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Research Paper

Polymeric Wound Dressings: from Classic Hydrogels to Self-Healing Systems

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ABSTRACT

The skin, as the largest organ, serves as a crucial barrier against external threats, and its repair in complex wounds such as diabetic ulcers and burns remains a major clinical challenge. Polymeric hydrogel dressings have gained prominence in wound care due to their biocompatibility, moisture retention, and ability to deliver therapeutic agents. However, conventional hydrogels are often limited by poor mechanical strength and lack of responsiveness. Recent advances have led to the development of self-healing hydrogels, which incorporate dynamic reversible bonds (e.g., Schiff base, boronate esters) to autonomously repair structural damage, enhance durability, and conform to irregular wound beds. Furthermore, integration of bioactive components such as antioxidants, antimicrobials, and growth factors has transformed these dressings from passive barriers into active, multifunctional platforms that accelerate healing. This review outlines the evolution from classical hydrogels to smart self-healing systems, highlights key mechanisms and applications, and discusses future directions for next-generation wound dressings.

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1. Introduction

The skin, which is the human body's largest organ, plays a crucial role in maintaining balance within the body and defending against microbial intrusion[1, 2]. The human tissue acts as a defense against various forces. However, when it is injured, it diminishes in its ability to protect and becomes vulnerable to bacterial microorganisms[3, 4]. Many superficial skin wounds typically recover within a week or two, however, severe injuries can be challenging to heal and may pose a life-threatening risk[5]. Skin injuries can significantly raise the likelihood of infections within the human body[6]. Injury is a term used to describe the damage to skin tissue and blood vessels. When the skin is injured by external factors or weakened because of issues with the immune system, it can result in the development of wounds, which can be either short-term or ongoing. The body responds to such skin damage through the process of wound healing. However, any disruptions or changes in this complex healing process at any stage can lead to the creation of scars instead of fully regenerating the skin[7]. The process of wound recovery is a complex event that demands a well-coordinated effort from a multitude of cells, which migrate, proliferate, and release growth factors and hormones[8]. Wound healing is an intricate and active procedure of tissue restoration that entails the tissue's reaction to damage and the process of renewing and reinstating functionality to impaired tissues. Typically, wounds recover in a well-organized, punctual, and effective way. The recovery process includes a sequence of synchronized actions such as bleeding, clotting, inflammatory response to injury, movement and division of connective tissue and parenchyma cells, angiogenesis, generation of the extracellular matrix (ECM), and ultimately, the remodeling phase leading to the maturation of proliferative epithelium accompanied by the development of scar tissue. To gain a deeper insight into the physiological processes occurring in the wound and its surrounding tissue, the process can be categorized into three distinct phases: (i) hemostasis and inflammation, encompassing blood coagulation, as well as humoral and cellular inflammation; (ii) proliferation, involving the development of granulation tissue; and (iii) remodeling, during which new epithelium formation and scarring occur (Figure 1)[9].

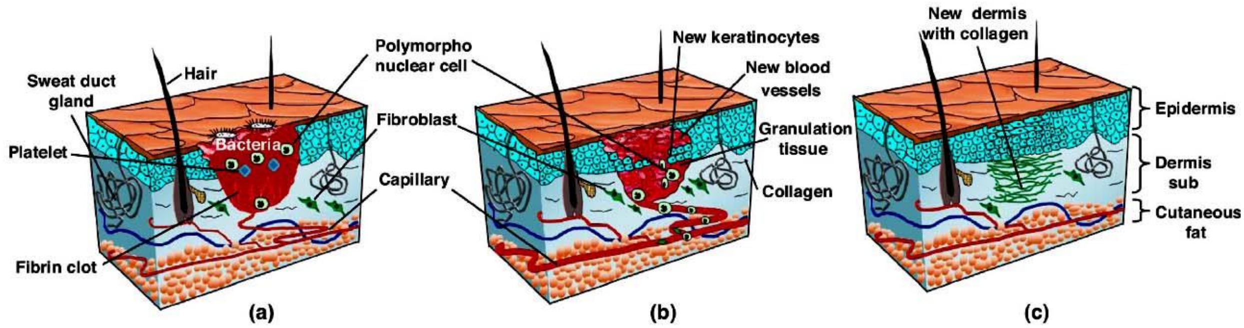

Fig. 1. Schematic illustrating the various stages of the wound healing process. a) Hemostasis and Inflammation: After an injury, blood clots form in the wounded area to stop bleeding and establish hemostasis. This is followed by an inflammatory phase characterized by hypoxia, with an influx of bacteria, neutrophils, and platelets in the wound bed. b) Proliferation Phase: Endothelial cells migrate to the clot, where they proliferate and create new blood vessels. Fibroblast cells then migrate to the wound site, depositing extracellular matrix and forming granulation tissue. Keratinocytes at the wound edge multiply and migrate downward through the damaged dermis and over the provisional matrix. c) Remodeling Phase: This stage involves wound contraction and collagen deposition by fibroblasts. Eventually, new epidermis completely covers the healed wound[9].

Based on how long it takes to heal and the type of healing process involved, wounds are classified as either acute or chronic[10]. Acute wounds typically heal in a structured and timely fashion, marked by four main stages: clotting, inflammation, cell growth, and tissue reorganization. Chronic wounds often get stuck in a particular stage, commonly the inflammatory phase, due to various reasons. Moreover, the unregulated activity of matrix metalloproteinases is a primary factor contributing to the long-lasting nature of non-healing ulcers. Chronic wounds typically arise from pressure ulcers, leg ulcers, and burns[10, 11].

Diabetes-related wounds are a common and severe issue for individuals with diabetes. The nerve damage and inadequate blood circulation that are characteristic of diabetes increase the susceptibility of their feet to developing skin injuries and experiencing slow healing processes. Additionally, nerve damage in the feet reduces sensation, leading to a diminished ability to detect pain or injury. Recently, various types of medical nanofibers have been created to address the chronic ulcers frequently observed in diabetic wounds[12]. In individuals with diabetes, endothelial cells exhibit an inadequate response to the cytokines that are released and are unable to facilitate fast angiogenesis. The limited supply of oxygen hampers the immune cells' capacity to combat environmental pathogens, leading to the rapid development of nonhealing wound ulcers. Chronic wounds are a major factor contributing to the need for limb amputations[6]. Clinicians face considerable difficulties in the management of diabetic wounds, a pervasive issue that has escalated with the increasing global prevalence of diabetes. Consequently, the field has seen the development of a spectrum of biofunctional wound dressings specifically designed to enhance the healing trajectory[13].

Burn injuries are a prevalent global issue that results in a significant number of casualties each year. Among the most severe types of burn injuries is third-degree burns, which pose a high risk of fatality. These injuries present two primary challenges for patients. Firstly, they lead to extensive skin damage, leaving the body vulnerable to microbial invasion, particularly from bacteria. Secondly, the immune system response results in the accumulation of wound exudates on the affected area, which can not only increase the likelihood of infection but also impede the healing process. Therefore, addressing these critical issues is crucial in developing effective wound dressings[14, 15].

To expedite the healing process and provide protection for wound sites, it is necessary to apply wound dressings[16]. Modern wound dressings are developed not just to shield and safeguard the injured region against external pathogens, but also to facilitate cellular restructuring and their assimilation into the body's tissues. In order to achieve these outcomes, a dressing should be (1) compatible with biology and non-irritating, (2) retain moisture in the area while simultaneously soaking up any discharge, (3) possess sufficient mechanical characteristics to uphold its form without compromising functionality, and (4) include attributes that encourage cell attachment, growth, and, if necessary, specialization[17]. To date, numerous wound dressings have been created to assist in wound healing, including nanocomposites, foams, membranes, and hydrogels. Among these options, hydrogels have garnered greater attention for their exceptional qualities. Hydrogel, a well-researched material in the realm of wound healing, provides advantageous features such as maintaining a moist wound environment, facilitating oxygen penetration, cooling the wound site, absorbing wound exudate to a certain extent, and displaying excellent biological compatibility[18]. One area that receives limited attention is the necessity for innovative wound dressings suitable for body parts prone to stretching or bending, such as joints like the elbow, knee, fingers, or wrist. Common dressings like bandages often cause discomfort and inconvenience for patients and offer limited reliability due to their insecure attachment to the wound site. Self-healing hydrogels possess an inherent capability to repair their original structure following damage, thereby prolonging the dressing's effectiveness, cutting down on costs and patient discomfort, and creating an optimal healing environment for the wound[17]. Dynamic covalent bonding has proven to be a highly effective approach in crafting self-repairing hydrogels, thanks to its ability to break and reform under gentle conditions. The typical reversible bonds utilized in self-healing hydrogels include Schiff base bonds, acylhydrazone bonds, and boronate esters[16]. Multifunctional self-healing hydrogels have garnered significant attention in biomedical fields recently due to their versatile characteristics. These include self-healing abilities, adhesion properties, conductivity, antibacterial features, and response to stimuli. Such hydrogels are able to fulfill a wide range of needs in applications such as wound dressings, delivery systems, and the fabrication of supports for tissue healing and growth[19].

2. The importance of wound dressings in wound healing

The body's innate capacity for tissue repair is frequently impaired by slow healing rates and a high vulnerability to infection, creating a demand for adjunctive therapies. To address this, diverse treatment modalities have been established, with wound dressings representing a key technological advancement in modern wound care[20]. Proper wound dressing plays a crucial role in the wound healing process, as it can expedite the healing of the wound[21]. Because of the various types of injuries and the progress in medical technology, different products have been created to heal diverse skin wounds[22]. An effective dressing should adhere minimally to the wound site, allowing for easy removal from the wound bed post-recovery without causing additional tissue damage. Consequently, an ideal wound dressing should possess suitable mechanical characteristics, sought-after flexibility, efficient water absorption, convenient application, cost-effectiveness, and antibacterial properties[14, 23].

Among the variety of advanced materials investigated for the purpose of wound management, hydrogel-based dressings have come to the forefront as revolutionary options because of their distinct physicochemical characteristics and flexible functionality[24].

In the 1960s, it was suggested that keeping chronic wounds moist is beneficial for healing[10, 11]. Because of their hydrophilic characteristics and adjustable chemical, mechanical, and biological properties, hydrogels have displayed significant potential for use in wound dressing. However, traditional hydrogels are only able to play a passive role in the wound healing process by simply keeping the wound moist, thus restricting their effectiveness in promoting wound healing[25].

Wound dressings should have the ability to shield wounds from injuries, dirt, and microbial contamination, while also being comfortable and simple to take off without harming the wound. While various wounds may require different dressing types, the optimal covering should be biocompatible, non-toxic, and hypoallergenic, resistant to sterilization, and able to preserve moisture at the wound site while eliminating excess fluids[26]. Wound dressings made from natural hydrogels, created using biopolymers like chitosan, sodium alginate, and cellulose, are increasingly being acknowledged in the field of wound treatment for their capacity to stimulate healing by being compatible with living organisms, retaining moisture, and breaking down naturally. These substances encourage an optimal environment for healing by aiding in the growth of cells and regeneration of tissues, all while forming a shield against infection. Elevating the healing efficacy of these hydrogels is crucial for chronic or infected wounds[24].

Creating wound dressings with exceptional therapeutic benefits, self-repairing capabilities, strong adherence, and appropriate mechanical characteristics is highly impactful in the field of healthcare, particularly for the healing of skin wounds in joints[27].

Considering the pivotal role of polymer wound dressings in modern tissue regeneration strategies, a thorough understanding of the structure, composition, and function of these systems is essential for the development of effective and targeted therapies. Therefore, this review article aims to elucidate the evolution and recent advancements in the field of polymer wound dressings, from classic hydrogels to self-healing systems. In this regard, various types of polymer wound dressings including hydrogels, foams, films, and nanofiber-based extracellular matrix mimics are introduced. Subsequently, the structural and functional features of classic hydrogels and self-healing mechanisms in advanced systems are analyzed. Furthermore, the role of bioactive agents, and future prospects in the development of next-generation wound dressings will be discussed.

2.1. Classification of polymer wound dressings

In the field of wound healing, wound dressings play a vital role by protecting the wound from outside elements and speeding up the healing process. When caring for a wound, it is important to use a dressing that can effectively absorb fluids and safeguard the wound area. The perfect wound dressing should have excellent porosity to promote adequate air circulation while effectively preventing infections and dehydration[28]. Conventional wound dressings such as gauze, bandages, and cotton pads do not possess antibacterial properties and often stick to the wound, leading to additional harm when replaced[29]. A wide range of natural and synthetic polymers have been extensively employed in wound healing applications, primarily owing to their inherent biocompatibility and biodegradability. To fulfill specific therapeutic roles, these polymers are engineered into various formats, including hydrogels, films, nanofibers and ECM-like substrates, for use as advanced wound dressings[12].

2.1.1. Hydrogels

The past several decades have seen considerable progress in the development of specialized dressings for chronic wound management. Conventional options, including cotton gauze, cotton wool, bandages, and other synthetic fillers, are characterized by a simple design that affords basic mechanical protection. However, this often results in wound dehydration, thereby delaying healing (healing time ≈30 days, infection rate ≈35%) and highlighting the need for more advanced solutions. Consequently, modern alternatives like hydrogels have gained prominence as ideal biomaterials for wound care[30]. Hydrogels, comprising hydrophilic polymeric networks, are particularly valued for their high-water retention, which supports the moist environments essential for accelerated healing. Furthermore, their tunable mechanical properties, biocompatibility, and potential for incorporating therapeutic agents make them adaptable to a variety of wound types and healing stages. These materials can also offer advanced functionalities, including antimicrobial activity, controlled drug release, and oxygen exchange while serving as soothing, protective barriers that promote tissue regeneration[24]. Hydrogels are extensive, water-attracting polymer networks formed through the crosslinking of soluble polymers, either chemically or physically. Their unique characteristics, including their sensitivity to physiological conditions, water-attracting properties, similar texture to soft tissue with high water content, and flexibility, make them ideal for use in biomedical applications[31]. The presence of moisture facilitated by hydrogels supports the cellular healing process in wounds and facilitates efficient removal of dead tissue and foreign substances through the absorbing properties of hydrogel materials[4].

However, despite their potential, the use of these materials in wound dressing is hindered by issues such as poor mechanical strength and inadequate versatility. These limitations constrain their effectiveness, especially in intricate wound conditions marked by infections, high levels of fluid discharge, and dead tissue. To maximize the benefits of natural hydrogels for wound treatment, it is crucial to overcome these constraints by improving material design, functionalization, and fabrication methods. Current approaches emphasize enhancing the structural and functional characteristics of hydrogels to enable them to adjust effectively to the complex requirements of wound recovery[24].

2.1.2. Foams and films

Foams possess protective properties, exceptional absorbency, insulating qualities, and the ability to conform to anatomical contours. Dressings made of foam, constructed from either polyurethane or silicone substances, exhibit semi-permeability and can be either hydrophilic or hydrophobic, while also serving as a barrier against bacteria. Foam dressings, a form of moisture-absorbing material designed to manage wound fluids while providing padding and bulk to the wound site, feature a porous structure that allows for oxygen and water penetration, absorbs moderate to high levels of wound exudate, and serves as a barrier against microbial invasion. Notably, foams possess a high absorbent capacity and exhibit shape memory properties that promote rapid clotting and are utilized to safeguard wounds and sustain a moist environment in the treatment of deep wounds. However, they are not recommended for dry wounds as they may lead to skin maceration[32].Hydrogels are recognized for their ability to retain moisture, whereas foam dressings provide excellent absorption of exudate. In the process of wound dressing, foams are created through the interaction of a solid polymer and dispersed air. These substances are designed for the treatment of moderate to minor wounds, including chronic wounds, burns, and deep ulcers. However, they are not suitable for necrotic wounds, dry wounds with epithelial tissue, or wounds that require frequent attention[33].

When considering the use of wound foam primarily for managing exudate, certain key factors play a crucial role in determining its effectiveness. The microstructural characteristics, including shape, size, interconnectivity, and distribution of voids, are vital in ensuring that the dressing functions optimally in terms of attributes like stiffness, compressibility, and permeability. These properties are directly influenced by the connectivity, density, and arrangement of the voids within the foam[33]. Figure 2 depicts the key factors involved in achieving an effective foam wound dressing.

Film dressings, thin and flexible polymers, are frequently used as semi-permeable coverings to shield wounds from outside elements and conform to various body shapes. These dressings typically allow oxygen and moisture vapor to pass through while preventing the entry of bacteria. Designed to manage superficial lacerations and lightly exuding wounds like thin burns, venous catheter sites, and donor locations for split-thickness skin grafts, film dressings are tailored for wounds with limited absorbency[32, 34]. The film dressing fits carefully to the wound with a great contact area[29]

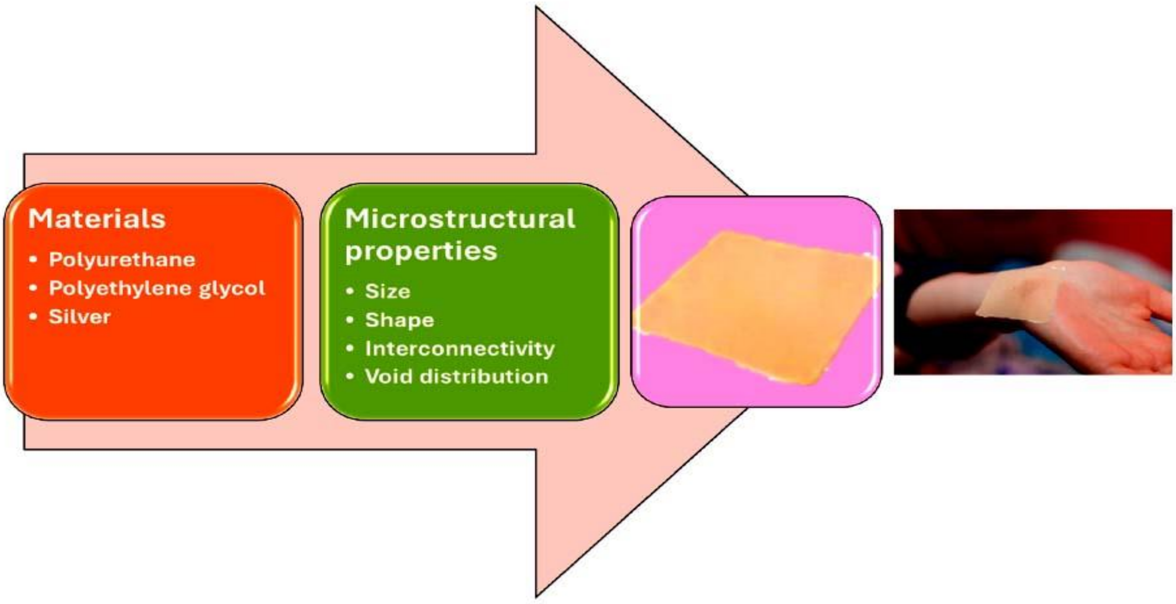

Fig. 2. Examples of factors that influence the ultimate performance of foam wound dressings[33].

Dharmalingam and colleagues developed hydrogel films that are functionalized with a combination of zinc oxide complex and grapefruit seed extract (GFSE). The objective of their research was to minimize the inherent toxicity of ZnO NPs by creating a zinc oxide complex using ZnO NPs and citric acid, provide a steady release of the essential mineral zinc to the wound area, speed up the wound healing process by regulating oxidative stress through GFSE, and inhibit the formation of biofilms at the wound site using both GFSE and the zinc oxide complex[35].

Liang et al. have created electroactive polyurethane elastomers with antioxidant properties and shape memory attributes utilizing a combination of polycaprolactone (PCL), poly(ethylene glycol) (PEG), and aniline trimer

(AT). These films, featuring a glass transition temperature (T_g) similar to that of the human body, demonstrate commendable shape memory capabilities. This characteristic is particularly advantageous for aiding in wound recovery by facilitating the closure of cracked wounds through shape recovery. Furthermore, the vancomycin-loaded film exhibits rapid release within the first hour, with complete release occurring within 24 hours. This speedy release is beneficial for combating infections in wounds and can significantly expedite the healing process in vivo[32].

Chopra and colleagues created honey hydrogel films using a combination of chitosan and polyvinyl alcohol (PVA) for potential use in wound healing. The films were produced through a solvent casting technique and were assessed for thickness, weight consistency, folding capability, moisture level, and moisture absorption. Their findings indicated the possible use of chitosan/PVA hydrogel films for wound dressing purposes[36].

Rashid and colleagues developed composite films containing curcumin entrapped in a combination of poly(vinyl alcohol) (PVA) and gelatin, using tannic acid (TA) for cross-linking. These biologically active dressings were created with the aim of promoting swift wound closure. The researchers conducted tests on the physical and chemical properties of the composite films, their performance in laboratory settings, and their effectiveness in promoting wound healing in living organisms. The outcomes of their study suggest that the curcumin-loaded composite films may serve as a promising method for facilitating efficient wound healing[37]. Yamdech and colleagues formulated a biomaterial by combining Silk sericin (SS) and curcumin (Cur) within sodium alginate/polyvinyl alcohol (SA/PVA) films, which were then crosslinked using calcium chloride. This resulted in a product with improved stability and antioxidant qualities[38].

Mosavi and colleagues developed bio-nanocomposite films through a solution-casting approach utilizing sodium alginate (SA) and xanthan gum (XG). These films were strengthened with a mix of Halloysite nanotubes (Hal) integrated with zinc oxide nanoparticles (ZnO-Hal) and licorice root extract (ZnO-Hal-LRE) at varying levels. The incorporation of ZnO-Hal-LRE nanohybrids notably improved the mechanical characteristics, heat resistance, and resistance to water vapor permeability of the films. Additionally, the addition of LRE to the nanohybrids boosted their antibacterial and antioxidant properties while promoting the viability of NIH-3T3 fibroblast cells [34].

2.1.3. Nanofibers and ECM-like substrates

Numerous methods are available for producing biomaterials specifically tailored for skin tissue engineering and facilitating wound healing without scarring. Each method has distinct benefits based on the intended characteristics of the end product. Some of these fabrication methods comprise 3D printing, freeze-drying, solvent-casting, self-assembly, and electrospinning. Wound recovery is an intricate biological function that, if hampered, may result in the development of scars. Electrospun nanofibrous bandages for wounds have become a hopeful choice for enhancing scarless wound recovery[7]. The nanofibers produced through electrospinning possess a high surface area to volume ratio and porous structure, enabling them to deliver a consistent supply of medication and oxygen to the affected area. By utilizing a range of polymer materials with diverse characteristics, the strength of the nanofibers is enhanced, thus facilitating the absorption of exudates[12].

Electrospinning presents numerous advantageous features that render it well-suited for applications in tissue engineering. To begin with, it enables convenient manufacturing and efficient scalability, making it feasible for widespread deployment. Furthermore, electrospinning demonstrates adaptability in its ability to work with a variety of materials, providing a broad array of choices for selecting biomaterials and incorporating therapeutic agents within nanofiber scaffolds. The resultant structures fashioned from nanofibers boast a notably expanded surface area, facilitating heightened cellular interactions and increased capacity for loading therapeutic agents. Additionally, the diameters of the electrospun nanofibers can be precisely regulated, offering possibilities for customizing scaffold properties to fulfill specific requirements. The pore size of the electrospun scaffold can be adjusted as well, ensuring optimal infiltration of cells and exchange of nutrients. Moreover, the mechanical characteristics of the electrospun biomaterials can be finely adjusted to closely resemble those of natural skin tissue (Figure 3A)[7].

Electrospinning is a widely recognized method in the field of skin tissue engineering, enabling the creation of biomaterials that hold significant potential for promoting wound healing without scarring. Figure 3B illustrates the evolution of research focused on using electrospinning for skin-related purposes spanning the years 1900 to 2023. Subsequent paragraphs will outline the fundamental principles of electrospinning[7].

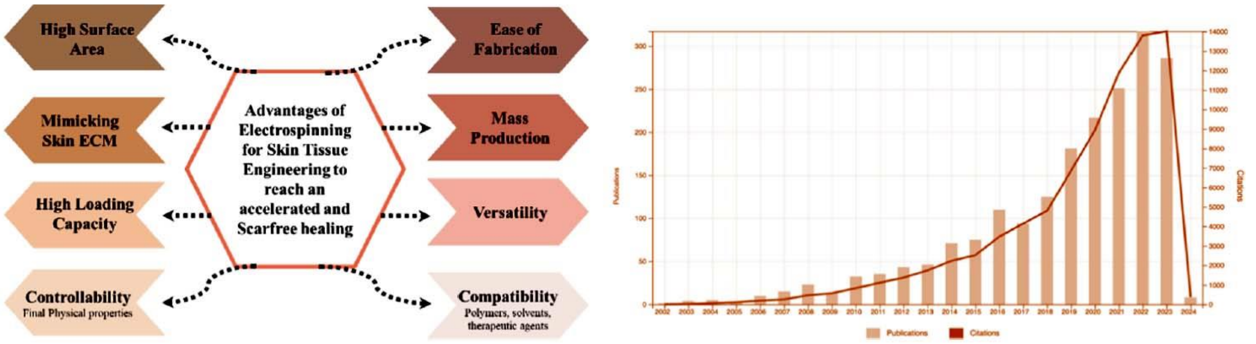

Fig. 3. A) The benefits of utilizing Electrospinning in the creation of scaffolds for wound treatment and achieving scar-free healing are evident. B) There has been a rise in the utilization of Electrospun membranes in wound healing applications, as indicated by the growing number of publications on the subject from 2002 to January 2024[7].

3. Traditional hydrogels

Traditional wound dressings such as gauze and tulle primarily serve to protect wounds while ensuring adequate air flow. Nonetheless, these dressings can cause discomfort and additional damage to the wound area due to their strong adhesion during changes. On the other hand, dressings based on hydrogel lessen discomfort for patients being treated by providing a cooling sensation and minimal adherence to tissues. Hydrogels are composed of approximately 90% water and 10% natural or synthetic polymers, and their significant water content contributes to the efficacy of hydrogel dressings in treating dry and necrotic wounds[4]. Compared to conventional wound dressings, the hydrogel was able to speed up the rate of wound closure by a period of 7 days. On the other hand, traditional hydrogel dressings generally only contain one active component, focusing on a singular aspect of the wound healing process. Additionally, traditional hydrogels are known to have limited long-term durability and are susceptible to lasting damage, not only compromising their effectiveness but also heightening the risk of infection due to microbial infiltration through cracks. Furthermore, while most hydrogel dressings are capable of absorbing wound fluid, they primarily serve as "passive" treatments that do not respond to changes in the wound condition[30]. Recent developments in wound dressings have greatly enhanced the treatment of both acute and chronic wounds by tackling issues like infection prevention, moisture regulation, and improved healing. Significant headway has been achieved, particularly in the utilization of hydrogels to produce tailored dressings. Hydrogels are recognized for their ability to sustain ideal levels of moisture[33]. The primary benefit of hydrogels lies in their significant surface-area-to-volume ratio, enabling quick reaction times and optimal engagement with nearby tissue[36].

3.1. Definition and structure

Hydrogels are polymeric gels that are hydrophilic in nature, able to expand in water and hold significant quantities of water while maintaining their three-dimensional structure[9]. Hydrogels can minimize infection risk by managing exudate and sustaining a hydrated wound bed, while their modification with multifunctional properties has been shown to promote the rapid repair of damaged tissues[39]. Because of their 3D composition, compatibility with living tissue, effective permeability, ability to conform to shapes, mechanical shielding, capacity to maintain a moist environment, and the ability to allow air flow, hydrogels are seen as prime options for dressing wounds. The unique properties of hydrogels have sparked growing attention in the field of wound care[33]. The permeable architecture of hydrogels facilitates the unimpeded exchange of gases (CO_2, O_2) and water vapor (H_2O), thereby permitting essential tissue respiration. Notably, their structure—comprising polymeric networks in an aqueous milieu—often exhibits an inherent biomimicry, resembling the native extracellular matrix (ECM). This similarity provides a conducive platform for the incorporation of cells and bioactive molecules, paving the way for next-generation, biologically active wound dressings[4].

Kalantariet al. conducted a study on the creation and assessment of a hydrogel made of polyvinyl alcohol and chitosan, which was enhanced with cerium oxide nanoparticles produced through green synthesis. They employed a Zingiber officinale extract to act as the reducing, capping, and stabilizing agent in the synthesis process, aimed at applications in wound healing. The formulation of the PVA/chitosan/CeO_2-NPs hydrogel was achieved through the freeze-thaw method, using 0 to 1% (wt) 5 nm cerium oxide nanoparticles. The findings demonstrated that the hydrogels containing 0.5% of CeO_2-NPs exhibited superior antibacterial properties against MRSA within 12 hours, while showing no significant effect on E. coli. Additionally, these hydrogels sustained the viability of healthy human dermal fibroblasts for over 5 days, with levels exceeding 90%, surpassing the outcomes of the control group[40].

3.2. Natural and synthetic polymers used

Natural hydrogels exhibit a diverse range of properties including biocompatibility, hemostasis, anti-inflammation, high water content, semi-transparency, and transparency, enabling easy monitoring of the microstructure of wound healing. These properties are akin to those found in the extracellular matrix (ECM) and various natural polymers like collagen, chitosan, fibrin, gelatin, cellulose, and hyaluronic acid that can be utilized. However, there are several challenges in practical applications that need to be addressed, such as enhancing antibacterial capabilities to prevent wound infections, increasing biodegradability to facilitate natural degradation post-use, and improving mechanical characteristics for applicability across different wound types[29, 33, 39]. In contrast to natural polymers, synthetic polymers can be readily manufactured on a large scale through various methods such as cross-linking, functionalization, or polymerization, allowing for precise control of their physicochemical properties and stability. The reproducibility of synthetic polymers is a significant advantage for their utilization in the medical sector. Furthermore, synthetic polymers have the ability to form a barrier against water and bacteria, while also facilitating adequate ventilation and transport of therapeutic substances. However, one disadvantage of synthetic polymers is their lack of bioactivity when compared to natural polymers[33]. When natural and synthetic polymers are combined, they create a novel hybrid category of hydrogels which offer enhanced mechanical properties, greater flexibility, improved biocompatibility and biodegradability, faster wound healing, increased adsorption capacity, and support healing processes[33].

4. Self-healing Hydrogels

The complex pathological microenvironment and irregular contours of diabetic wounds present a major challenge. While hydrogels are soft, tissue-like materials ideal for dressings, these factors hinder their ability to promote regeneration across the wound's full depth[41]. Given that wound healing is a complex process comprising four overlapping phases, the demand for specific active agents varies significantly throughout its progression. In response, hydrogel technology has progressed, evolving into a class of multifunctional "smart" materials. To enhance their durability and longevity, self-healing properties—the capacity to autonomously recover structure and function after repeated injury—have been engineered into these hydrogels, emerging as a central theme in contemporary scientific inquiry[30]. Creating wound dressing hydrogels that possess effective healing properties and appropriate strength and ability to repair themselves is essential in the field of medical care[8]. Currently, there is a significant focus on self-healing hydrogels. These materials possess the ability to autonomously repair themselves and restore their original functionality after being damaged. This characteristic not only prolongs the durability of the materials but also contributes to promoting wound healing and thwarting bacterial infections[16].

Treating diabetic wounds presents challenges in clinical settings due to their ineffective healing, frequently resulting in serious issues like infections and the need for amputations. Hydrogels with sophisticated self-healing capabilities offer significant potential for diabetic wound treatment. These hydrogels can adaptively respond to alterations in the wound setting and showcase enhanced mechanical attributes, besides possessing the ability to autonomously repair damage[30]. Self-healing hydrogels possess commendable mechanical robustness, the capacity to withstand significant external pressure, and the inherent capability to autonomously mend, thereby establishing a resilient connection between the injury and the substance[42]. Self-healing hydrogels possess the ability to recover their structure autonomously after injury, a characteristic rooted in dynamic, reversible crosslinks—either physical or chemical. This property, combined with their capacity for targeted delivery with excellent biocompatibility and the sustained maintenance of structural integrity, positions them as an outstanding candidate for smart wound dressing applications[30]. A critical gap persists in clinical wound care: the absence of dressings that concurrently exhibit potent efficacy against drug-resistant bacterial strains and intrinsic self-healing properties[43]. Bacterial biofilm infections pose a significant risk to individuals' lives. A self-healing hydrogel formulation containing Clindamycin (Cly) has the potential to be developed. Importantly, the antibacterial hydrogels with self-healing properties hold tremendous potential as an effective wound dressing for treating bacterial biofilm infections[42].

4.1. Definition and mechanism of self-healing (dynamic bonds)

The self-repairing mechanism of hydrogels shows resemblances to biological systems. The process of healing advances in a series of five distinct sequential stages: surface rearrangement, surface proximity, wetting, diffusion, and randomization. These stages rely on the molecular interplay between two surfaces that are damaged, ultimately resulting in the regeneration or reconstruction of the weakened bonds to promote healing. Nonetheless, these bonds are limited to being reversible and dynamic in nature, involving both physical and chemical properties[44]. Hydrogels are highly promising for wound dressing due to their three-dimensional network structure, which confers essential properties such as exudate absorption, moisture retention, and oxygen permeability. However, to withstand mechanical stress and prevent failure from movement at the wound site, these dressings require robust self-healing capabilities[43]. The utility of traditional hydrogel dressings is limited by their susceptibility to mechanical damage and inability to self-repair. Self-healing hydrogels address this limitation by autonomously recovering their integrity post-fracture, which enhances durability and lowers the potential for infection[45]. Self-healing hydrogels are materials capable of regenerating following mechanical damage. This ability is driven by the presence of reversible covalent and non-covalent bonds within the polymer network, allowing for reorganization and restoration of integrity. Key self-healing mechanisms utilized in hydrogel development are outlined in Figure 4. As these materials can recapture their original structure, they can maintain their mechanical strength for longer periods compared to traditional gels, even under repeated stress. Frequently, self-repairing hydrogels are designed to be injectable, since they can recover their properties post-injection, facilitating the painless application of dressings that conform to complex wound shapes without disturbing the wound site. Consequently, due to their extended lifespan, reduced need for replacement, and lower risk of fatigue-related failures, these materials enhance safety and cost-efficiency, making them highly appealing for various biomedical applications—from sustained drug delivery to advanced wound care solutions[17].

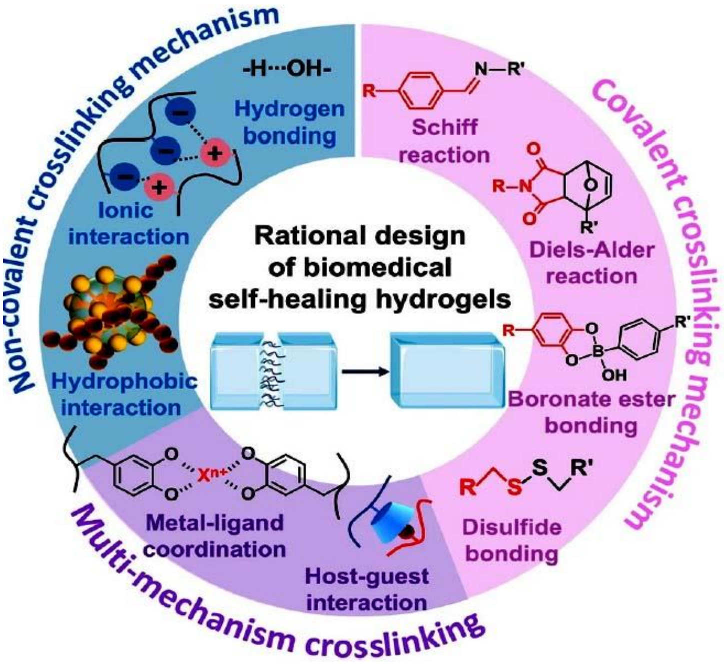

Fig. 4. Self-healing chemistries and mechanisms for self-healing hydrogels: dynamic covalent bonds, non-covalent interactions, and multi-mechanism interactions[17].

Self-healing in these hydrogels arises from a dynamic equilibrium, where structural units undergo reversible dissociation and reorganization. This cyclical process constitutes the core self-healing mechanism, which in turn regulates the macroscopic functionality of the wound dressing.

The choice of cross-linking techniques for the production of self-repairing hydrogels has emerged as a central concern. Currently, two primary approaches, namely dynamic covalent bonding (such as Schiff base bonds, acylhydrazone bonds, and boronate esters) and non-covalent interactions (including hydrogen bonding, electrostatic interaction, metal-coordination, ionic bonding, host–guest interaction, and hydrophobic interaction), have been employed in the fabrication of self-healing hydrogels[16]. Among these, the Schiff base bond is one of the most widely employed, forming dynamic networks that are stronger than those based on disulfide or acylhydrazone bonds. Furthermore, Schiff base formation offers additional advantages, including mild reaction conditions, a fast kinetics, and excellent biocompatibility[43, 46].

4.2. Polymers in Use

Self-healing hydrogels are intelligent materials capable of autonomous repair, rendering them highly promising for wound dressing applications. Their distinctive characteristic, in contrast to conventional hydrogels, is the incorporation of reversible dynamic bonds, a fundamental element in fabricating biologically relevant self-healing systems[30]. Hydrogel materials are increasingly recognized as highly favorable options for wound coverings due to their moist and permeable molecular composition[16]. Hydrogels have a self-repairing mechanism enabled by the reversible nature of their cross-linking structure, which includes both dynamic cross-links and non-covalent connections that can regenerate spontaneously upon damage[42].

Natural polymers—including plant-derived examples like gum arabic, alginate, and cellulose, as well as animal-derived ones like gelatin, collagen, hyaluronic acid, and chitosan—are frequently chemically modified. This modification introduces dynamic bonds into their structure, which are essential for imparting the requisite self-healing capabilities. Synthetic polymers offer significant benefits due to their precise synthetic and processing methods, contrasting with natural polymers that exhibit intrinsic fluctuations between batches[47]. Polyvinyl alcohol (PVA), a synthetic polymer commonly used in self-healing hydrogels, is chosen for its hydrophilic properties, compatibility with living organisms, biodegradability, and the ability to reform its original shape through the formation of hydrogen bonds between its numerous hydroxyl groups. However, hydrogels comprised solely of PVA encounter difficulties with flexibility and strength, necessitating the incorporation of a cross-linking agent to address these challenges[42]. Chitosan is an excellent biocompatible material, characterized by its non-toxicity, lack of odor, biodegradability, and inherent antibacterial properties. Furthermore, its abundance of amino groups facilitates its use in the preparation of injectable, self-healing hydrogels[18]. In the structure of chitosan, numerous hydroxyl and amino groups are present that can be altered to create both dynamic covalent bonds and non-covalent bonds, enabling the development of self-repairing hydrogels based on chitosan[16]. Chitosan, known for its biocompatibility, ability to allow oxygen to pass through, hemostatic properties, and antimicrobial effects, is advantageous in wound care. It has the capability to form self-healing hydrogels by creating reversible crosslinks. These crosslinks include dynamic covalent bonds like Schiff base bonds, boronate esters, and acylhydrazone bonds, as well as physical interactions such as hydrogen bonding, electrostatic interaction, ionic bonding, metal-coordination, host–guest interactions, and hydrophobic interaction. Hence, in response to the growing intricacy of wound conditions, researchers have developed a range of self-healing hydrogel dressings using chitosan in recent times. [16].

Alginate, a polysaccharide with a structure analogous to the native extracellular matrix, is commonly employed in the fabrication of hydrogel wound dressings. Adhesive hydrogels derived from alginate can maintain a moist periwound environment, absorb exudate, and promote healing. Key methods for preparing these hydrogels include crosslinking with divalent cations, amidation reactions, and carboxyl-based chemical modifications. For instance, a self-healing hydrogel exhibiting both conductivity and adhesiveness was synthesized by grafting alginate with poly(β-carboxyethyl acrylate-co-acrylamide). This copolymer provides abundant carboxylic and carbonyl groups, enabling the formation of dynamic bonds that facilitate self-repair[45]. A self-healing hydrogel comprised of a blend of natural and synthetic polymers is referred to as a hybrid polymeric hydrogel. Researchers have created an injectable hydrogel with self-healing properties that respond to changes in pH. This was achieved by forming a dynamic covalent Schiff-base bond between the amine groups of N-carboxyethyl chitosan (CEC) and benzaldehyde groups from poly (ethylene glycol) (PEGDA)[47]. Qiao et al. created dialdehyde-terminated PEG (PEG–CHO) and adipic dihydrazide-modified alginate (ALG-ADH) with aldehyde and hydrazide active sites, respectively. This formulation enabled the formation of dynamic acylhydrazone bonds in the alginate hydrogel, resulting in exceptional self-healing capabilities[48]. Oxidized sodium alginate (OSA), derived from the oxidation of sodium alginate, contains an aldehyde group that significantly enhances the cross-linking capability of sodium alginate with various molecules. Dopamine (DA) is a highly adhesive substance naturally secreted by mussels. By attaching DA, the tissue adhesion of OSA was further enhanced[43].

4.3. Research Examples and Laboratory Studies

Mohammadi et al. have successfully developed a self-healing wound dressing hydrogel based on chitosan, polyvinyl alcohol, and borax. Their investigation results indicated that the synthesized hydrogels possess suitable mechanical strength, high self-healing properties, and non-toxicity. Rheological studies revealed that hydrogels with higher borax content exhibit higher storage modulus at all frequencies. The use of these hydrogels enhances L929 cell migration and wound healing. Furthermore, it significantly improves the expression of growth factor genes[8]. The complex pathological microenvironment and irregular contours of diabetic wounds present a major challenge. While hydrogels are soft, tissue-like materials ideal for dressings, these factors hinder their ability to promote regeneration across the wound's full depth. Zeng et al. developed a glucose-responsive and self-adaptive phenylboronic acid (PBA) hydrogel cross-linked via dynamic borate bonds. This hydrogel was designed to solubilize potent antioxidant flavonoids, forming a system termed Gel Flavonoids (Figure 5). Capable of spontaneously conforming to irregular wound shapes, the Gel-Flavonoid system releases flavonoids in a high-glucose microenvironment to effectively scavenge reactive oxygen species (ROS). The optimized Gel-Flavonoid system promotes wound healing by modulating macrophage activity via CD36, which activates lipid metabolism to concurrently suppress inflammation and stimulate fibroblasts and endothelial cells. This leads to significantly enhanced healing rates (>93% in 14 days) and whole-layer regeneration compared to commercial (3M) dressings[41].

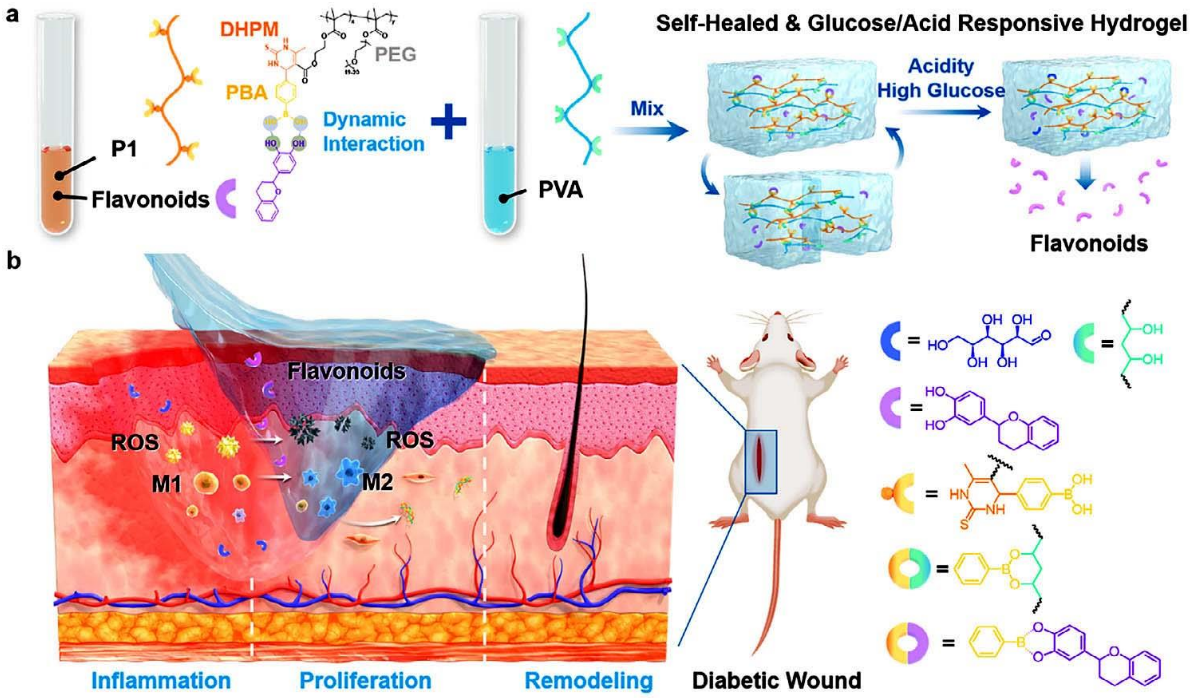

Fig. 5. Schematic illustration of the therapeutic mechanism and preparation of the Gel-Flavonoid system for diabetic wound healing. a) Fabrication procedure of the self-healing Gel-Flavonoid hydrogel. A P1 solution, functionalized with antioxidant groups, was first mixed with flavonoids to enhance their solubility. This mixture was then combined with a polyvinyl alcohol (PVA) solution to form the final hydrogel network. (PBA: phenylboronic acid; DHPM: dihydropyrimidinone; PEG: Polyethylene Glycol). b) Proposed mechanism by which the Gel-Flavonoid system promotes full-thickness chronic wound healing in a diabetic Sprague–Dawley (SD) rat model, facilitating progression from the inflammatory to the remodeling phase. In the high-glucose and acidic wound microenvironment, the dynamic borate bonds between flavonoids and the P1 polymer are cleaved. The subsequent release of flavonoids: (i) scavenges reactive oxygen species (ROS), alleviating oxidative stress; (ii) remodels the immune microenvironment by polarizing macrophages from a pro-inflammatory M1 to a pro-healing M2 phenotype; and (iii) enhances vascular and hair follicle regeneration through immune regulation, collectively achieving whole-layer skin regeneration[41].

Qiao et al. developed a series of adhesive, self-healing, conductive, and antibacterial hydrogel dressings for infected wound repair. These hydrogels were based on a network of oxidized sodium alginate-grafted dopamine and carboxymethyl chitosan cross-linked with Fe^{3+} (OSD/CMC/Fe), which was further modified with polydopamine-encapsulated poly (thiophene-3-acetic acid) (PA) to form the OSD/CMC/Fe/PA hydrogel. Figure 6 illustrates the general design strategy employed for the development of the wound-healing hydrogel. The dynamic nature of the Schiff base and Fe^{3+} coordination bonds within the hydrogel network enables autonomous self-repair following disruption. This intrinsic self-healing property allows the dressing to adapt conformally to complex wound surfaces. Characterization of the OSD/CMC/Fe/PA hydrogel confirmed its high electrical conductivity and effective photothermal antibacterial properties upon NIR light exposure. The hydrogels were also found to possess tunable rheological behavior, mechanically robust properties, and pronounced antioxidant, tissue-adhesive, and hemostatic functions. Evaluation in a murine model demonstrated that all hydrogel dressings promoted markedly improved healing outcomes in infected full-thickness skin wounds[43].

Alifah and colleagues created a self-repairing hydrogel wound dressing using a blend of polyvinyl alcohol and borax, with clindamycin as the active ingredient. Four different combinations of PVA, borax, and clindamycin were utilized in the production of these self-repairing hydrogels, labeled as F1 (4%:0.8%:1%), F2 (4%:1.2%:1%), F3 (1.6%:1%), and F4 (4%:1.6%:0). The findings indicated that F4 exhibited superior physicochemical characteristics, such as a self-repairing time of 11.81 ± 0.34 minutes, swelling ratio of 85.99 ± 0.12%, pH level of 7.63 ± 0.32, and drug loading of 98.34 ± 11.47%. The self-repairing ability was attributed to the B–O–C cross-linking interaction between PVA and borax as indicated by FTIR spectra[42].

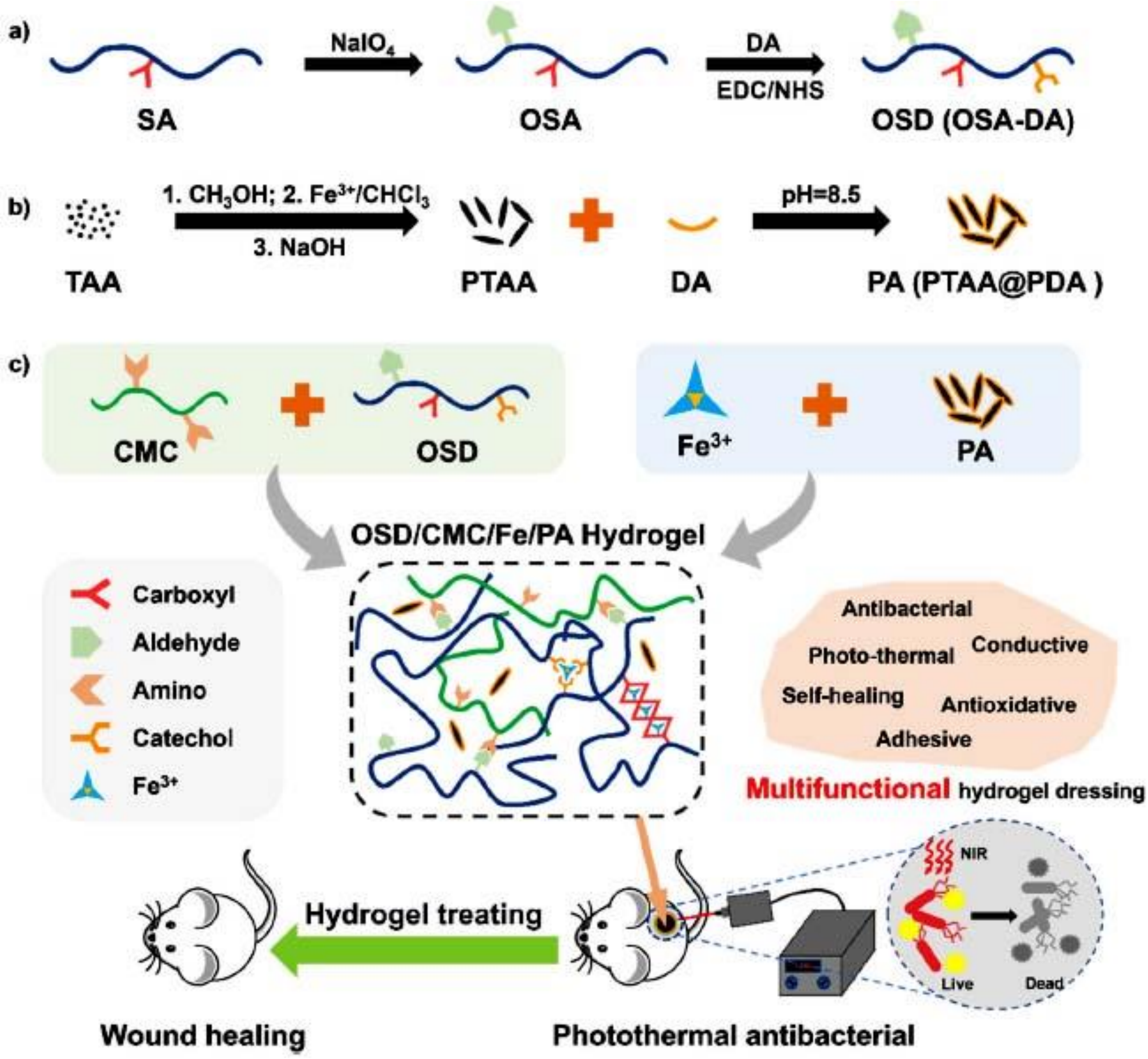

Fig. 6. a) Synthetic pathway for oxidized sodium alginate-grafted dopamine (OSD). b) Preparation process for polydopamine-encapsulated poly (thiophene-3-acetic acid) (PA). c) Illustration of the fabrication and operational application of the OSD/CMC/Fe/PA hydrogel dressing[43].

Qu et al. created a novel type of injectable micelle/hydrogel composites capable of self-healing and with multiple functions to serve as wound dressings for skin injuries. Through the integration of dynamic Schiff base and copolymer micelle cross-linking within a single system, they developed a range of hydrogels by blending quaternized chitosan (QCS) and benzaldehyde-terminated Pluronic®F127 (PF127-CHO) under physiological conditions. The hydrogel dressings displayed appropriate elasticity and pressure-resistance, with a modulus similar to that of human skin. They also demonstrated strong adhesion and quick self-repair capabilities to withstand deformation. These hydrogels showed effective blood clotting ability and compatibility with living tissues. Additionally, the hydrogel containing curcumin exhibited excellent antioxidant properties and release patterns responsive to pH levels. In animal studies, the curcumin-loaded hydrogels notably enhanced the speed of wound healing, leading to increased thickness of granulation tissue and collagen content, as well as heightened production of vascular endothelial growth factor (VEGF) in a model of full-thickness skin injury[27].

Li and colleagues created a novel type of hybrid hydrogel by combining a star-shaped cross-linker called octa-functionalized POSS-PEG-CHO with hydroxypropyl trimethyl ammonium chloride chitosan (HACC) through a Schiff base reaction. These Chitosan-based POSS-PEG hybrid hydrogels displayed robust mechanical properties, injectability, impressive self-healing capabilities, favorable cytocompatibility, and antibacterial features. Additionally, the hybrid hydrogels were able to enhance cell migration and growth, leading to significant improvements in wound healing for diabetic mice[18]. Cui et al. developed a self-repairing antibacterial hydrogel for treating wounds infected with S. aureus. Incorporating dynamic imine bonds, the hydrogel can autonomously heal and adjust its properties, enabling it to conform to irregular wounds and enhance therapeutic safety. Furthermore, by utilizing quaternized chitosan, the hydrogels demonstrated remarkable antimicrobial characteristics and excellent biocompatibility. Evaluation in a rat model of skin wound infections revealed that the hydrogels' remarkable antimicrobial effects expedited wound healing[16].

Chen and colleagues documented findings on a chitosan-derived antibacterial hydrogel that possesses the ability to be injected and self-repair in the context of wound healing related to bacterial infections. Their hydrogel dressing was created through the coordination of thiol-modified chitosan with silver ions, subsequently chemically linked with genipin. The outcomes of their study demonstrated that the developed hydrogel composite exhibited outstanding antibacterial efficacy, self-healing characteristics, and injection capabilities[49].

Salem El-Sayed and colleagues developed a self-healing hydrogel containing 9-Aminoacridine and kanamycin sulfate through the grafting of poly(β-carboxyethyl acrylate-co-acrylamide) onto sodium alginate. The biological assessment demonstrated the hydrogel's excellent biocompatibility, as it did not show any adverse effects on normal human melanocyte cells. Moreover, the hydrogel exhibited strong antibacterial properties against the various bacterial strains tested in the study. Analysis of the rheological characteristics of the hydrogel revealed that it behaves as a non-Newtonian fluid[45].

Geng et al. developed a hydrogel system consisting of polyvinyl alcohol (PVA), borax, and puerarin (BP) that self-assembled through boronic ester bonds. This BP hydrogel displayed impressive physical properties such as flexibility, injectability, malleability, self-repair abilities, and strong compressive strength, along with favorable biocompatibility. In a rat model of chronic wounds in diabetic individuals, the BP hydrogel notably expedited the wound healing process, as demonstrated by histological staining with hematoxylin and eosin (HE), as well as Masson and picrosirius red (PSR) staining. Analyses involving RNA sequencing and multiple immunohistochemistry (mIHC) illustrated that the BP hydrogel functions therapeutically by influencing macrophage polarization, enhancing angiogenesis, and controlling collagen restructuring[50].

5. Active Ingredients in Wound Dressings

The management of diabetic wounds is further challenged by their characteristically irregular contours, which complicate effective healing. This has generated an urgent requirement for innovative hydrogel-based solutions that can not only conform to these intricate geometries but also adapt to the pathophysiological complexity of the diabetic wound environment. Recently, smart self-healing hydrogels have surfaced as a particularly attractive option for this application. A principal strategy to augment their utility involves the incorporation of functional polymers or bioactive substances into the hydrogel matrix, thereby countering the prevalent issue of single-function systems that are efficacious only in discrete phases of the healing process[30]. Additional biological effects could potentially arise when natural and synthetic materials are mixed to carefully design the architecture of the polymer network in the gel, allowing for the creation of wound dressings that possess unique wound healing properties, such as regulated drug delivery[4]. An ideal wound healing agent or dressing serves multiple functions, including protection from bacterial infection, reduction of inflammation, and induction of cell proliferation for tissue reconstruction. Furthermore, it should attenuate the burden of free radicals, which are considered a principal driver of inflammatory responses in wound healing[12].

5.1. Antioxidants: Controlling ROS, Reducing Inflammation

Reactive oxygen species (ROS) are molecules produced during aerobic respiration and play crucial roles in various cellular and biochemical functions such as acting as internal signaling molecules, promoting cellular differentiation, supporting the immune system, and regulating cell death processes. When it comes to wound healing, the immune system harnesses ROS to combat microorganisms that may be present in the injury site. However, prolonged exposure to high levels of ROS can result in oxidative stress, which can harm cells. Oxidative stress plays a significant role in the wound healing process by typically inhibiting the proper remodeling of skin tissues. This stress can lead to DNA damage, the degradation of lipids, reduced enzyme activity, and is recognized as a primary contributor to inflammation at the wound site[12].

An appropriate level of ROS is necessary for the healing of wounds as they function as molecules that signal the enhancement of antimicrobial properties and support the restructuring of blood vessels. Nonetheless, a surplus production of ROS in diabetic wounds can overpower the body's antioxidant mechanisms, resulting in harm to tissues and cell demise, thereby impeding the healing process[30]. Antioxidants are crucial for the process of wound healing as they counteract reactive oxygen species (ROS), which are highly active molecules that can cause severe harm to cells. By integrating compounds that scavenge ROS into wound dressings, the skin's healing capacity is greatly improved. Utilizing drug-infused biomaterials containing antioxidants not only shields against oxidative stress but also delivers supplementary advantages like reducing inflammation and fighting against microbial growth, proving to be a promising strategy for treating wounds[38].

In general, low levels of reactive oxygen species (ROS) are produced as part of the normal process of wound healing to effectively combat invading pathogens and facilitate intracellular signaling, particularly in the context of angiogenesis. To mitigate the harmful effects of ROS, all mammalian cells possess both an antioxidant enzyme system and small antioxidant molecules capable of neutralizing radicals or repairing oxidized molecules at the site of injury. However, in cases of excessive oxidative stress, these protective agents may not be produced in adequate quantities to restore the balance of redox reactions, leading to oxidative stress and contributing to prolonged inflammation, a key factor in the development of chronic nonhealing wounds[9]. Antioxidants have the ability to enhance the healing of wounds and may effectively eliminate free radicals when applied externally[12]. The inflammatory response is significantly driven by ROS, which serve as secondary messengers to activate a range of transcription factors. Given this central role, the proficient management and removal of ROS is a crucial therapeutic objective for difficult-to-heal wounds. The core mechanism underpinning ROS-responsiveness lies in the pronounced chemical reactivity of ROS, which enables targeted interactions with specific functional groups. Integration of chemical units like thioethers, thioketals, selenoethers, and thiophenes allows for this; their selective oxidation by ROS induces controlled transformations in the hydrogel's microstructure and macroscopic properties[30]. Antioxidants help prevent the harmful effects of oxidation and are vital for maintaining the body's physiological balance. Consequently, using antioxidants to mitigate ROS damage is a key focus in skin repair research. Conventional wound dressings frequently fail to provide adequate hemostasis, adhesion, and moisture. In response, new drug carriers such as nanofibers and hydrogels have become a major research focus. These systems optimize drug therapy by increasing efficiency, ensuring safer targeted delivery, reducing application frequency, and mitigating drug odors. Thus, the careful pairing of antioxidants with advanced carriers is fundamental to innovating skin repair technologies[51]. Antioxidant dressing acts by modulating the initial inflammatory phase, preventing the excessive activation of cells that can disrupt healing. This intervention allows for a more regulated and sequential transition through the critical phases of wound repair: inflammation, proliferation, and remodeling[52].

Antioxidants are chemical compounds capable of donating electrons to reactive molecules like ROS. This activity prevents ROS from oxidizing critical biological molecules, including proteins and DNA. Antioxidants are broadly classified into two categories based on their mechanism: enzymatic and non-enzymatic. Non-enzymatic antioxidants, such as vitamin E, vitamin C, glutathione, and flavonoids, are typically low molecular weight compounds. In contrast, enzymatic antioxidants, which include superoxide dismutase, catalase, glutathione peroxidases, and thioredoxins, catalyze complex reaction cascades to neutralize ROS, converting them into stable molecules like water and oxygen. Due to this function, they are often termed ROS scavengers[52].

To maintain ROS at physiological levels, antioxidants act as electron donors. This activity prevents ROS from oxidizing and damaging other cellular molecules. Antioxidants—including both nonenzymatic types (e.g., glutathione, ascorbic acid, and α-tocopherol) and enzymatic types (e.g., catalase and peroxiredoxin)—demonstrate the potential to restore elevated ROS to normal levels, thereby stimulating healing. By modulating ROS in this way, antioxidants can support their beneficial physiological functions and consequently accelerate the wound healing process[53].

To improve the antioxidant capabilities of biofilms, there has been considerable focus on using natural substances and medicinal plants. Herbs present a safe and economical option for dressing wounds, delivering various advantages with reduced adverse reactions when compared to artificial drugs. Scientific investigations have delved into the healing properties of medicinal herbs via detailed mechanistic analyses[34]. Within the diabetic microenvironment, the accumulation of intracellular oxidants triggers excessive ROS generation, which in turn induces immune dysregulation and persistent inflammation. Naturally occurring flavonoids, which are readily available and biocompatible, are recognized for their potent antioxidant activity. Notably, those featuring o-diphenol structures such as catechin, quercetin, and myricetin have demonstrated promising therapeutic efficacy in the treatment of diabetic wounds[41].

The regrowth and restructuring of epithelial tissues in a wound may face hindrance not only due to external microbial intrusion, but also as a result of the elevated levels of reactive oxygen species (ROS) present in the wound's surroundings, including hydrogen peroxide (H_2O_2), superoxide anion radical ($\bullet O^{2-}$), hydroxyl radical ($\bullet OH$), hypochlorous acid (HClO), among others, which can trigger cell death and programmed cell death. Tannic acid (TA), a plant-derived compound that contains multiple catechol groups known for their beneficial antioxidative, antibacterial, hemostatic, and anti-inflammatory properties, aids in controlling ROS levels in the wound environment and expedites the healing of the wound[39].

Licorice, derived from the root and rhizome of Glycyrrhiza glabra, has a long history of medicinal use spanning millennia. The plant's distinct components have been identified for their diverse beneficial properties including anti-inflammatory, antioxidant, antibacterial, antiviral, antitussive, anti-cancer, and antiulcer effects. Particularly noteworthy are Glycyrrhizin, a triterpenoid saponin, and Glabridin, an active isoflavone, which stand out as key contributors to licorice's medicinal benefits[20, 34]. Mousavi and colleagues demonstrated that the inclusion of licorice root extract in the nanocomposite composition notably enhanced its antioxidant efficacy against DPPH free radicals. Of all oxygen radicals, the hydroxyl radical (OH•) is highly reactive and is responsible for oxidative harm to almost all biomolecules[34].

Curcumin, a conventional herbal remedy known for its anti-inflammatory and free-radical fighting properties, has emerged as a promising therapeutic approach for enhancing wound recovery. This natural polyphenolic antioxidant is derived from the rhizome of Curcuma longa, a plant belonging to the Zingiberaceae family, and shows potential for promoting wound-healing processes[9] (Figure 7).

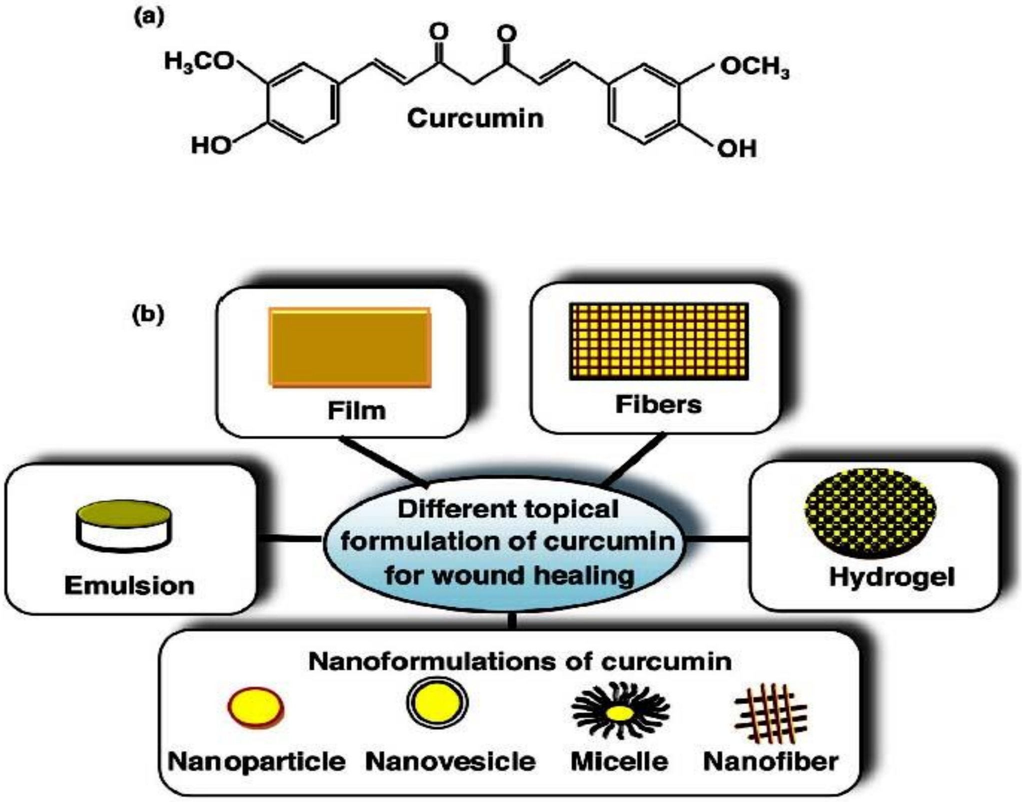

Fig. 7. a) The structural representation of curcumin. b) Various topical compositions of curcumin utilized in wound healing purposes[9].

Curcumin exhibits strong ability to remove ROS, leading to heightened synthesis of antioxidant enzymes in the injured area amid the inflammation stage. Additionally, it accelerates the movement of fibroblast cells, supports the development of granulation tissue and collagen, and aids in the re-growth of epithelial cells during the proliferation phase. Furthermore, curcumin is crucial during the remodeling period as it boosts wound contraction by augmenting cytokine levels to stimulate fibroblast proliferation[27]. The amount of antioxidants in a wound dressing depends on the type of wound and the dressing and varies for different dressings[52].

5.2. Antibacterial agents and Medications: Prevention of Infections

Inflammation plays a crucial role in the stages of wound healing and is typically regarded as the initial phase in achieving effective wound recovery. Since tissue injuries trigger immediate acute inflammation, managing this inflammatory response can enhance the overall process of wound healing[12]. Microorganisms are primarily responsible for causing infections, with open wounds serving as the most common entry point for these microbes to infiltrate the body. Once they penetrate the body, they quickly spread to deeper tissue layers and begin to multiply, forming colonies that can result in internal infections. The solution for these types of infections involves using wound dressings with improved antimicrobial capabilities to promote fast healing. Having antibacterial qualities is crucial for effective wound recovery[21, 24]. Creating wound dressings that have antimicrobial capabilities and great biocompatibility is crucial. While antibiotics can effectively inhibit the growth of bacteria, excessive use of them may result in bacteria developing a resistance[29].

To engineer an effective antibacterial hydrogel, the selection of a potent antibacterial strategy is paramount. Common non-antibiotic approaches include metal ions, natural biological macromolecules, and photothermal agents. Silver nano particles (AgNPs) are extensively utilized as antimicrobial agents because of their comprehensive effectiveness against bacteria, fungi, and viruses. The bacterial cell membranes are disrupted by Ag ions, affecting cellular functions and thereby proving to be highly efficient in warding off wound infections. By being integrated into hydrogel matrices, AgNPs can be evenly distributed, ensuring ongoing antimicrobial efficacy at the wound location and decreasing the likelihood of infection[24, 33].

Zinc oxide nanoparticles (ZnO NPs) are effective antimicrobial agents that offer broad-spectrum protection and are considered safe for biological use. The antimicrobial effectiveness of ZnO NPs is attributed to three key factors: the production of reactive oxygen species (ROS), the release of Zn^{2+} ions, and electrostatic interaction through binding to cell membranes. ZnO NPs also demonstrate potential in promoting the growth and multiplication of fibroblasts to expedite the healing of wounds. Furthermore, when incorporated into hydrogel materials, ZnO NPs are anticipated to improve mechanical properties through interactions such as hydrogen bonds, van der Waals forces, and electrostatic attractions. These findings suggest that ZnO NPs hold promise as valuable components in hydrogel materials for enhancing wound healing. Currently, several studies focusing on integrating ZnO NPs into hydrogels for the treatment of wounds have reported successful outcomes[2, 23, 39]. Copper nanoparticles have the ability to permeate the cell membrane in the presence of bacteria and viruses, leading to their eradication by generating potentially toxic substances that release oxygen[33]. Cerium oxide nanoparticles (CeO2-NPs) have the ability to inhibit the accumulation of reactive oxygen species (ROS), protect cells from damage, and decrease inflammation, thereby promoting a more favorable environment for local healing[40].

However, the utility of metal ions is often constrained by potential cytotoxicity and cost. Similarly, while natural macromolecules like chitosan possess inherent antibacterial activity, they are frequently inadequate for addressing robust biofilm-associated infections. In contrast, photothermal antibacterial therapy has emerged as a promising strategy to eradicate severe infections by leveraging the deep tissue penetration of near-infrared (NIR) light. Realizing this modality requires the incorporation of a photothermal agent into the hydrogel matrix. In this context, poly(thiophene-3-acetic acid) (PTAA) presents a highly promising candidate for antibacterial wound dressings, owing to its excellent biocompatibility, chemical stability, and efficient photothermal conversion properties[43].

Another approach to reducing wound infections involves the use of antibiotic-containing hydrogels, which have proven effective in antibacterial treatment since the discovery of ampicillin by Alexander Fleming. Antibiotics play a crucial role in preventing infection during wound healing and are classified into five main groups: beta-lactams, tetracyclines, fluoroquinolones, macrolides, and aminoglycosides. Some commonly used antibiotics in this context are Gentamicin, Ciprofloxacin, Vancomycin, and Moxifloxacin[4, 33]. The active drug compounds that are released are essential in the process of wound healing, with curcumin being particularly notable for its significant influence on all stages of wound healing[27].

Natural extracts that consist of secondary metabolites are valuable resources in the field of medicine for the development of drugs in biomedical applications. Herbal extracts containing a combination of bioactive components have been widely used for wound healing treatments since ancient times. Many of these extracts exhibit biocompatibility, anti-inflammatory properties, resistance to oxidation, and are capable of enhancing cell behavior during the process of wound contraction[32]. Curcumin is widely recognized for its ability to reduce inflammation, as evidenced by various studies, including clinical trials. It has been shown to impact a range of inflammatory cytokines in various diseases. A key benefit of curcumin in regulating inflammation is its ability to inhibit the production of two crucial cytokines, tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1), which are released by monocytes and macrophages to control inflammatory reactions[12].

The compound 18β-glycyrrhetinic acid (Gly), derived from glycyrrhizic acid (glycyrrhizin) found in the root of Glycyrrhiza glabra (licorice), is known for its calming, anti-inflammatory, and antioxidant characteristics. It serves as an active component in various commercially accessible products, including dietary supplements, as well as dermatological and topical applications. Its anti-inflammatory properties can be attributed to (i) reducing the expression of pro-inflammatory cytokines like interleukin (IL)-6, IL-10, IL-1, and (ii) inhibiting factors such as tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and nuclear factor-κB (NF-κB). Although licorice root has traditionally been known for its anti-inflammatory, antioxidant, and antimicrobial qualities, its potential effectiveness in treating burn wounds in humans has not been thoroughly examined[54]. The anti-inflammatory, antioxidant, and antimicrobial properties of licorice root (Glycyrrhiza glabra) have been well-known for a considerable time. Mohammadi and colleagues examine how a 5% gel containing Glycyrrhiza glabra in a guar gum base affects wound healing and scarring in individuals with second-degree burns The results of their study showed topical application of licorice root gel significantly accelerated burn wound healing and scar resolution compared to standard treatment[15].

Numerous extracts, including lawsone, berberine, ostholamide, aloe vera, gymnema sylvestre, tea tree oil, among others, have been incorporated into various formulations for wound dressings to expedite wound contraction. Nonetheless, the intricate process of isolating and purifying these extracts continues to present a challenge[32]. Puerarin, a potent compound derived from the ancient Chinese remedy Pueraria lobata, has been utilized in managing diabetes due to its advantageous antioxidant, anti-inflammatory, antibacterial, and pro-angiogenesis attributes. However, its effectiveness is impeded by limited water solubility and bioavailability[50].

5.3. Growth factors and angiogenic substances

Advances in understanding the complex wound healing cascade have enabled the identification of key cell-derived signaling proteins, such as growth factors and cytokines, which mediate critical processes including cell proliferation and angiogenesis. This knowledge has directly informed the development of a novel class of bioactive hydrogel dressings that are engineered to deliver these therapeutic molecules or even cells themselves to the wound site[4]. Growth factors play a critical role throughout various stages of wound healing, such as promoting cell growth, guiding mesenchymal cell activity, and aiding in extracellular matrix production. Hydrogels have the capability to be infused with therapeutic substances, cells, diverse molecules, and growth factors that expedite wound closure and prevent infections. Key growth factors like platelet-derived growth factor (PDGF), transforming growth factor-beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF) have been shown to be crucial in the regeneration process[4, 24, 33]. Revascularization of wounds played a crucial role in the healing process, promoting faster recovery. The activity of vascular endothelial growth factor (VEGF) spurred the growth and movement of endothelial cells, leading to expedited angiogenesis and the delivery of vital nutrients[50]. The results from experiments conducted with rat models highlight the effectiveness of utilizing a combination of different growth factors to improve the speed of healing and facilitate skin regeneration rather than just repairing the skin. Research in this area emphasizes the importance of customizing how various growth factors are released to maximize their availability during different stages of healing, which can have a substantial impact on the overall outcomes of the healing process. Additionally, the findings indicate that incorporating natural polymers as bases may increase the efficiency of growth factors, leading to a quicker healing process. Figure 8 provides a thorough summary of the growth factors that have the potential to expedite wound healing[7].

Inorganic biological substances such as bioactive glass (BG) and biological ceramics, possessing biocompatibility, biodegradability, and the ability to promote tissue regeneration, have been widely utilized in the restoration of bone tissue. Studies have indicated that the homogeneous distribution of BG nanoparticles may enhance the healing of long-lasting wounds by stimulating angiogenesis. The antimicrobial properties inherent in biological ceramics and BG offer favorable prospects for their use in wound healing processes[32].

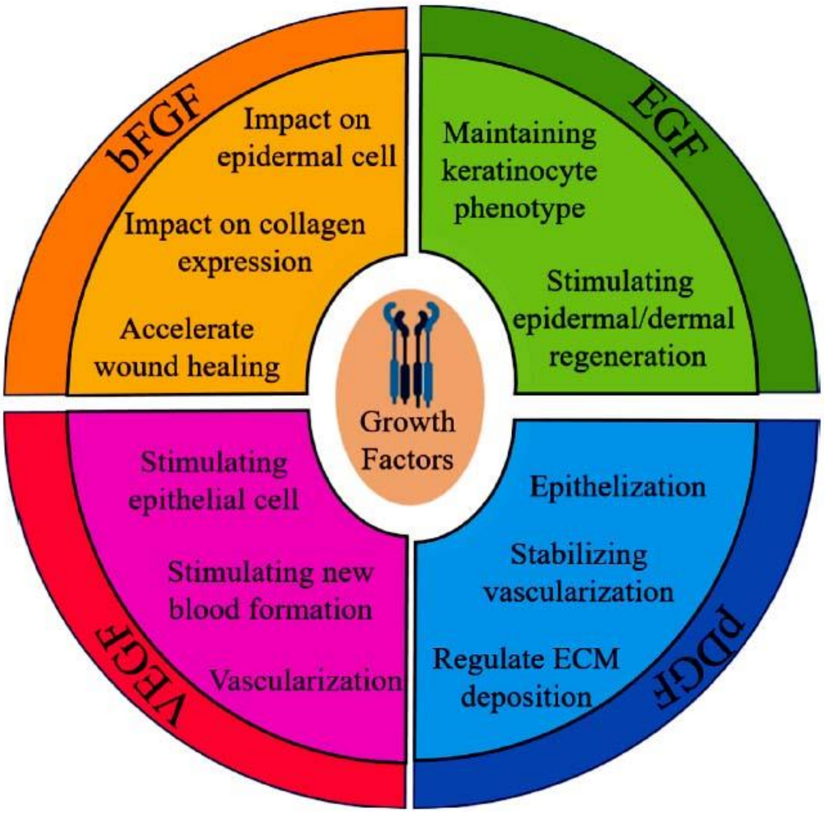

Fig. 8. loaded growth factors found in nanofiber wound dressings promote quicker and scarless healing, playing a crucial role in the wound healing process[7].

5.4. Multifunctional combination

Traditional wound dressings made of hydrogel have limited capabilities, primarily serving as a physical barrier and absorbing exudates, which do not fully address the complex needs of the entire wound healing process. In recent years, there have been numerous reports on the development of chitosan-based self-healing hydrogels with multiple functions specifically designed for wound repair[16]. Multi-functional hydrogels have garnered significant interest due to their impressive mechanical attributes, antibacterial qualities, and biocompatibility[55]. Wound infections that lead to slow wound healing and deterioration present a significant clinical obstacle. The utilization of multifunctional hydrogel dressings has emerged as a promising approach in addressing this challenge, garnering considerable interest for their potential to prevent wound infections and enhance the healing process[39].

Qu and colleagues described a new type of wound dressing specifically designed for treating skin wounds on joints. This injectable hydrogel combines several beneficial features, such as natural antibacterial properties, adhesiveness, ability to stop bleeding, responsiveness to pH levels, desirable strength, and ability to heal on its own. Their research demonstrated the remarkable healing effects of this dressing on wounds using a comprehensive skin defect model, showcasing improvements in healing rate, thickness of granulation tissue, and organization of collagen[27].

Liu et al. developed a hybrid hydrogel comprising gelatin (GL), tannic acid (TA), oxidized sodium alginate (OSA), and zinc oxide nanoparticles (ZnO NPs) using primarily a double network cross-linking technique. The composite hydrogels displayed enhanced mechanical characteristics as a result of the modification of the structure of GL network by TA, the Schiff base reaction between GL and OSA, and the reinforcing impact of ZnO NPs. Simultaneously, the composite hydrogel exhibited notable antimicrobial activity against both Staphylococcus aureus (S. aureus) (97.8 % ± 0.9 %) and Escherichia coli (E. coli) (96.6 % ± 1.2 %), attributable to the combined effects of TA and ZnO NPs. Additionally, due to the beneficial antioxidative properties of TA, the sustained release of Zn^{2+} with effective bactericidal capabilities, and the facilitation of skin epithelial tissue regeneration in BALB/c mice over time, the versatile hydrogel demonstrated a significant therapeutic impact on wound healing and promising applications across various fields[39]. Zhang et al. developed a multifunctional PVA/chitosan hydrogel incorporated with a gelatin network. The results confirmed its effectiveness in controlling wound bleeding, offering a promising new direction for clinical wound management[55].

The increasing misuse of antibiotics leading to bacterial resistance poses a significant challenge in treating bacterial infections in wounds. Conventional antimicrobial dressings often struggle to both prevent bacterial infections and promote wound healing effectively. To tackle this issue, researchers have successfully developed a wound dressing using a polysaccharide self-healing hydrogel (CPP@PDA/Que3) by incorporating quercetin and polydopamine nanoparticles into a carboxymethyl chitosan matrix. This innovative dressing can be locally injected to form a protective barrier over the wound, efficiently stopping bleeding and swiftly reducing inflammation. Additionally, the CPP@PDA/Que3 hydrogel demonstrates exceptional antioxidant and antibacterial properties due to the combination of quercetin and near-infrared (NIR) photothermal therapy[56].

6. Conclusions

Wound healing is a highly complex biological process that requires precise coordination among diverse cell types, signaling molecules, and extracellular matrix components. Disruptions in this process, particularly in chronic wounds such as diabetic ulcers and severe burns, significantly impair patient quality of life and pose substantial clinical burdens. Hydrogel-based dressings have long been favored in wound management due to their favorable biocompatibility, ability to maintain a moist microenvironment, and flexibility. However, traditional hydrogels often suffer from limited mechanical strength, susceptibility to damage, and a passive role in healing, restricting their efficacy in dynamic and irregular wound beds. The advent of self-healing hydrogels represents a transformative advancement, effectively addressing these limitations. By incorporating dynamic, reversible bonds—such as Schiff bases, acylhydrazones, boronate esters, and various non-covalent interactions—these intelligent materials can autonomously repair structural damage, recover mechanical functionality, and adapt to wound contours. This self-repair capability not only extends the dressing's lifespan and reduces replacement frequency but also minimizes patient discomfort and infection risk by maintaining a continuous, conformal barrier. Furthermore, the integration of multifunctional components—including antioxidants (e.g., curcumin, flavonoids) to scavenge reactive oxygen species, antimicrobial agents (e.g., metal nanoparticles, natural extracts) to prevent infection, and growth factors (e.g., VEGF, bFGF) to promote angiogenesis and tissue regeneration—has elevated hydrogels from passive coverings to active therapeutic platforms.

In conclusion, the evolution from classical hydrogels to smart, self-healing systems marks a significant paradigm shift in wound care. These innovative dressings offer enhanced durability, adaptability, and therapeutic efficacy, holding great promise for improving outcomes in acute and chronic wound management. Future research must focus on optimizing their mechanical properties, biocompatibility, and large-scale manufacturability to facilitate clinical translation and personalized medicine approaches.

7. Future Perspectives:

Despite remarkable progress, several challenges and opportunities lie ahead in the field of advanced wound dressings. Future research should focus on the following key directions:

1. Personalized and Precision Medicine: Developing dressings that can be tailored to individual patient profiles (e.g., wound type, microbiome, metabolic status) using biomarkers and point-of-care diagnostics. Integration of biosensors for real-time monitoring of wound parameters (pH, temperature, infection markers) could enable adaptive treatment and early intervention.
2. Enhanced Biofunctionality and Multimodality: Designing next-generation hydrogels that combine self-healing with multiple stimuli-responsiveness (e.g., to ROS, glucose, bacterial enzymes) and diverse therapeutic actions. Exploring synergies between different bioactive agents (e.g., combining antimicrobial peptides with immunomodulators) could address complex, multifactorial wound pathologies more effectively.
3. Advanced Fabrication and 3D Bioprinting: Leveraging technologies like 3D bioprinting to create dressings with spatially controlled architecture, gradient properties, and even embedded living cells (e.g., fibroblasts, stem cells) for true tissue regeneration rather than mere repair. This could be pivotal for treating full-thickness wounds and achieving scarless healing.
4. Combatting Antimicrobial Resistance (AMR): Prioritizing the development of non-antibiotic antimicrobial strategies (e.g., photothermal therapy, quorum sensing inhibitors, cationic polymers) and smart systems that release antimicrobials only in response to infection cues, thereby reducing the risk of resistance development.

By addressing these frontiers, the next generation of polymeric wound dressings has the potential to revolutionize wound care, shifting from generic, passive products to intelligent, personalized therapeutic systems that significantly improve healing outcomes and patient quality of life.

Conflict of interest

The author declares no conflict of interest.

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