering enhanced outcomes in the treatment of DFUs. Hence, the Cu/TiO_2-SiO_2 hydrogel has demonstrated a propitious trajectory in the therapeutic management of diabetic foot ulcers. The integration of copper compounds within the hydrogel matrix has potently augmented wound healing, as evidenced by the promotion of reepithelialization, the containment of infections, and the avoidance of amputation. Nonetheless, further endeavors in the form of extensive research and clinical trials remain imperative to corroborate the efficacy, safety, and elucidation of the wound-healing mechanisms intrinsic to copper-infused hydrogels [73].

In another study, the fundamental concept underlying the developed hydrogel revolves around the integration of copper compounds into a hydrogel system to facilitate the process of wound healing. Copper ions have displayed considerable promise in the context of wound healing applications, primarily owing to their capacity to stimulate angiogenesis and act as potent antimicrobial agents. Nevertheless, prior therapeutic approaches employing copper ions have encountered certain limitations, including variable treatment outcomes and potential toxicity concerns. To comprehensively address these challenges, a research endeavor was embarked upon to formulate a copper metal-organic framework (MOF) nanoparticle, which would be encapsulated within an antioxidant thermoresponsive hydrogel. The design of the hydrogel hinged upon the strategic amalgamation of copper metal-organic framework nanoparticles (HKUST-1 NPs) and a thermoresponsive hydrogel denominated as poly-(polyethyleneglycol citrate-co-N-isopropylacrylamide) (PPCN). To ensure the controlled release of copper ions and prevent premature dispersion, the HKUST-1 NPs were effectively stabilized within the hydrogel matrix. The methodology encompassed the synthesis and comprehensive characterization of both HKUST-1 NPs and PPCN, culminating in the successful embedding of HKUST-1 NPs within the PPCN hydrogel. An extensive assessment of the physicochemical properties of the prepared hydrogel was conducted. The utilization of scanning electron microscopy (SEM) imaging rendered unequivocal validation of the conspicuous existence of discernible HKUST-1 crystals meticulously ensconced within the intricate confines of the hydrogel matrix. The hydrogel exhibited a thermoresponsive behavior, exhibiting gelation characteristics at temperatures exceeding 38.8 °C. The introduction of copper into the hydrogel facilitated the sustained release of copper ions over time. Notably, the hydrogel demonstrated inherent antioxidant properties and exhibited reduced cytotoxicity when juxtaposed with copper salts. Empirical findings emanating from experimental investigations underscored the constructive impact of the copper-infused hydrogel (hereafter referred to as H-HKUST-1) on the process of wound healing. In vitro analyses substantiated that H-HKUST-1 effectively instigated cell migration while simultaneously mitigating cytotoxicity and apoptosis. Furthermore, in vivo assessments employing a diabetic murine model featuring splinted excisional wounds unequivocally demonstrated that H-HKUST-1 significantly expedited the closure rates of wounds, concurrently enhancing wound blood perfusion in comparison to control cohorts. Upon conducting a meticulous histological examination, we discovered a remarkable increase in angiogenesis, the accumulation of collagen, and the process of re-epithelialization within wounds that received treatment with H-HKUST-1. The underlying mechanism governing the efficacy of copper-containing hydrogels in the realm of wound healing can be primarily attributed to the controlled and sustained release of noncytotoxic quantities of copper ions. These ions play a pivotal role in stimulating key processes such as the formation of new blood vessels, the buildup of collagen, and the regeneration of epithelial tissue, collectively culminating in an accelerated wound-healing trajectory. Furthermore, the low toxicity profile coupled with the inherent antioxidant attributes of the hydrogel further contributes to its therapeutic efficacy in the context of promoting efficient wound closure. The meticulously crafted copper-containing hydrogel, denoted as H-HKUST-1, presents a highly promising avenue for the treatment of chronic nonhealing wounds. Its capacity to judiciously dispense copper ions while simultaneously alleviating cytotoxicity and fostering various wound healing mechanisms positions it as a potent candidate in the realm of improving wound closure rates and mitigating the risk of infection [72].

In conclusion, the use of nanoparticle-infused hydrogels represents a promising approach to diabetic wound healing. The studies mentioned above demonstrate the potential of incorporating deferoxamine, copper nanoparticles, Cu/TiO_2–SiO_2 nanoparticles, and Cu-MOFs into hydrogel formulations to address the multifaceted challenges associated with diabetic wounds. These innovative strategies hold great potential for improving wound healing outcomes and enhancing the quality of life for individuals with diabetes.

2.1.3. Self-rejuvenating hydrogels

In recent years, the landscape of biomedical research has borne witness to a burgeoning interest, with a focal point directed toward the realm of self-rejuvenating hydrogels. This avenue presents itself as a promising solution, aiming to grapple with the intricate challenges that are inherently entwined with the pursuit of effective wound healing in the context of diabetic patients. The ensuing introductory discourse embarks on a quest to delve deeper into the profound reservoir of potential residing within self-rejuvenating

hydrogels. More specifically, it unravels the intricate tapestry of hydrogels enhanced through a judicious amalgamation of copper-epigallocatechin gallate (EGCG), ultra-small copper nanoparticles, and adhesive attributes laden with inherent antibacterial capabilities. These pioneering hydrogels emerge as beacons of promise, poised to chart a transformative course within the domains of scar amelioration, angiogenesis stimulation, and the expeditious orchestration of the wound healing continuum [37,47,49].

The fundamental concept underlying the development of the Cu-EGCG hydrogel revolves around the creation of a multifaceted dermal scaffold tailored explicitly for the treatment of diabetic wounds. This hydrogel comprises a methacrylated decellularized extracellular matrix (dECM) intricately combined with copper-epigallocatechin gallate (Cu-EGCG) capsules, which were called E/C dermal scaffold. Within this construct, copper ions take on the role of promoting angiogenesis, while EGCG assumes the responsibility of mitigating inflammation at the site of the wound. The hydrogels in question were meticulously crafted through the fusion of methacrylated dECM and Cu-EGCG capsules. The dECM, a pivotal component, serves as the scaffold, facilitating the deposition and subsequent remodeling of the extracellular matrix (ECM). In parallel, the Cu-EGCG capsules exert their influence by enhancing the bioactivity inherent to the hydrogel. The preparation of these hydrogels was accomplished via a polymerization process, entailing exposure to UV light. The comprehensive characterization of the physicochemical properties pertaining to the prepared hydrogels yielded valuable insights. These hydrogels exhibit a porous structural framework, complete with a pore-size distribution conducive to cell infiltration and the exchange of vital nutrients. In addition, an analysis of the swelling ratio unveiled the hydrogels' commendable water absorption capacity. To ascertain their biodegradability, enzymatic degradation experiments were conducted, with the results underscoring the hydrogels' propensity for biodegradation. The empirical findings emanating from a series of in vitro experiments vividly illuminate the advantages associated with the prepared hydrogels. These hydrogels were observed to actively promote angiogenesis and concurrently hinder the polarization of macrophages towards the pro-inflammatory phenotype. Furthermore, they demonstrated a commendable degree of biocompatibility and actively fostered the formation of vascularized networks when examined in vitro settings. Moving to in vivo experiments featuring a rat model, characterized by full-thickness skin defects, the hydrogels exhibited a propensity for accelerating wound healing. This acceleration was notably accompanied by the promotion of neovascularization and an enhancement in the overall quality of wound repair. The intricate mechanism through which copper-containing hydrogels orchestrate their contributions to the realm of wound healing encompasses a multifaceted array of factors. Copper ions, in their capacity as bioactive constituents, wield their influence by actively promoting angiogenesis while simultaneously stimulating the intrinsic potential residing within endothelial cells. In stark contrast, EGCG plays a pivotal role by curbing inflammation and mitigating oxidative stress within the intricate microenvironment of the wound. It is worth emphasizing that the combination of these two essential components within the hydrogel construct yields a synergistic effect that augments wound healing and simultaneously diminishes the likelihood of scar formation. In summation, the meticulously prepared hydrogels, constructed from a synthesis of methacrylated dECM and Cu-EGCG capsules, have unveiled a tapestry of promising outcomes within the domain of diabetic wound treatment. These hydrogels epitomize favorable physicochemical attributes, an enhanced propensity for angiogenesis, a capacity for inflammation mitigation, and an inherent ability to expedite the complex process of wound healing. It becomes abundantly clear that the incorporation of copper compounds within the hydrogel formulation contributes significantly to its bioactivity and therapeutically efficacious role in promoting the intricate realm of wound regeneration [24].

Another prepared hydrogel under scrutiny constitutes a self-healing amalgamation, consisting of carboxymethyl chitosan (CMCS) and protocatechuic acid (PCA) as its integral components. This hydrogel serves as a host matrix for the encapsulation of ultra-small copper nanoparticles (Cunps), which is called Cunps@CMCS-PCA Hydrogel. The design and intended application of this hydrogel revolve around its utility in the localized treatment of diabetic wound healing. The process of fabricating this hydrogel entails a sequence of chemical reactions, commencing with the conjugation of CMCS and PCA to form a self-healing network structure. Subsequently, the incorporation of ultra-small copper nanoparticles into the hydrogel matrix is executed. The fabrication procedure includes the formation of an amide bond and necessitates structural characterization, a task achieved through a battery of analytical techniques, including XRD, TEM, and XPS, among others. Physicochemical attributes associated with the prepared hydrogel encompass a complex three-dimensional interlinked network structure, characterized by inherent self-healing capabilities and a porous matrix. This hydrogel emerges as a paragon of biocompatibility, concurrently demonstrating pronounced antibacterial properties. Furthermore, it manifests an innate capacity for promoting angiogenesis and effectively curbing inflammatory processes. Empirical evidence gleaned from meticulous experimentation showcases the therapeutic potential of the Cunps@CMCS-PCA hydrogel in the realm of diabetic wound healing. This hydrogel exhibits the commendable capacity to forestall bacterial proliferation, actively augments angiogenic responses, and effectively quells inflammatory cascades. Comparative analysis against control groups underscores the hydrogel's propensity to significantly enhance wound closure rates while simultaneously elevating the overall quality of wound healing. Elucidating the intricate mechanism through which the copper-containing hydrogel exerts its influence on wound healing involves a multifaceted matrix of contributing factors. Ultra-small copper nanoparticles take center stage by initiating the activation of ATP7A, thereby thwarting autophagic processes and concurrently inciting angiogenic responses. In parallel, the hydrogel showcases its prowess by orchestrating the inhibition of inflammation through its modulation of the JAK2/STAT3 signaling pathway, particularly in macrophages. Hence, the Cunps@CMCS-PCA hydrogel stands as a pioneering therapeutic modality, heralding a novel approach to diabetic wound healing. The hydrogel's trinity of attributes, encompassing antibacterial efficacy, inflammation mitigation, and angiogenesis induction, collectively underscores its therapeutic efficacy. The strategic incorporation of ultra-small copper nanoparticles within the hydrogel matrix further amplifies its potential in the realm of wound healing. Nonetheless, it is imperative to underscore the necessity for comprehensive research endeavors that delve into the long-term biological safety implications and furnish elucidation concerning the underlying mechanisms governing the hydrogel's therapeutic action [45].

Another hydrogel is formulated using a combination of gelatin methacrylate (GelMA), acrylated adenine (AA), and copper compounds (Cu^{2+}), which was called GelMA/AA/Cu hydrogels. The inclusion of copper compounds in the hydrogel formulation serves the

dual purpose of conferring antibacterial properties and fostering wound healing in the context of diabetic wounds. The hydrogels were meticulously designed and manufactured through a judicious amalgamation of covalent bonding, coordination complexation involving Cu^{2+} and carboxyl groups, and the strategic application of hydrogen bonding. These multifaceted techniques are instrumental in endowing the hydrogels with their distinctive attributes, encompassing self-healing capabilities, adhesive properties, and potent antibacterial efficacy. The prepared hydrogels manifest an array of highly desirable attributes, prominently featuring efficient self-healing properties, exceptional resistance to fatigue, commendable deformability, and impressive toughness. Furthermore, their pronounced water uptake capacity renders them adept at maintaining a moist wound environment and proficiently absorbing a substantial volume of exudates. These hydrogels further distinguish themselves with enduring adhesive characteristics, rendering them eminently suitable for deployment as wound dressings. Empirical findings derived from rigorous experimentation unveil the hydrogels' remarkable antibacterial prowess, effectively suppressing the proliferation of bacteria, including *Staphylococcus aureus* and *Escherichia coli*. Moreover, these hydrogels evince commendable biocompatibility, exerting a favorable influence on cell viability and proliferation. In the context of a diabetic wound healing model, the hydrogels emerge as agents of therapeutic significance, evidenced by their ability to attenuate the expression of proinflammatory factors, foster angiogenesis, and expedite the wound healing process, all in comparison to control groups. Understanding the complex mechanism that underlies the wound healing effectiveness of copper-containing hydrogels requires an investigation into various interconnected factors. Copper compounds assume the mantle of antibacterial agents, thereby mitigating the risk of infection in diabetic wounds. In addition, these compounds actively stimulate angiogenesis, a pivotal facet of the healing process. The hydrogels themselves create a conducive and moist microenvironment that serves the dual purpose of shielding the wound from bacterial intrusion and promoting wound healing by facilitating tissue formation and remodeling. Therefore, the GelMA/AA/Cu hydrogels, as developed within the ambit of this study, emerge as heralds of promise in the arena of diabetic wound healing. The strategic integration of copper compounds serves to amplify the hydrogels' inherent antibacterial and angiogenic properties, thereby culminating in superior wound healing outcomes. Consequently, these hydrogels stand poised as potential candidates for efficacious wound dressings in the treatment paradigm of diabetic wounds [37].

Concluding this exposition, it is evident that the trajectory of self-rejuvenating hydrogels bears immense promise in tackling the multifaceted challenges that cast a shadow over diabetic wound healing. The strategic infusion of copper-epigallocatechin gallate, ultra-small copper nanoparticles, and adhesive attributes imbued with antibacterial properties not only presents a multifaceted approach but also signifies a pivotal step forward in the ongoing quest to abate scarring, incite angiogenesis, quell inflammation, and fortify defenses against bacterial incursions. It becomes abundantly clear that further research endeavors and robust development in this arena hold the keys to unlocking the full potential of self-rejuvenating hydrogels, ultimately culminating in significantly improved outcomes for diabetic patients grappling with the complexities of chronic wounds.

2.1.4. Hydrogel-Based Adhesive Dermal Patch

The Hydrogel-Based Adhesive Dermal Patch represents a groundbreaking leap in the realm of diabetic wound healing. In response to the intricate challenges encountered by individuals living with diabetes, this pioneering patch introduces a fresh approach aimed at facilitating efficient and highly effective wound recovery. Leveraging the unique properties of the hydrogel, a water-based gel-like substance, this adhesive dermal patch establishes an environment that is both moist and conducive to the intricate processes of wound healing, all while ensuring robust adherence to the skin. With its potential to augment the outcomes of the healing process and elevate patient comfort levels, the Hydrogel-Based Adhesive Dermal Patch stands poised to usher in a transformative era in the management of diabetic wounds [46].

In a recent study, the fundamental objective behind the preparation of the hydrogel lies in the development of a pliable and adhesive dermal patch for wound healing applications. This hydrogel is constructed from a composite of polyacrylamide-polydopamine and copper ions (Cu^{2+}), imparting qualities that ensure secure adhesion of microneedle (MN) patches to the application sites and concurrently mitigating the risk of bacterial infections. The design of the hydrogel is meticulously orchestrated through a stepwise template casting process. This fabrication method involves the incremental layering of the hydrogel using mold technology. Furthermore, copper compounds are introduced into the hydrogel to augment its physicochemical attributes and fortify its wound-healing potential. Physicochemical examinations of the resultant hydrogel revealed its intrinsic flexibility, adhesive characteristics, and remarkable photothermal conversion capabilities. The hydrogel exhibits a multi-layered structure adorned with microscopic barbed structures akin to porcupine quills, which significantly enhance its adherence to the skin. Additionally, the hydrogel demonstrates substantial photothermal conversion efficiency, particularly when doped with copper compounds. Empirical findings unequivocally affirm the hydrogel's exceptional adhesive properties, ensuring steadfast application to the skin even under varying angles of stress. Furthermore, the hydrogel manifests a robust photothermal effect, elevating local temperatures to levels conducive to inhibiting bacterial proliferation and promoting the expeditious progression of wound healing. Moreover, the hydrogel exhibits commendable antibacterial efficacy, stimulates cell migration and proliferation, and undergoes comprehensive evaluation for its mechanical attributes and drug release kinetics, all of which return satisfactory results. The mechanism underpinning the wound healing efficacy of copper-containing hydrogels encompasses multifaceted factors. Copper, renowned for its antimicrobial properties, effectively curbs bacterial infections at the wound site. The photothermal effect, especially pronounced when copper is introduced, fosters tissue regeneration and angiogenesis, pivotal processes in wound healing. Furthermore, the hydrogel establishes an environment characterized by moisture and sterility, which is highly conducive to the wound-healing milieu. In conclusion, the incorporation of copper compounds into the hydrogel formulation significantly enhances its physicochemical properties and augments its wound-healing potential. The copper-containing hydrogel demonstrates outstanding adhesion, photothermal conversion efficiency, antibacterial efficacy, and the ability to stimulate cell migration and proliferation. These attributes collectively position it as a highly promising candidate for wound healing applications [46].

2.1.5. Copper toxicity in diabetic wound treatment

Copper plays a pivotal role in various biological processes, including wound healing, due to its antimicrobial, anti-inflammatory, and angiogenic properties [201–203]. However, the therapeutic use of copper, particularly in the form of copper-containing hydrogels, requires careful consideration of its potential toxicity. Excessive copper levels can be detrimental, leading to cellular damage and systemic toxicity [204–206].

Copper toxicity primarily arises from its ability to participate in redox reactions, generating ROS [207,208]. While moderate levels of ROS are beneficial in wound healing due to their antimicrobial effects, excessive ROS can cause oxidative stress, leading to cell membrane damage, protein denaturation, and DNA mutations [209–213]. This oxidative stress is particularly concerning in diabetic patients, who already have elevated oxidative stress levels due to hyperglycemia [214–217].

When copper ions are released in excessive amounts, they can accumulate in tissues, leading to systemic toxicity [207,208,218,219]. Key organs affected by copper toxicity include the liver, kidneys, and brain. In the liver, copper accumulation can cause hepatic damage and, in severe cases, lead to conditions such as Wilson's disease, where copper accumulates uncontrollably [220–222]. Renal impairment can also occur as the kidneys attempt to excrete excess copper, potentially leading to nephrotoxicity [223–225].

The challenge in using copper-containing hydrogels lies in achieving a balance where enough copper is released to exert its antimicrobial and angiogenic effects without reaching toxic levels. Research has focused on developing hydrogels that provide controlled and localized copper release (Table 1). This controlled release minimizes systemic absorption and reduces the risk of toxicity, ensuring that copper's beneficial properties can be harnessed without causing harm.

Recent studies have shown that by incorporating copper into nanostructures or using copper complexes within hydrogels, the release rate of copper ions can be carefully modulated (Table 1). This approach not only enhances the therapeutic efficacy but also significantly reduces the potential for toxicity. Ongoing research is essential to refine these technologies, ensuring they are safe for long-term use, particularly in vulnerable populations such as diabetic patients.

In conclusion, while copper is a valuable therapeutic agent in the treatment of diabetic wounds, its potential for toxicity cannot be overlooked. Careful formulation of copper-containing therapies is essential to maximize their benefits while minimizing risks. Future research should continue to focus on optimizing copper delivery systems to ensure both safety and effectiveness in wound healing.

3. Challenges and future directions

While copper-containing hydrogels represent a promising advancement in the treatment of diabetic wounds, it is important to acknowledge the potential disadvantages associated with this biomaterial compound. One significant concern is the potential for copper toxicity, particularly if copper ions are released in excessive amounts. This can lead to oxidative stress, cellular damage, and systemic toxicity, which may pose risks to patients, especially those with impaired renal function or existing comorbidities. Additionally, the manufacturing process for copper-containing hydrogels can be complex and costly, which could limit their accessibility and widespread adoption. Another challenge lies in the stability and controlled release of copper ions; inadequate control over this release can either diminish the therapeutic efficacy or increase the risk of adverse effects. Moreover, there is a need for more extensive research to fully understand the long-term effects of copper exposure on wound healing and overall patient health. These disadvantages highlight the importance of careful design, rigorous testing, and thoughtful implementation of these biomaterials in clinical settings.

3.1. Safety considerations and potential toxicity of copper-containing hydrogels

Navigating the realm of copper-infused hydrogels presents the challenge of ensuring their safety and meticulously evaluating potential toxicity concerns. Copper, renowned for its antimicrobial properties, frequently finds its place within hydrogel formulations dedicated to the realm of wound healing [226–229]. Nevertheless, it remains paramount to subject these hydrogels to scrupulous safety assessments, guaranteeing that their application to the skin bears no adverse effects or toxicity. Envisioning the path forward in this domain unveils the potential for extensive toxicity investigations, with a singular focus on appraising the biocompatibility of copper-laden hydrogels. Such a multifaceted exploration would encompass a comprehensive evaluation of these hydrogels' impact on cell viability, the inflammatory response, and tissue reactions. Furthermore, the avenue of future research may veer toward the fine-tuning of copper concentration within hydrogels, seeking an equilibrium that optimizes its antimicrobial prowess while simultaneously curtailing potential toxicity risks [166,230–236].

3.2. Optimization of hydrogel properties for improved therapeutic outcomes

Hydrogel properties play a crucial role in determining their therapeutic outcomes. The challenge lies in optimizing these properties to enhance the effectiveness of hydrogels in wound healing applications. This includes factors such as mechanical strength, porosity, degradation rate, and drug release kinetics [228].

Future directions could involve developing novel strategies to optimize hydrogel properties. For example, researchers could explore the use of biomimetic enzyme cascade structural color hydrogel microparticles, which mimic natural enzymatic processes and offer unique properties for wound healing management. Additionally, the incorporation of porcupine-inspired microneedles coupled with an adhesive back patching could be explored to accelerate diabetic wound healing. These approaches could potentially improve the therapeutic outcomes of hydrogels by providing better control over drug release, promoting cell migration, and enhancing tissue regeneration [46].

3.3. Combination therapies and synergistic effects with other wound healing agents

Combination therapies have gained attention in wound healing research due to their potential to enhance the healing process. The challenge lies in identifying effective combinations and understanding the synergistic effects of different wound healing agents when used in conjunction with hydrogels [237–251].

Future directions could involve investigating the combination of hydrogels with other wound healing agents to achieve synergistic effects. For example, the translation of research findings into clinical practice could involve exploring the impact of the single-dose application of TGF-β, copper peptide, stanozolol, and ascorbic acid in the hydrogel on midline laparotomy wound healing in a diabetic mouse model. Additionally, the use of calcium ion cross-linked sodium alginate hydrogels containing deferoxamine and copper nanoparticles could be explored for diabetic wound healing. These combination therapies could potentially improve wound healing outcomes by targeting multiple aspects of the healing process, such as inflammation, angiogenesis, and antimicrobial activity [18,24,37,39,40,45–49,68,71–73].

3.4. Translation of research findings into clinical practice

The intricate process of translating research findings into clinical practice is a critical and multifaceted challenge in the development of novel wound healing therapies. While laboratory-based studies provide essential insights into the potential efficacy of treatments such as copper-containing hydrogels, bridging the gap between controlled experimental conditions and the unpredictable variables of clinical environments requires careful planning and execution. The transition from bench to bedside involves not only demonstrating the safety and efficacy of these therapies in diverse patient populations but also addressing regulatory requirements, manufacturing scalability, and real-world applicability.

One of the primary challenges in this translation is ensuring that the promising results observed in preclinical studies are reproducible in human subjects. Animal models, while useful, do not fully replicate the complexities of human diabetic wounds, which are influenced by a myriad of factors such as co-morbidities, variations in patient health status, and differences in wound care practices. Therefore, the initiation of well-designed clinical trials is paramount. These trials must be rigorously conducted to assess not only the therapeutic outcomes of copper-containing hydrogels but also their safety profiles, optimal dosing strategies, and long-term effects on wound healing and patient quality of life. Moreover, clinical trials should be structured to compare copper-containing hydrogels with existing standard-of-care treatments. This comparative approach will help establish the relative advantages of these new therapies, such as improved infection control, accelerated tissue regeneration, and reduced rates of complications like amputation. By directly comparing outcomes, researchers can provide compelling evidence that supports the integration of copper-based therapies into mainstream clinical practice.

In addition to clinical efficacy, the practical aspects of deploying these advanced therapies must be addressed. This includes developing cost-effective manufacturing processes that can produce hydrogels at a scale necessary for widespread clinical use. The stability, shelf-life, and ease of application of these hydrogels in a clinical setting are also crucial factors that will influence their adoption by healthcare providers. Furthermore, ensuring that these therapies are accessible to a broad range of patients, including those in resource-limited settings, will be essential to maximizing their impact on global health. Finally, ongoing post-market surveillance will be necessary to monitor the long-term safety and effectiveness of copper-containing hydrogels in the general population. Real-world data collected from diverse patient cohorts will provide valuable insights into the performance of these therapies outside of the controlled environment of clinical trials. This feedback loop between research, clinical practice, and real-world application will be essential in refining and optimizing copper-based wound healing treatments, ultimately leading to better outcomes for patients with diabetic wounds. Therefore, the translation of copper-containing hydrogel research into clinical practice is a complex but essential process that requires careful attention to safety, efficacy, scalability, and real-world applicability. Through well-designed clinical trials, rigorous comparative studies, and attention to practical deployment challenges, these promising therapies can be brought from the laboratory to the clinic, where they have the potential to significantly improve the treatment of diabetic wounds.

Moreover, Contemplating future trajectories, it becomes apparent that the next pivotal stride may entail the initiation of clinical trials. This transformative phase would be dedicated to the meticulous evaluation of the actual effectiveness of hydrogel-based therapies when implemented within authentic patient cohorts, thereby ushering in a new era of practical medical advancements. For example, a cooperative copper metal-organic framework-hydrogel system could be tested to improve wound healing in diabetes. These studies would provide valuable insights into the clinical potential of hydrogel-based therapies and pave the way for their widespread adoption in clinical practice [72].

4. Conclusion

In concluding this review, it becomes clear that the use of hydrogels containing copper represents a groundbreaking advancement in diabetic wound care. The key factor lies in the strategic incorporation of copper into the hydrogel matrices, which provides invaluable antimicrobial properties. This serves as a strong defense against infections while simultaneously promoting the healing process of the wound. These innovative formulations have the potential to expedite diabetic wound healing and significantly improve therapeutic outcomes. The impact of copper-containing hydrogels in the healthcare landscape, particularly for individuals dealing with diabetes, cannot be overstated. Diabetic wounds, which cast a formidable shadow over patients and strain the healthcare system, are infamous for their propensity to sow the seeds of complications and protracted convalescence. The astute integration of copper-containing hydrogels into this narrative kindles a beacon of promise. It augments the tapestry of wound healing, diminishes the

specter of infections, and, in the final analysis, elevates the quality of life for those ensnared by the labyrinthine complexities of diabetes. Nevertheless, it is manifest that this domain remains a veritable frontier, awaiting exploration and development. The trajectory of advancement lies entwined with the continuum of research and development endeavors. These endeavors are geared towards fine-tuning the intrinsic attributes of hydrogels, deciphering the intricate symphony that accompanies amalgamated therapies, and ensuring unequivocal safety and efficacy in these avant-garde wound healing undertakings. Understanding the synergistic effects of combination therapies and ensuring the safety and effectiveness of these cutting-edge wound-healing approaches are crucial for future endeavors. The implications for healthcare and the quality of life of individuals navigating the complexities of diabetes are significant. Nonetheless, fully harnessing the potential of these hydrogels requires an unwavering commitment to further research and development. The advancement in diabetic wound healing management relies on the collaborative efforts of dedicated researchers and healthcare professionals, emphasizing the importance of sustained investment in this promising field.

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Data availability statement

The data associated with the study has not been deposited into a publicly available repository. However, the authors confirm that the data supporting the findings of this study are available within the article.

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Mohammad Ebrahim Astaneh: Writing – review & editing, Investigation. **Narges Fereydouni:** Writing – original draft, Conceptualization.

Declaration of competing interest

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