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REVIEW PAPER

Multifunctional polymeric wound dressings

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Abstract

Wound healing is a multifaceted process influenced by various biological and mechanical factors, necessitating personalized treatment approaches. Wound dressings have become a crucial component of wound care due to their non-invasive nature and ability to create a controlled healing environment. However, traditional dressings often lack the mechanical strength and bioactivity required for optimal healing, driving research into biomaterials and advanced fabrication techniques to enhance their functionality. Recent advancements have culminated in the development of biofunctional wound dressings that exhibit high biocompatibility, non-toxicity, and the ability to accelerate the healing process while maintaining mechanical integrity suitable for different wound types. These next-generation dressings incorporate protective barriers, absorb wound exudates, and provide antimicrobial, anti-inflammatory, and tissue-regenerating properties. The integration of multifunctional and smart wound dressings with nanofibrous scaffolds, platelet-rich fibrin, and 3D-printed biomaterials has enhanced their therapeutic efficiency by mimicking the natural extracellular matrix and enabling controlled drug delivery. Additionally, sensor-integrated dressings capable of real-time wound monitoring and stimulus-responsive drug release represent a promising avenue for personalized wound care management. This review provides a comprehensive analysis of modern wound dressing technologies, their classification, and the biomaterials utilized in their fabrication. It also highlights the advantages of biofunctional and smart dressings in promoting efficient wound healing and tissue regeneration.

Keywords Wound dressing · Wound healing · Multifunctional · Smart · Biopolymer · Nanofibrous scaffold · Platelet-rich fibrin · 3D-printed biomaterials

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Introduction

A wound is defined as the destruction and deterioration of the integrity of tissues due to physical or chemical reasons. The classification of wounds is determined by factors such as healing time, wound depth, wound type, and cause of injury. The healing process of a wound is classified into two categories: acute and chronic. The depth of a wound is categorized into three types: superficial, deep dermal, and full-thickness. The cause of injury can be categorized into three types: traumatic, iatrogenic, and burns. Finally, wounds can be categorized into different shapes, such as abrasions, cuts, bruises, and penetrating and fragmented wounds. The healing process of a wound is a dynamic and complex process involving the structural or functional repair of injured tissue. The study of wound healing is approached through a systematic, four-stage process. The initial phase, hemostasis, is the body's immediate response to injury, aimed at halting bleeding and preventing further damage to surrounding tissues and organs. Subsequent to hemostasis, the inflammatory response initiates, during which dead and damaged cells, microorganisms, and wound residue are removed, and the inflammatory response is activated. This is followed by the proliferation phase, which lasts for approximately 2 weeks. During this phase, the momentary scaffold plug undergoes several stages of transformation, eventually becoming a permanent tissue plug. Subsequently, in the restructuring phase, the newly formed capillary density regresses to the average vessel density, and scar maturation and collagen remodeling occur. A dressing is a sterile compress used to prevent further damage to the injured tissue and to protect the area from the risk of infection. The ideal wound dressing possesses several key features. These include sterility, biocompatibility, non-toxicity, and non-allergenicity, the provision of heat insulation and gas exchange, the absorption of wound exudate, and the prevention of adhesion to the wound (Fig. 1).

The evolution of wound dressings has been a continuous process since 2000 BC, with innovations tailored to address the fundamental characteristics and requirements of various wound types. Conventional dressings, which remain

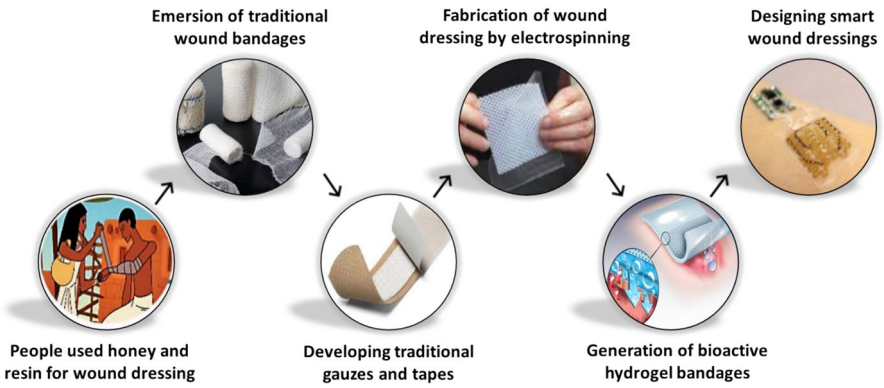


Fig. 1 Historical development of wound dressing

prevalent in contemporary practice, have been developed for purposes such as controlling bleeding, protecting tissue from secondary injury, removing excess exudate, and preventing infection. Examples of conventional dressings include gauze and bandages, clear films, foams, hydrogels, hydrocolloids, hydroconductive, and capillary dressings. Bioactive dressings, in contrast, contain active ingredients such as growth factors and vitamins, and are used for various types of wounds. They are produced from biopolymers such as alginate, chitin, and chitosan.

A notable category of wound dressings is that of drug-loaded wound dressings. These are formed by loading drugs and antimicrobial agents onto the wound dressings, with the drug released in the target tissue via an in situ release feature. This prevents the occurrence of side effects in non-target tissues. Based on the substance loaded into them, drug-loaded wound dressings are classified as dressings that release antibacterial agents, release anti-inflammatory drugs, or contain biological factors.

Wound

Damages and deformations to the skin are the result of diseases experienced in daily life or accidents. A wound is defined as the deterioration of skin or tissue integrity due to mechanical, thermal, electrical, chemical injuries, or medical and physiological disorders. Therefore, it is imperative to prioritize skin protection against external factors. The healing time of wounds varies significantly and is influenced by various factors, including the anatomical location, the affected vessel, and the extent of fluid loss [1, 2]. The formation of a wound invariably compromises the protective function of the skin. The occurrence of a wound leads to the exposure of underlying anatomical structures to the external environment. The presence of microorganisms in the immediate vicinity of the wound can facilitate the entry of these organisms into the body through this opening, which is contingent upon the nature of the wound, and can lead to severe complications [3]. The classification of wounds is typically based on their severity and healing time, with wounds being categorized into two primary groups: acute and chronic wounds. Acute wounds are defined as those originating from within the cell or system, encompassing categories such as crush injuries, abrasions, hematomas, sprains, metabolic disorders, and foot ulcers. In contrast, chronic wounds are characterized by a disruption in tissue homeostasis, resulting from biosynthesis and subsequent destruction events [4]. The treatment of wounds commences with their formation, and wound care is tailored to the specific characteristics of each wound. Consequently, the approach to wound care should be guided by the severity of the injury and the individualized healing process.

Wound healing

Wound healing is a complex and dynamic process involving the repair of structural or functional defects in cellular structures and tissue layers [5, 6]. As soon as a superficial wound is formed, various mechanisms are activated to clear the

wound surface of pathogens and to perform primary structural repair of the tissue. This complex healing process combines various inflammatory cells, cytokines, chemokines, nutrients, and matrix molecules released into the wound bed [7].

The utilization of dressings is aimed at safeguarding the wound during the initial 48 h in such healing wounds. The scar tissue barrier system should be designed to obviate the necessity for additional dressing after this period. Wound dressings employed for wounds that heal with primary intent should be transparent for unobstructed inspection, facilitate the absorption of exudate, and possess a waterproof barrier [8]. The selected wound dressing should foster the formation of granulation tissue in secondary wound healing. The promotion of epithelialization is further accelerated by the need for moist wound healing. The autolysis process is also promoted by the presence of a moisture environment. The time required to change a wound dressing varies depending on whether the wound is acute or chronic. It is especially important to wrap wounds with dressings that fit perfectly to their shape and can be removed without causing damage [8].

Traditionally, wound healing processes have been divided into four successive phases (Fig. 2).

Hemostasis is defined as the body's primary response to injury, occurring as platelets and inflammatory cells gather at the site of injury to halt blood loss and avert organ dysfunction. This initial phase of hemostasis establishes a provisional barrier to stop further blood loss and initiates the process of wound healing [6, 9]. Concurrent with the hemostatic response is the onset of inflammation. During this phase, dead and damaged cells, microorganisms, and wound residue are removed. Neutrophils, lymphocytes, and monocytes accumulate at the injury site. Neutrophils protect against infection by producing protease and reactive oxygen species (ROS). Subsequent to the accumulation of neutrophils, lymphocytes and monocytes differentiate into macrophages, which phagocytize bacteria, foreign particles, and damaged tissue. The release of cytokines by these cells activates

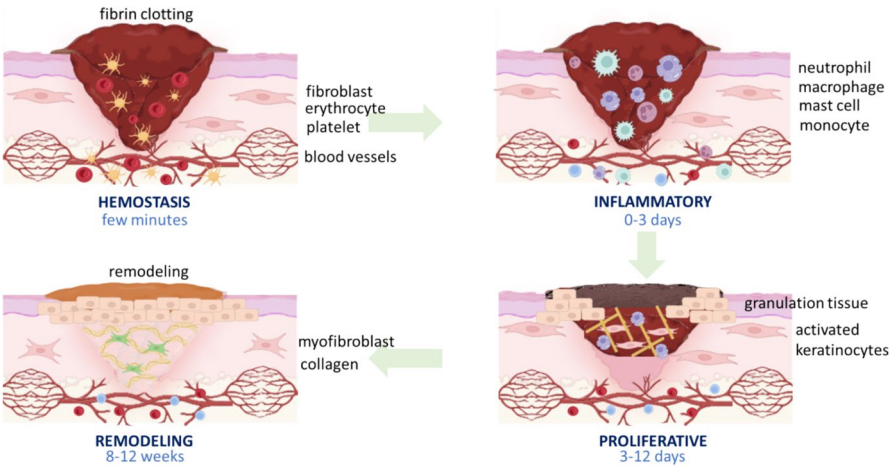


Fig. 2 Schematization of wound healing path

the inflammatory response and, in addition, induces apoptosis in cells [5]. The proliferative phase, which lasts approximately two weeks, commences on the third day post-injury with the migration of fibroblasts and myofibroblasts. During this phase, fibroblast migration is followed by collagen synthesis and angiogenesis. At this stage, the transient scaffold plug is transformed into a permanent tissue plug through subsequent stages, including angiogenesis, granulation tissue formation, re-epithelialization, and wound contraction [5]. In the final remodeling step, the majority of newly formed capillaries regress to a level that returns to average vessel density. Scar maturation and collagen remodeling continue for up to two years, exhibiting a protracted recovery period in adults, although it progresses more rapidly in infants [5].

Wound dressing

A wound is defined as damage to tissues and deterioration of anatomical structure and function due to physical, thermal, mechanical, and electrical reasons. Wound healing time, wound depth, wound type, wound location, clinical appearance, etc., are classified according to factors [5, 9]. Wounds are divided into acute and chronic wounds according to the healing process. Acute wounds are healed in a minimum time and regularly without the need for any external support. Chronic wounds, on the other hand, exhibit a protracted healing phase, often spanning weeks or even months, and may not heal entirely or may heal in a different manner than expected [9].

The classification of wounds is further complicated by the consideration of wound depth, with wounds being classified as superficial, deep dermal, or full-thickness wounds. Superficial wounds are limited to the epidermal layer and typically take approximately 10 days to heal. In contrast, deep dermal wounds, also referred to as split-thickness scars, extend deeper into the tissue layers. Unlike superficial wounds, these wounds exhibit a prolonged healing time of 10 days to 3 weeks, characterized by the formation of scar tissue and re-epithelialization. In cases of full-thickness wounds, the healing time is extended due to damage to both the dermis and hypodermis [9].

The classification of wounds can be further categorized based on their shape, including abrasions, cuts, bruises, penetrating, and fragmented wounds. Clean wounds pose no risk of infection and are far from the digestive and respiratory systems. Such wounds become contaminated with microorganisms present in the tissue. Clean contaminated wounds, close to the digestive and respiratory systems and without tissue fluid loss, but contaminated wounds are non-purulent inflammatory wounds that are formed by microorganism contamination during surgery. In contrast, dirty and infected wounds are wounds on which purulent inflammation has occurred due to the contamination of microbes from the environment [9].

The classification of wounds is determined by the etiology, which can be traumatic, iatrogenic, or burn-related [9]. The practice of wound dressing has its origins in antiquity, with methods that were developed based on insights from

ancient civilizations' medicinal texts. The Egyptian period is considered the origin of modern wound dressing, a three-step process involving the application of a plaster, followed by washing the wound and bandaging [12]. In contemporary times, wound dressings encompass a wide array of materials, including oil, medicinal herbs, mud, and clay [10]. A dressing is defined as a sterile compress that functions as a barrier, aiming to protect the tissues in the affected area from additional damage and the risk of infection, while also facilitating the healing process [11]. The dressing plays a pivotal role in the wound healing process by safeguarding the wound from potentially harmful microorganisms [9]. In addition to their protective function, wound dressings facilitate collagen synthesis and re-epithelialization, which are crucial processes in wound healing. Furthermore, wound dressings that reduce the pH of the wound can accelerate the healing process by inducing hypoxia. The selection of a wound dressing should be made with consideration for the specific characteristics of the wound, ensuring that it is suitable for the wound's needs, does not cause additional damage during replacement, reduces the wound pH, and effectively absorbs exudate. The findings of numerous studies consistently demonstrate that wounds maintained moist heal more rapidly and effectively than dry wounds. Consequently, ensuring wound moisture is paramount. Additionally, the ideal wound dressing should be breathable, as wounds require oxygen during the healing phase and in daily life to facilitate effective healing [9].

The ideal wound dressing must possess certain properties. It should provide a moist environment for the wound and protection against infection. The dressing must be sterile, biocompatible, and non-toxic or allergic. It should provide thermal insulation to stop bleeding, relieve pain in the wound area, and regulate blood flow in the capillaries. The dressing should support angiogenesis, tissue synthesis, and cell proliferation. It should not prevent gas exchange between the tissue and the environment and should absorb the excess exudate formed on the wound surface. It is imperative that the material does not adhere to the wound and that it can be readily detached without causing harm to the healing process [11] (Fig. 3).

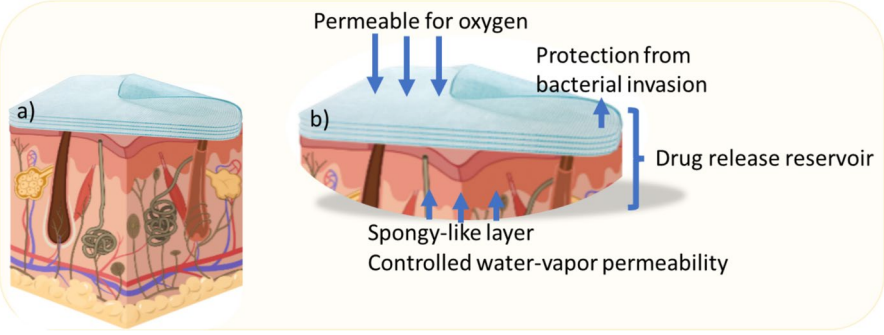


Fig. 3 Schematic representations of skin structure (**a**), and design of an ideal wound dressing (**b**)

Polymers for wound dressings

Natural polymers

Polysaccharides are a class of natural polymers that have gained significant attention in the field of tissue regeneration due to their ability to promote healing and support the regeneration of damaged tissue. These polymers stand out due to their unique combinations of properties, which contribute to their effectiveness. In addition to their biocompatibility, polysaccharides exhibit antimicrobial and anti-inflammatory properties, making them a promising candidate for use in medical applications. Their ability to reconstruct the extracellular matrix (ECM) architecture provides a distinct advantage over other polymers, making them a valuable addition to the field. Furthermore, they do not elicit an adverse immunogenic response during the wound healing process, instead interacting with immune system components to stimulate macrophages [12, 13].

Carbohydrate-based natural polymers

Animal origin carbonhydrates

Chitosan

Chitin, otherwise known as poly-β-(1 $\rightarrow$4)-*N*-acetyl-D-glucosamine, is a prevalent natural marine biopolymer. It is produced industrially from the shells of crustaceans such as crabs, shrimps, and lobsters. The primary chitin derivative is β-(1–4)– 2-amino- 2-deoxy-D-glucopyranose, more commonly referred to as chitosan. Chitosan is a linear polysaccharide comprising *N*-acetyl-glucosamine and *N*-glucosamine units, which are produced by subjecting chitin to *N*-deacetylation at temperatures of 180 °C using solid NaOH. The degree of deacetylation (DDA), defined as the number of *N*-glucosamine units, exerts a pivotal influence on the physicochemical characteristics of chitosan. The DDA of chitosan directly influences its physicochemical properties, biodegradability, and immunological activity. The DDA of chitosan can be measured by various methods, including the ninhydrin test, linear potentiometric titration, and near-infrared spectroscopy. However, due to its hygroscopic nature, the sample must undergo complete drying prior to measurement. Chitosan exhibits solubility in diluted organic acids, such as acetic acid, citric acid, and lactic acid, due to the presence of a primary amino group, with a pH lower than 6.5. The formation of polyelectrolytes from amino groups contributes to its insolubility in water, despite its high water absorption capacity compared to cellulose. In comparison with chitin, which necessitates a highly toxic solvent such as lithium chloride, the solubility of chitosan is regarded as a significant advantage, particularly in biological applications [14] (Fig. 4).

The physicochemical properties of chitosan, which possesses a variable molecular weight, such as viscosity, solubility, elasticity, and tear strength, are influenced by its molecular weight. For instance, chitosan with an average molecular weight exhibits the strongest antimicrobial properties, while chitosan with the lowest molecular weight demonstrates the highest inhibitory effect on phytopathogens. Additionally,

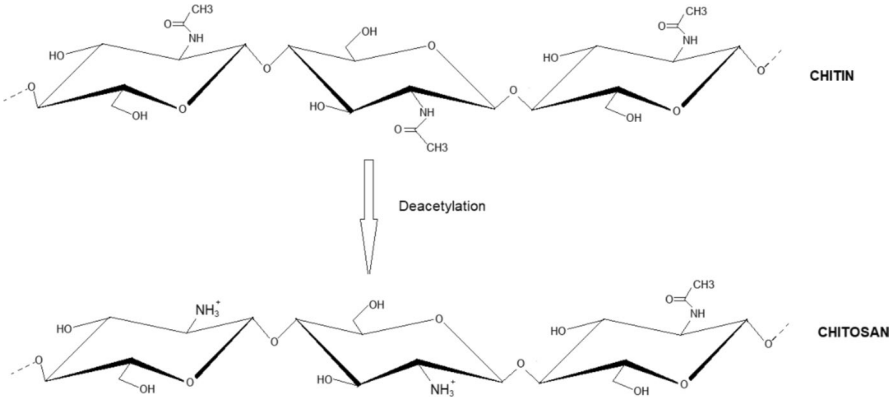


Fig. 4 Structure of chitosan

irrespective of the change in molecular weight, chitosan remains one of the most potent antibiotics against gram-positive bacteria. Chitosan's chemical composition includes three putative functional groups: the amino group, the acetamido group, and the primary/secondary hydroxyl group, which facilitate the modification process to yield various derivatives. However, the mechanical properties and water solubility of chitosan-based materials are limited, which hinders their applications in fields such as wound healing and drug delivery. Consequently, the synthesis and utilization of chitosan derivatives is recommended to enhance the efficacy and versatility of these materials.

Graft polymerization, a process in which side chains of natural and synthetic polymers are added results in the creation of new material types and the optimization of the properties of the original polymer. This process has been employed to enhance the hydrophobic properties of the chitosan backbone, thereby producing amphiphilic derivatives. Furthermore, the incorporation of alkyl chains into the chitosan backbone through hydrophobic interactions has been demonstrated to enhance its physicochemical properties. Additionally, the blending or combination of chitosan with other polymers is recognized as a significant method to enhance the mechanical properties of the resulting composite [14].

Chitosan and its derivatives have been shown to possess significant antimicrobial properties, making them suitable for a variety of medical and food applications. The antimicrobial efficacy of chitosan can be influenced by numerous parameters, including its molecular weight. Studies have demonstrated the antimicrobial effect of low molecular weight chitosan on human wound pathogens. Another factor that affects the antimicrobial property of chitosan is DDA. The positive charge density in the CS, which is responsible for interacting with the cell wall, is influenced by DDA. Variables such as pH, solubility, and ambient temperature also play a role. It is imperative to note that numerous parameters have the capacity to influence the antimicrobial activity of chitosan [14]. The utilization of chitosan in an active dressing, when considered in isolation, is not conducive to the development of controlled release formulations. To address this limitation, the incorporation of

crosslinking agents, also referred to as cross-linkers, becomes essential. These agents serve to establish intermolecular bridges between the polysaccharide segments of chitosan, thereby facilitating chemical or physical crosslinking with the polymer. This process enables the precise modulation of drug release. Moreover, these crosslinking agents contribute to the enhancement of mechanical properties and the attainment of high drug loading capacity within controlled release systems. In addition, the combination of chitosan and crosslinking agents results in a more stable system than either agent alone, exhibiting enhanced resistance to extreme conditions such as high temperatures and low pH levels [12]. Mehrabani et al. developed silk fibroin/chitin nanocomposite scaffolds for wound dressing applications. These scaffolds possess inherent biodegradable and biocompatible properties, making them highly effective for wound treatment. The addition of Ag nanoparticles to the silk fibroin/chitin nanocomposite scaffold further enhances its antibacterial properties. This incorporation method led to an enhancement in the amount of silver nanoparticles, resulting in the production of low porosity scaffolds. The tensile strength of the scaffold was observed to increase with the addition of Ag nanoparticles, and the silk fibroin/chitin/AgNP scaffold was found to be effective for wound dressing applications [15].

Hyaluronic acid

Hyaluronic acid, a naturally derived polysaccharide, is regarded as one of the most effective ingredients for skin repair. Hyaluronic acid, an unsulfated, anionic glycosaminoglycan, possesses a high molecular weight. In addition to being a primary component of the extracellular matrix (ECM), it is employed in the formulation of wound dressings due to its biocompatibility and ability to regulate biological processes. Its hydrophilicity and moisturizing properties contribute to wound surface hydration, thereby reducing the risk of biofilm formation. Hyaluronic acid plays a pivotal role in various biological processes, including tissue homeostasis, angiogenesis, tumor biology, and anti-apoptosis activity. Additionally, it is highly significant in tissue regeneration and wound healing processes due to its biocompatibility, biodegradability, and viscoelastic properties [12, 16].

Plant origin carbonhydrates

Alginates

Alginate is a linear anionic polysaccharide composed of repeating β− 1,4-linked D-mannuronic acid (M) and L-guluronic acid (G) units in varying proportions, extracted from brown algae or bacteria. It is also known as alginic acid salts and forms salts with different solubility in water, thereby forming solutions with different degrees of viscosity [6, 17].

Alginate's high G-block content facilitates the formation of solid hydrogels [6]. The flexibility or stiffness of the resulting gel is influenced by the guluronic content, the distribution of monomers in the polymer chain, the charge, and the volume of carboxyl groups [17]. Each of these hydrogels, when bound to divalent

cations such as Ca^{2+}, exhibits a regular binding pattern to two opposing G blocks, forming the so-called egg-box conformation. Conversely, alginate's high M block content exhibits immunostimulatory activity and reduced adhesive properties [9]. Alginates are derived from diverse natural sources, exhibiting variations in their M-G content and block length [17]. Alginates possess characteristics such as hydrophilicity, biocompatibility, and substantial liquid absorption capacity, rendering them a significant material for wound dressings. Alginate has been demonstrated to activate macrophages and accelerate chronic wound healing, particularly by stimulating monocytes and producing interleukin- 6 (IL- 6) and tumor necrosis factor α (TNF-α). Alginate-based dressings can be applied in the form of hydrogels, films, foams, nanofibers, membranes, and sponges. Films and membranes are compatible and adhesive. Foams, on the other hand, consist of solid, porous matrices that can absorb exudate and conform to body surfaces. However, they are generally non-adhesive and require the use of secondary dressings. Alginate nanofibers and hydrofiber blankets can form gels upon contact with liquid and are highly absorbent. Nonetheless, they should not be used on dry wounds, as they can produce fibrous residue [6].

Alginate hydrogels, akin to other hydrogels, possess hydrophilic properties, as well as biodegradability, moisture permeability, and fluid absorption. They are nontoxic and exhibit high liquid absorbency, and they can form a hydrogel on the wound surface to maintain the moist environment that is imperative for wound healing. The most salient feature of alginate hydrogels is their inability to adhere to scar tissue unless dried, thereby preventing secondary damage to the wound surface during removal [6]. Mudlovu et al. obtained an alginate-chitosan-based wound dressing material, which is prepared via three steps: crosslinking of polymers, lyophilization, and pulverization. Calcium chloride was used as a cross-linker to improve the hemostatic properties of the wound. Consequently, a film suitable for wound dressing was formulated using alginate and chitosan [18]. In a separate study, Hajili et al. investigated the antibacterial and anti-inflammatory properties of lavender in alginate/PEO nanofibers, aiming to explore the potential of LEO in enhancing the healing of burn wounds [19].

Pectin

Pectin, a polysaccharide derived from plants, is characterized by its heterogeneity, which is attributed to the presence of two main domains: homogalacturonan (HGA) and rhamnogalacturonan (RG). The HGA domain facilitates the crosslinking of pectin in the presence of multivalent cations, while the RG domain contributes to the biological activity of pectin. Pectin's biocompatibility and mucoadhesive properties render it a suitable candidate for diverse biomedical applications, including anticancer therapy, drug delivery systems, bone regeneration, and wound healing. Its use in nanofiber wound dressings is notable for both its accessibility and cost-effectiveness, and its capacity to facilitate topical drug administration, thereby enhancing skin protection and promoting the healing process [12].

Dextran

Dextran, a polysaccharide that is obtained from bacteria and is soluble in water, is considered to be an analogue of extracellular matrix glycosaminoglycans. It has been demonstrated to interact with glucan receptors on fibroblasts; consequently, it is utilized in biomedical applications, such as wound treatment. It is combined with hydrophobic polymers in wound dressing synthesis due to its biocompatible, biodegradable, and hydrophilic nature. This combination enhances the mechanical strength and thermal stability of the resulting product [12].

Pullulan

Pullulan, a polysaccharide produced by Aureobasidium pullulans using starch, forms flexible fibers and films that are ideal for use in the production of dressings. Like other polysaccharides, it has properties such as biocompatibility, biodegradability, and non-toxicity. However, pullulan has a unique chemical structure that differs from other polysaccharides. This structure gives pullulan a high water absorption capacity, excellent water solubility, and adhesive properties [12].

Cellulose

Cellulose, a polysaccharide that is found in nature and abundantly present in plants, possesses several advantageous properties that make it a promising material for biomedical applications. Its biocompatibility and biodegradability are key advantages, while its low cost and low solubility in organic solvents are significant benefits. The tendency of cellulose to form mixtures is minimal, which is also beneficial for its biomedical applications. To further enhance its properties and expand the range of applications, research is being conducted on various cellulose derivatives. Among these, cellulose acetate stands out as a particularly studied derivative due to its biocompatibility, biodegradability, non-toxicity, and high hydrophilicity. However, its mechanical properties are insufficient, necessitating the incorporation of polymers such as polycaprolactone and polyvinyl alcohol to enhance its mechanical stability [12].

Konjac glucomannan

Konjac glucomannan (KGM) is a non-toxic polysaccharide composed of glucose and mannose linearly linked by glycosidic bonds. KGM, whose aqueous solution is highly viscous, has outstanding biocompatibility, nutritional value, stability, and specific slow-release performance. The acetyl and hydroxyl groups in its structure provide KGM with high water affinity. This feature endows the KGM-based material with high elasticity and effective exudate absorption, particularly in wound dressings [16]. In a related study, Ismail et al. fabricated a gellan gum (GG) matrix with titanium dioxide nanoparticles (TiO2 NPs) for wound treatment. The resulting GG/TiO_2NPs film demonstrated favorable mechanical properties and swelling capacity, along with noteworthy antimicrobial activity and healing properties. Consequently, the GG/TiO_2NPs film emerges as a promising candidate for utilization as a wound dressing [20].

Protein-based natural polymers Collagen

Collagen, a biocompatible protein found in abundance in the connective tissues of the human body, has been utilized in the form of collagen-derived dressings for a considerable period. The first documented use of collagen occurred through injection beneath the dermis in the wound area. According to the extant literature, collagen has been employed in the treatment of dermal injuries in various forms, including suspension, foam, suture, sponge, gel, and wound dressing materials. However, there is a paucity of literature addressing the use of collagen as a wound dressing membrane. Historically, collagen-rich pig skin has been utilized as a wound dressing for treatment of various injuries. Recently, the use of biodegradable collagen type I membranes has emerged in cases such as burn wounds and surgical defects of the oral mucosa, where rapid epithelialization is imperative. In addition to their role in hemostasis to support wound healing, collagen membranes are susceptible to high permeability, which can compromise their effectiveness [21].

Gelatin

Gelatin (GE), a protein polymer of animal origin, is obtained by the hydrolysis of collagen and is found in the skin, bone, and connective tissues of mammals and marine animals. Gelatin is used in the production of wound dressings due to its easy availability and low cost. In the production of gelatin-based films, the addition of plasticizers is necessary to improve the film properties. Glycerol, a plasticizer that can form a suitable active ingredient carrier with gelatin, is used in gelatin-based film formation [16]. Based on their results, they proposed that the bioactive, biodegradable, and non-toxic CAL/gelatin/chitosan membranes could be a promising candidate for wound dressing applications [22].

Sericin

Sericin, a hydrophilic polypeptide that constitutes another component of silk fibers, possesses a variety of biological activities, including antioxidant, antibacterial, anticoagulant, cell proliferative, and wound healing properties, as well as non-toxic, biodegradable, biocompatible, and bio-adhesive characteristics. However, its brittle and amorphous structure imposes limitations on its applications in the biomedical field. However, its mechanical properties can be enhanced through copolymerization or crosslinking with other polymers [16].

Starch

Starch, a carbohydrate polymer composed of amylose and amylopectin molecules in variable proportions, is a readily available, economical, and biodegradable material. Its mechanical properties are enhanced by increasing the amylose

content, though chemical modifications cannot sufficiently improve its strength for use in dressing design. Due to its inherent weakness and inadequate film-forming capacity, starch necessitates incorporation with other polymers for effective utilization in wound dressings [16]. In a study by Aritra Das et al., polyvinyl alcohol/starch/glycerol/citric acid (PVA/St/Gl/CA) films were developed for wound dressing applications. These films were then compared with PVA composite films. The PVA composite films exhibited superior swelling potential, enhanced solubility, reduced elastic modulus, noteworthy in vitro degradation, and effective antibacterial activity. The PVA/CA/St/Gl films, fabricated with enhanced flexibility, reduced elastic modulus, elevated solubility, and augmented swelling potential, emerged as optimal materials for wound dressing applications [23].

Keratin

Keratin, a structural fibrous protein that is abundant in cysteine and found in hair, nails, wool, feathers, and horns, is of significant importance to human skin. Keratin, which can be obtained from wool without the need for hydrolysis of peptide bonds, plays an important role in wound healing. It can be incorporated into dressings and creams, where it exerts a therapeutic effect on chronic wounds [16].

Silk fibroin

Silk fibroin (SF), a fibrous protein composed of glycine, alanine, and serine, is obtained from the cocoons of silkworms, insects, and spiders. It possesses a structure that prevents the formation of exudate and exhibits favorable mechanical properties. SF is one of the primary components of silk fiber and can be completely degraded by naturally occurring proteolytic enzymes. Additionally, it functions as a suitable substrate for cell adhesion and proliferation [16]. In order to obtain a synergistic antibacterial activity, CS and ZnONPs were coated on SF/PVA films. The coating was made by a sonochemical process, and the CS/ZnONP-coated SF/PVA films exhibited excellent antibacterial activity against gram-positive and gram-negative bacteria in wound dressing [24].

Synthetic polymers

Polyvinyl alcohol (PVA) PVA, a water-soluble polymer, has garnered significant attention due to its remarkable film-forming capabilities, ease of processability, commendable mechanical properties, and chemical stability. Its employment in conjunction with natural polymers is aimed at enhancing the mechanical properties of the resultant composite. The polymer's non-toxic, biocompatible, and biodegradable nature is particularly advantageous, as are its notable mechanical properties. However, it is important to note that PVA lacks inherent antibacterial properties [16]. In a separate study, Chen assembled graphene oxide with polyhexamethylene guanidine (PHMG) through covalent bonding to form modified graphene oxide, which was then

combined with a PVA/chitosan matrix. This PVA/Chi/mGO composite was identified as a promising material for wound dressing applications [25]. Aritra Das et al. manufactured polyvinyl alcohol/starch/glycerol/citric acid (PVA/St/Gl/CA) films for use in wound dressing applications [26].

Polyacrylic acid (PAA) The polymer under consideration is mucoadhesive and soluble in aqueous media. It has been demonstrated to enhance the swelling and adhesion capacity of films. In acidic environments, the polymer is responsible for mucoadhesion. It has been shown to bind with other polymers, making it suitable for use in controlled drug delivery systems [16].

Polycaprolactone (PCL) PCL, a polyester with a partially crystalline structure, is a stabilized, elastomeric, and highly flexible material with a low melting point. It is frequently utilized as a matrix in wound dressings, forming a cost-effective and biodegradable material through its bonding with starch [16]. In a recent study, Fawal et al. fabricated a scaffold based on gelatin and polycaprolactone (PCL) for wound dressing applications. They obtained an antimicrobial and antioxidant scaffold from polycaprolactone and gelatin polymers incorporated with oregano oil using the electrospinning technique [27].

Polyethylene glycol (PEG) This polyether boasts a water-soluble and flexible structure, manifesting in diverse shapes and configurations. When its molecular weight is less than 20,000 g/mol, it is designated as PEG, while above 20,000 g/mol it is termed polyethylene oxide (PEO). These polyethers exhibit neither toxic nor immunogenic properties; however, their primary disadvantage lies in their non-biodegradable nature [16]. In a recent study, Dubey et al. developed a PEGylated graphene oxide (GO)-silver nanoparticle (AgNP)-curcumin (CUR)-loaded chitosan (CS)/PVA hybrid system for wound dressing [28].

Polyvinylpyrrolidone (PVP) Polyvinylpyrrolidone (PVP) is a biocompatible, hydrophilic polymer that has been utilized as a biomaterial or additive in various pharmaceutical formulations. It possesses low tensile strength and thermal stability [16].

Polylactic acid (PLA) The polymer exhibits biocompatible and biodegradable properties, is non-toxic, absorbent, and low cost. However, its lack of flexibility is overcome by the formation of bonds with other polymers. The polymer has the characteristics of high polarity, high density, and low thermal stability, which limits its applications [16]. In a notable study, Bita Darabian et al. utilized a solvent casting method to prepare a porous wound dressing, employing poly (lactic acid) (PLA), polyethylene glycol (PEG), and triacetin (TA). The addition of metronidazole to the PLA/PEG/TA blend was intentional, serving to enhance the antibacterial properties of the composite. The resultant blend demonstrated notable biodegradability, a crucial property that is essential for wound dressings [29].

Polydimethylsiloxane (PDMS) The material is regarded as a superior polymer due to its flexibility, thermotolerance, resistance to oxidation, ease of production, and opti-

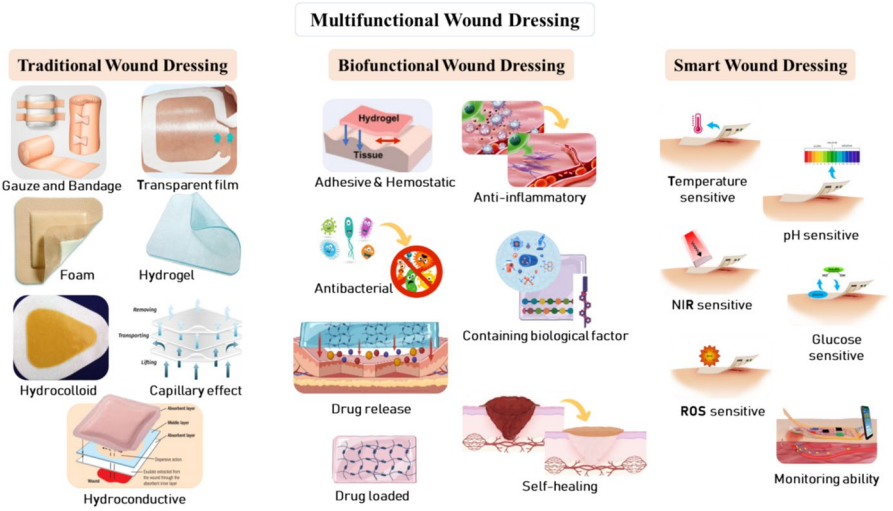


Fig. 5 Multifunctional wound dressings

cal transparency. Nevertheless, its low biocompatibility and hydrophobicity limit its biomedical applications, and its surface properties require enhancement [16].

Types of wound dressing

The practice of applying wound dressings has existed since 2000 BC, with continuous development of these treatments throughout history. The evolution of dressings has been driven by considerations of the fundamental characteristics and requirements of different wounds. This ongoing process of innovation ensures that a wide range of dressing options are available, each tailored to address the specific needs of the wound [30] (Fig. 5).

The primary function of dressings is to control hemorrhaging from a wound and to facilitat its healing process. The evolution of various types of wound dressings demonstrates their unique properties during the wound healing process [30].

Traditional dressings

A plethora of wound dressings have been developed for utilization in wound treatment from historical to contemporary periods. One such category of dressings, traditional wound dressings, which are frequently employed in the present day, aim to control bleeding and promote wound healing. Fundamentally, a dressing serves the purpose of protecting the wound from secondary injury, facilitating the removal of excess exudate, and preventing infection. Each form of traditional wound dressings, which can be found in various forms, possesses its own characteristics [30] (Fig 6).

Gauzes and bandages Gauze and bandages are dry dressings with a long history of use. They are among the oldest and least expensive types of traditional dressings,

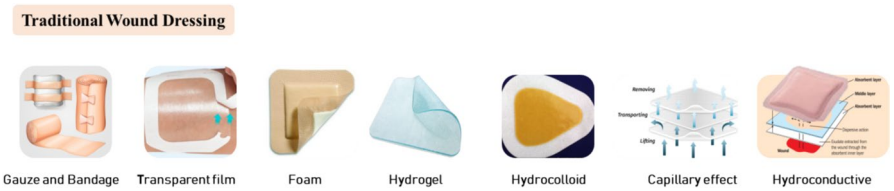


Fig. 6 Traditional wound dressings

and they are frequently employed to close wounds that are infected or exude a large amount of fluid [30, 31]. However, despite their extensive use, gauze adheres to the wound area, resulting in trauma, mechanical debridement, and pain during removal. Consequently, it is not regarded as an ideal wound dressing [8]. Furthermore, it has been observed that gauze can activate the immune system, leading to granuloma formation by leaving residue behind [31].

Transparent films Transparent films constitute a dressing that provides a moist environment for the wound while preventing both gas exchange and bacterial contamination. They also adapt to the wound surface with ease and can be easily separated from the wound surface. However, since they lack swelling properties, they are not recommended for use in the treatment of heavily exuding and infected wounds [30, 31]. The presence of exudate and infection on the wound surface simultaneously has been demonstrated to increase the growth rate of bacteria in the wound [31]. Although the adhesive used today does not harm the skin, it is important to exercise caution when using it on sensitive skin. The presence of a transparent layer on the wound surface facilitates postoperative wound monitoring [8].

Foams Foams possess the capacity to absorb substantial quantities of liquid while providing insulation and facilitating gas exchange, functions that transparent film covers are incapable of performing. The porous nature of foams facilitates wound healing by means of the absorption of wound exudates. The high degree of absorbency exhibited by foams is a result of their unique structural properties. Due to these properties, foams can be employed for extended periods of time on uninfected wounds. However, for infected wounds, daily replacement is recommended. It is critical to note that the adhesive properties of the foam may potentially lead to tissue damage and discomfort during removal, owing to the coagulation of exudate and blood absorbed by the foam [30, 32].

Hydrogels Hydrogels are a class of wound dressings that have garnered particular attention due to their unique properties that promote wound healing. These dressings, with their water content ranging from 80 to 90% and their strong hydrophilic properties, provide essential moisture to the wound and maintain a favorable moisture environment [31]. Hydrogels facilitate gas exchange at the wound surface, contributing to tissue granulation. Notably, they are pain-free and do not cause any trauma during removal. The absorption of exudate from the wound surface by hydrogels has been

demonstrated to stimulate fibroblast proliferation, a critical aspect of wound healing. This process has also been shown to influence key events such as keratinocyte migration and epithelialization [30]. The development of hydrogel dressings with injectable, self-healing, antibacterial, and antioxidant properties has been a focus of ongoing research. However, its effectiveness against microorganism contamination is inferior to that of other wound dressings, which has led to its use in conjunction with various substances. The development and utilization of hydrogels for wound healing has been a primary focus of studies due to their superior wound healing properties when compared to gauze [10]. The majority of hydrogels are produced using alginate polymers, and under suitable conditions, cross-linked hydrogels formed by alginates can be employed for these dressings. The superior absorbency of alginates distinguishes alginate-derived hydrogels from other hydrogel systems. Due to its hemostatic feature, it is also very effective in providing benefit to bleeding [32].

In addition to alginates, collagen, and chitosan, which have been investigated for use as hydrogel formers, are materials of interest for this application. Chitosan, a polysaccharide, has been researched for wound dressing design due to its superior healing properties, antibacterial and hemostatic properties. However, the complexity of its production is a significant disadvantage for this substance. Collagen supports wound healing because it is a naturally occurring protein in the tissue and can easily interact with fibroblasts and endothelial cells in the wound. Collagen-based dressings are distinguished by their high water absorption capacity and favorable mechanical properties. However, their frequent replacement is necessary due to pathogen contamination, which is contingent on the source of collagen, and their low stability [32].

Hydrocolloids Hydrocolloids, which contain hydrophilic substances such as gelatin, pectin, sodium alginate, and sodium carboxymethyl cellulose, are an elastic matrix gelation system that can absorb large amounts of liquid. They can be used in wound care, similar to hydrogels, and have properties such as maintaining the wound environment moist and protecting the wound against pathogens. Hydrocolloids seal the wound surface more efficiently, preventing the wound from needing secondary dressings, unlike hydrogels. It has been demonstrated that hydrocolloids can promote wound healing through acceleration of the inflammatory response. However, their strong adhesion can result in tissue damage during removal, and their use on infected wounds is contraindicated due to their occlusive nature [32].

Hydroconductive dressings Hydroconductive dressings, recently introduced as a multi-layered exudate-absorbent and self-removing dressing, are being studied in the innovative dressing category [32]. These dressings have a special multi-layered structure that can remove wound bed debris and subsequently eliminate wound bed deposits (by-products) [31].

Capillary effective wound dressings Capillary dressings are utilized in wounds where the primary objective is effective drainage management. This three-layer dressing exhibits the capacity to draw exudate toward the core absorbent layer. The layered

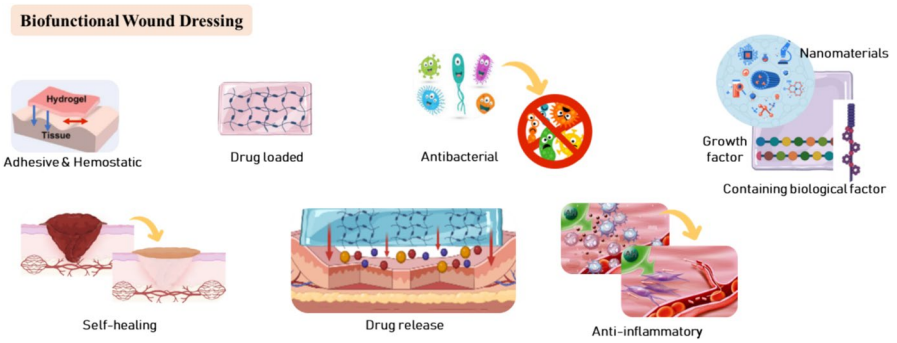


Fig. 7 Biofunctinal wound dressings

structure of the dressing facilitates rapid capillary mobility. Consequently, it is imperative to monitor the dressing closely to prevent desiccation [8].

Biofunctional wound dressings

Bioactive dressing Bioactive dressings are a class of dressings made of materials that can be used for various types of wounds, support tissue regeneration, and show endogenous activity. This dressing class can deliver bioactive compounds to the wound area when the level of destructive cytokines increases in the wound environment and can create an active and dynamic interaction with the wound environment [10]. These dressings are produced from various biopolymers, including alginate, chitosan, chitin, collagen, and are applied in the form of hydrogel, film, sponge, foam, and nanofiber [11, 31]. Additionally, bioactive dressings containing drug delivery systems also have active ingredients such as antimicrobial peptides, stem cells, plant metabolites, growth factors, and vitamins [11]. Types of biofunctional wound dressings are shown in (Fig. 7).

Drug-loaded dressings The objective of the development of dressings is to enhance the treatment of chronic lesions, prolonged inflammatory phases, and delayed wound closure. To this end, a system has been designed for in situ release by loading drugs and antimicrobial agents into wound dressings. Its in situ release feature is intended to prevent adverse effects that may occur in non-target tissues [31].

Dressings that release antibacterial agents The incorporation of antimicrobial agents during the preparation of wound dressings constitutes the most prevalent and elementary method employed in the management of infected wounds. Silver ions have been utilized for an extended duration due to their antimicrobial properties, exhibiting effectiveness against bacteria, viruses, and fungi while concurrently reducing inflammation. However, the penetration of thick wounds by silver ions is impeded. Iodine, another agent with recognized antimicrobial properties, has been employed as an antiseptic since its discovery. Elemental iodine is predominantly bound to a carrier molecule to mitigate adverse effects associated with its use. Povidone-iodine

and cadexomer iodine are predominantly employed in wound dressings. Despite conflicting results regarding the potential toxicity of povidone-iodine in animal tests, human experiments have substantiated its effectiveness in reducing microbial load [31]. Another substance considered for use as an antimicrobial agent in wound dressings is antibiotics. Antibiotics represent a potent approach to combating infections, with a long history of integration into diverse drug delivery systems. However, the incorporation of antibiotics into wound dressing designs has not yielded successful outcomes in clinical trials, possibly due to the development of bacterial resistance that can result from long-term antibiotic use [31].

Dressings that release anti-ınflammatory drugs Pain resulting from physical trauma, dressing changes, debridement, and protracted inflammatory responses is a prevalent affliction that impedes patients' quality of life. Moreover, stress induced by pain diminishes the immune system's capacity to respond effectively and prolongs the healing process of wounds. The employment of ibuprofen, lidocaine, and opioids as anti-inflammatory medications is a customary approach in the management of chronic wounds, a phenomenon that has prompted numerous researchers to incorporate these drugs into their studies. The findings of numerous studies have demonstrated that patients treated with ibuprofen-loaded dressings have a significant analgesic effect compared to patients treated with conventional methods [31].

Wound dressings containing biological factors Recent studies have examined the development of wound dressings through the use of released biological factors. The objective of this research is to engineer wound dressings that exhibit enhanced activity in the wound healing process. Among these factors, growth factors (GFs) represent biomacromolecules that play a role in the wound healing process. Numerous delivery systems have been designed to facilitate the localized release of GFs in both free and nanoparticle-encapsulated forms. However, due to the substantial cost associated with their production, these systems have primarily been explored in research studies [31].

Smart wound dressing

The process of wound healing is influenced by various factors, including temperature, pH, glucose levels, and numerous additional elements. Wound dressings, which are designed to adapt to these factors, play a crucial role in wound healing by ensuring a favorable wound environment [30] (Fig. 8).

pH-sensitive dressings The pH value of the internal environment of the human body is predominantly 7, which is neutral. In contrast, the pH of the skin is between 4 and 6. Disruptions to the acidic environment of the skin, such as those caused by deterioration on the skin surface, can lead to adverse outcomes. The pH values of these lesions, which are referred to as wounds, exhibit variability depending on the nature of the lesion, with chronic wounds being characterized by a pH value greater than 7 [30]. The pH value plays a pivotal role in the process of wound heal-

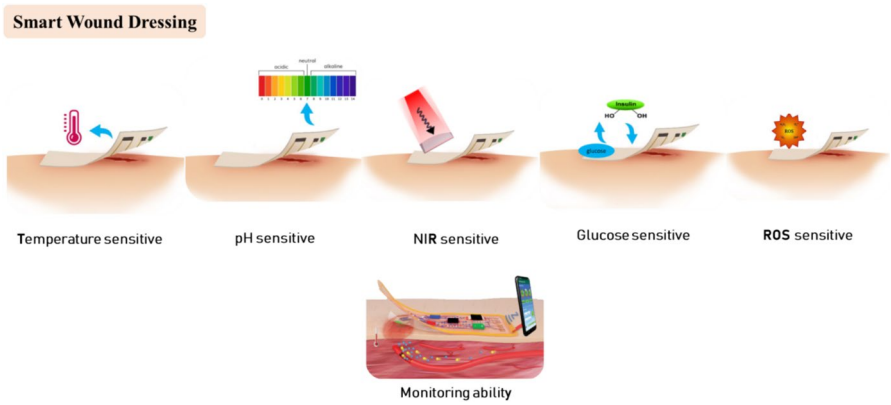


Fig. 8 Smart wound dressings

ing, underscoring its significance as a diagnostic criterion for evaluating the healing process and identifying non-healing wounds. The pH values of wounds provide crucial insights into their respective phases of the healing process. For instance, the wound repair mechanism operates in an acidic environment, resulting in a pH range of 5 to 6 for healing or acute wounds. In contrast, wounds that are difficult to heal, also known as non-healing wounds, exhibit a pH value between 7 and 9 [33]. Such variations in wound pH levels are indicative of the risk of bacterial infection at the wound site. Most pathogens require an alkaline environment for optimal proliferation and multiplication [10]. In acute wounds, the pH can be reduced to prevent bacterial growth by the activity of neutrophils, but chronic wounds remain in alkaline conditions for extended periods, making them susceptible to bacterial infection [32]. To address this, wound dressings that are sensitive to pH changes have been developed for the treatment of infected and chronic wounds [33]. These dressings can be categorized into two types based on the stimuli they respond to: those driven by externally controlled pH chanes and those that are responsive to local pH changes. The former type of material is characterized by its ability to be externally controlled through the implementation of a stimulus mechanism, thereby modulating the pH level of the surrounding environment.

Temperature-sensitive dressings Temperature is a pivotal criterion in all cellular activities, the functioning of every system in the body, and wound healing [33]. In addition to the pH of the injured tissue being different from the pH of the healthy tissue, there is also a difference between their temperatures. When a wound is formed in healthy tissue and the wound becomes infected, an increase in temperature occurs [30]. The temperature fluctuations during the wound healing process are significant as they influence the enzymatic and chemical processes within the body. A rapid escalation in wound temperature serves as a crucial indicator of infection and inflammation [32]. However, elevated wound temperature alone does not necessarily indicate infection. Infection is typically identified by the presence

of concomitant factors such as redness, swelling, pain, and an increase in temperature [33].

In light of these considerations, there is a growing interest in the development of temperature-sensitive wound dressings that can administer drugs and other agents to expedite the healing process. A notable example of such a wound dressing is a hydrogel developed by Montaser et al., which is based on sodium alginate-graft-NIPAM (N-isopropyl acrylamide) and polyvinyl alcohol (PVA) [34]. In this study, the anti-inflammatory drug was encapsulated in the hydrogel and released at different temperatures. The release process is facilitated by NIPAM, which is heat sensitive [30].

Near-infrared (NIR) photosensitive dressing The most detrimental factors that impede the wound healing process are infection and inflammation. To address these issues, researchers have developed near-infrared (NIR) light-sensitive dressings. These specialized dressings are designed to protect against infection and reduce inflammation. During treatment with NIR, some of the dressings exhibit photothermal activity, while others produce gas. These two different types of NIR-sensitive dressings contribute to wound healing in distinct ways [30]. One type of NIR-sensitive wound dressing that exhibits photothermal activity was designed by Zhao et al. [35]. This dressing is designed to treat multidrug-resistant bacterial infections and is a double mesh hydrogel produced by crosslinking catechol from dopamine and hydrogen bonding between Fe^{3+} and ureido-pyrimidinone. Catechol-Fe^{3+} increases the hydrogel temperature when NIR irradiation is applied, exhibiting photothermal sensitive properties. The temperature increase in the hydrogel kills the microorganisms in the wound area and protects the wound from possible infection [30].

Glucose-sensitive dressing The healing process of chronic wounds, such as diabetic ulcers, in individuals with diabetes is often challenging due to angiogenesis disorders, which lead to delayed wound healing and various complications. In the healing process of such wounds, the use of a wound dressing sensitive to the amount of glucose in the blood has proven to be advantageous [30]. The wound dressing developed by Zhao et al. [36] features a drug release system that is activated in the presence of glucose. The primary advantage of this dressing is its ability to integrate wound healing with disease treatment, effectively addressing both wound healing and blood sugar control [30]. Another study on glucose-sensitive dressing was conducted by Bhadauriya et al. [37], who developed a dressing by incorporating yeast extract-immobilized copper nanoparticles into the carbon nanofiber (CNF) matrix. The yeast extract present in the dressing has the capacity to convert glucose to ethanol, thereby facilitating wound respiration and promoting cell growth and granular tissue formation. In vitro tests have demonstrated that copper nanoparticles, when incorporated into the wound dressing as an antibacterial component, result in a substantial reduction in bacterial colonies. Furthermore, experiments conducted on rats with diabetic wounds have shown that this dressing leads to a reduction in inflammation and an increase in neovascular

numbers. However, it is important to note that the toxic effect of ethanol produced by glucose consumption in the dressing poses a significant safety concern [30].

ROS-sensitive dressing Reactive oxygen species (ROS), which play a critical role in the recruitment of immune cells and the elimination of bacteria, are vital for wound healing. However, an excessive accumulation of ROS in and around the wound can result in the damage of biomolecules, such as proteins and DNA, and can impede the wound healing process. Therefore, the removal (scavenging) of excess ROS is imperative. In vitro studies have demonstrated that scavenging excess ROS can promote fibroblast growth and wound healing in animals [30].

Ceria crystals, nanocrystals, have been utilized in ROS-scavenging agents. Wu et al. [37] developed a ROS-scavenging tissue adhesive from ceria crystals and mesoporous silica to accelerate wound healing. In vitro studies demonstrate that ceria-mesoporous silica nanoparticles (ceria-MSN) applied to an incision on a rat exhibit effective ROS-scavenging and wound healing properties. The most salient finding of this study is that the developed wound dressing facilitates wound healing and closure, while concomitantly breaking down the excess ROS accumulated in the wound area [30].

Cheng et al. have developed a sprayable hydrogel modified with UV-triggered dopamine, in which cerium oxide nanoparticles function as a ROS scavenger. While this hydrogel demonstrates remarkable efficacy in ROS breakdown, concerns have been raised regarding the potential entry of cerium oxide nanoparticles into the circulatory system, which could lead to adverse effects [30].

Bilayer wound dressing

Recent advancements in wound care have given rise to the development of bilayer wound dressings that emulate the structural and biological characteristics of skin, thereby enhancing functionality. These dressings are generally composed of two distinct layers: an outer protective barrier and an inner bioactive layer that directly interacts with the wound bed. The bilayer design offers numerous advantages over traditional single-layer dressings. The outer layer's primary functions include mechanical protection, moisture retention, and prevention of microbial contamination. The outer layer is typically composed of hydrophobic or semipermeable materials that permit gas exchange while impeding external infections. In contrast, the inner layer plays a pivotal role in promoting cell adhesion, moisture retention, and the controlled release of bioactive agents. This layer is generally composed of hydrophilic polymers, such as chitosan, collagen, or hyaluronic acid, which facilitate cellular interactions and wound re-epithelialization [38–43].

In recent years, double-layer wound dressings have undergone substantial advancements, largely attributable to the emergence of bioengineering materials and refined manufacturing methodologies. These developments encompass the incorporation of hybrid biomaterials, which enhance biocompatibility, mechanical strength,

and degradation rates. Crosslinking techniques have been introduced to enhance the stability and controlled release properties of bioactive agents [45].

Materials such as polylactic acid (PLA) and polyurethane (PU) have been investigated for their ability to increase mechanical stability while maintaining flexibility, which is crucial for wound dressing. The incorporation of bioactive molecules, such as silver nanoparticles and curcumin, has been demonstrated to be effective in reducing bacterial colonization and inflammation, thereby accelerating the wound healing process. These advancements encompass the incorporation of hybrid biomaterials, which enhance biocompatibility, mechanical strength, and degradation rates. Moreover, novel crosslinking techniques have been developed to enhance the stability and controlled release properties of bioactive agents [44, 45, 47].

The ımportance of their nanofibrous sublayer

The incorporation of nanofibrous substrates into double-layer wound dressings constitutes a pivotal component, as these substrates function as interlayers between the external barrier and the wound bed. The nanofibrous networks bear a striking resemblance to the natural extracellular matrix (ECM), thereby providing a biomimetic scaffold conducive to cell migration and tissue regeneration. The high surface area-to-volume ratio of nanofibrous substrates enables several key functions, including:

- Enhanced cell adhesion and proliferation,
- Controlled release of therapeutic agents such as antimicrobial compounds, growth factors, or anti-inflammatory drugs,
- Increased moisture retention required to maintain an optimal wound healing environment [38–43].

Electrospinning is one of the most commonly used techniques to produce nanofibrous layers in wound dressings. The employment of biocompatible polymers, including polyvinyl alcohol (PVA), chitosan, gelatin, and polyurethane, has led to the successful design of nanofibrous substrates that demonstrate superior mechanical strength, degradability, and bioactivity. The incorporation of bioactive molecules, such as curcumin and zinc oxide nanoparticles (ZnO NPs), further enhances the antimicrobial and anti-inflammatory properties of these dressings [38–43].

The role of platelet-rich fibrin (PRF) in wound healing

Platelet-based products, including platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and advanced fibrin matrices, have garnered considerable attention in the realm of wound healing research. These autologous materials are abundant in bioactive molecules that facilitate tissue regeneration and modulate inflammatory responses [41, 44–46].

Platelet-rich plasma (PRP)

PRP is obtained from the patient's blood by centrifugation, resulting in a plasma fraction with a high concentration of platelets and growth factors. It has been widely used in chronic wound management due to its ability to:

- Stimulate angiogenesis via vascular endothelial growth factor (VEGF),
- Increase fibroblast proliferation and extracellular matrix formation,
- Reduce inflammation via anti-inflammatory cytokines [45].

Notwithstanding the aforementioned advantages, PRP necessitates the incorporation of anticoagulants to avert clotting, a process that may curtail its long-term bioavailability at the site of injury.

Platelet-rich fibrin (PRF)

PRF, a second-generation platelet-based biomaterial, has been engineered to circumvent several of the constraints inherent to PRP. Unlike PRP, PRF is obtained without the use of anticoagulants and forms a natural fibrin matrix that acts as a sustained release system for growth factors. The main benefits of PRF are as follows:

- Sustained release of bioactive molecules such as Transforming Growth Factor Beta (TGF-β),
- Increased wound contraction and fibroblast migration,
- Improved epithelialization and reduced scarring [44].

Several clinical studies have confirmed the efficacy of PRF-based wound dressings in treating chronic ulcers and diabetic foot wounds. In addition, PRF-loaded hydrogels have been the focus of investigation for burn treatments, exhibiting promising results such as improved epithelialization and reduced inflammation [47]. PRF is an autologous fibrin matrix derived from the patient's own blood and contains a high concentration of growth factors such as:

Transforming Growth Factor Beta (TGF-β), which regulates inflammation and tissue remodeling, Vascular Endothelial Growth Factor (VEGF), which promotes angiogenesis, and Platelet-Derived Growth Factor (PDGF), which stimulates cell proliferation and migration [45].

A substantial body of clinical research has validated the efficacy of PRF-based wound dressings in the treatment of chronic ulcers and diabetic foot wounds. Studies have demonstrated that PRF enhances fibroblast proliferation and accelerates collagen deposition, resulting in expedited wound closure. Moreover, PRF-loaded hydrogels have been effectively employed in burn treatments, exhibiting enhanced epithelialization and reduced scarring [44].

In light of the rapid advancements in PRF-based dressings, their integration with nanofibrous bilayer wound dressings has demonstrated potential to expedite wound closure, mitigate bacterial infections, and augment tissue regeneration.

Advanced platelet-based biomaterials

Recent research has introduced advanced platelet-based matrices that combine PRP and PRF with nanofiber scaffolds or hydrogels. These hybrid materials offer the following benefits:

- Controlled degradation rates and long-term bioavailability.
- Targeted delivery of antimicrobial peptides.
- Improved mechanical properties for large wound defects [45].

Three-dimensional (3D) printed scaffolds for wound healing

3D bioprinting has emerged as a promising technique for fabricating wound dressings with highly controlled architectures and bioactive properties. These scaffolds allow for precise manipulation of pore structures, mechanical properties, and cell loading capabilities, making them highly effective in promoting wound healing [45, 48].

3D bioprinting has emerged as a promising technique for fabricating wound dressings with highly controlled architectures and bioactive properties. These scaffolds allow for precise manipulation of pore structures, mechanical properties, and cell loading capabilities, making them highly effective in promoting wound healing [44]. Additionally, the incorporation of nanocomposite materials in 3D-printed scaffolds has been demonstrated to enhance mechanical stability and optimize drug release kinetics [47].

Recent advancements in 3D-printed scaffolds have investigated the utilization of advanced biomaterials, such as graphene oxide and silk fibroin, which provide enhanced cell adhesion and mechanical properties. These materials facilitate the formation of a microenvironment conducive to skin regeneration and angiogenesis [45].

Overview of multifunctional wound dressings

Hydrogels

In a recent study, Jeeraporn Baukum and colleagues developed an alginate/gelatin hydrogel via solvent casting for use in wound dressings. This hydrogel incorporated Ag nanoparticles (AgNPs), which exhibited antibacterial activity against *S. aureus*, *P. aeruginosa*, and *E. coli*. The use of $CaCl_2$ as a crosslinking agent for the hydrogel was also demonstrated. The study's findings indicated that the Alg/Gel hydrogel, containing AgNPs, exhibited promise as a wound dressing material [49]. In a related study, Chen et al. fabricated an alginate-chitosan hydrogel incorporating gelatin microspheres. The antibacterial properties of the hydrogel were demonstrated using *E. coli* and *S. aureus*. The study's findings

demonstrated that the fabricated composite hydrogel exhibited the capacity to function as an antibacterial agent against the aforementioned bacteria, thereby substantiating its suitability for utilization in antibacterial wound dressing applications [50]. The green synthesis process utilizes an extract of a plant to mitigate the toxicity of the resulting compounds. In a related study, Kalantari et al. [51] obtained CeO_2 NPs through the use of a Zingiber officinale extract via a green synthesis approach. The researchers then formed a PVA/chitosan/CeO_2 NPs hydrogel by subjecting it to the freeze–thaw process. The incorporation of CeO_2 nanoparticles in the PVA/Chi hydrogels is of particular significance for wound dressing applications, as CeO_2 nanoparticles have been shown to effectively reduce wound infections without the need for antibiotic treatment.

Ulu et al. [52] developed a hydrogel film composed of a blend of chitosan, poly(propylene glycol), and TiO_2 nanoparticles. The incorporation of TiO_2 nanoparticles into the Chi/PPG film resulted in a reduction in porosity and an enhancement in tensile strength. Notably, the antimicrobial efficacy of the Chi/PRP/TiO_2 hydrogel film was found to be particularly pronounced. In a related study, Bagherifard and colleagues examined thermally actuated wound dressings. In this study, thermo-responsive particles of poly(Nisopropylacrylamide) (pNIPAM) were prepared and incorporated into a flexible hydrogel with the drug. Then, the loaded hydrogel was attached to the wound dressing material [53].

Katarina Nešović and Vesna Mišković-Stanković studied the release of silver from poly(vinyl alcohol)-based hydrogels containing silver nanoparticles (AgNPs). The synthesis of these silver nanoparticles was accomplished through an electrochemical process, a method that has been employed to enhance antibacterial activity and facilitate the release of antibacterial agents. The resultant hydrogels possess the potential to promote long-term wound healing and chronic wound care, playing a crucial role in preventing and treating persistent infections [54]. In a related study, Rao et al. [55] obtained hyaluronic acid (HA) and zinc oxide (ZnO) nanocomposite hydrogels. To assess their biocompatibility, the HA/ZnO hydrogels were exposed to human skin fibroblasts. The results demonstrated that the HA/ZnO hydrogels exhibited favorable biodegradability and swelling properties, along with high hemocompatibility, which enhanced antibacterial activity and blood coagulation. Furthermore, the antibacterial tests against *S. aureus* and *E. coli* pathogens revealed the HA/ZnO hydrogels to be effective against these pathogens. Consequently, these findings suggest that the HA/ZnO hydrogels have the potential to serve as a suitable material for future wound dressing applications.

Liyaskina et al. [56] fabricated a bacterial cellulose hydrogel with fusidic acid to investigate its antibacterial activity against *S. aureus*. Fusidic acid, an antibiotic isolated from the fungus Fusidium coccineum, exhibits low toxicity and resistance, making it a promising candidate for treating diseases caused by methicillin-resistant *Staphylococcus aureus* (MRSA) strains.

Sponge

In a recent study, Tchemtchoua and colleagues fabricated chitosan/PEG nanofibers and compared them with films and sponges for the proliferation of various cells, including fibroblasts, keratinocytes, and endothelial cells. The experimental results demonstrated that the Chi/PEG nanofibers exhibited significant potential as a wound dressing material, as they promoted accelerated re-epithelialization, enhanced vascularization, and remodeling of granulation tissue [57].

In a separate study, Raluca Ioana Baron et al. developed biocompatible sponges for the treatment of heavily scarred wounds, burns, and other skin conditions. These sponges were fabricated by combining PVA with polysaccharides [58]. Sonia Nohemi Ramirez-Barron et al. prepared gelatin/gallic acid/ZnO nanocomposite materials. The mechanical and biological properties of the gelatin/gallic acid/ZnO nanocomposites were significantly affected by the addition of ZnO nanoparticles, and the material containing ZnO nanoparticles exhibited antimicrobial properties, suggesting its promise for wound and burn applications [59].

The GO (graphene oxide)/PVA (polyvinyl alcohol) nanocomposite sponges were prepared by the freeze-drying method. It was determined that increasing the amount of GO in the nanocomposite sponges resulted in an increase in Young's modulus and tensile strength. Furthermore, the hemolysis assay revealed that PVA/GO nanocomposite sponges exhibited blood compatibility. In addition, an antibacterial test was conducted to assess the antibacterial efficacy against *S. aureus* and *E. coli*. The results of this study indicated that PVA/GO nanocomposite sponges have potential applications in wound dressings [60].

Nanofibers

Abdelgawad et al. produced a nanofiber composed of a blend of chitosan and polyvinyl alcohol (PVA). This nanofiber was then cross-linked with glutaraldehyde, and Ag nanoparticles were added to the nanofiber for use in wound dressing applications. The antibacterial properties of the resulting nanofibers were evaluated through a series of tests, which revealed that the PVA/CS/AgNP nanofibers demonstrated resistance to *E. coli*. It was observed that as the amount of chitosan in the nanofiber increased, the bacteria exhibited a decrease in their population [61]. Consequently, the prepared nanofibers have emerged as a promising material for wound dressing applications. In a related study, Ojha et al. utilized the electrospinning technique to prepare chitosan/PEO nanofibers for wound healing applications. The pristine PEO nanofibers exhibited superior tensile strength compared to the prepared Chi/PEO nanofibers. Subsequently, Sadri et al. incorporated tea extract and glutaraldehyde vapor into the Chi/PEO nanofibers, aiming to produce an eco-friendly material. This material demonstrated antibacterial activity against both gram-positive and gram-negative bacteria, highlighting its potential for wound dressing applications [62]. In a related study, Zhang et al. [63] fabricated NP-alginate high porosity fibers for wound dressing applications. However, this material was not suitable due to mechanical problems.

To address this challenge, they incorporated hydroxyapatite and silica gel into the alginate, enhancing its mechanical properties for effective wound healing. The resultant wound dressing material exhibited enhanced mechanical properties and no significant levels of cell toxicity [64].

PVA/CS/Tetracycline hydrochloride (TCH) mats were fabricated by the electrospinning method for wound dressing applications. The PVA/CS/TCH nanofiber mats exhibited significant antibacterial activity against *E. coli* and *S. epidermidis* and were found to be cytocompatible. The PVA/CS/TCH nanofiber mats were determined to be efficient materials in wound dressing applications thanks to their many advantages [65].

In a similar vein, cellulose acetate (CA) nanofiber mats loaded with gallic acid (GA) were fabricated by electrospinning and exhibited antibacterial activity against *S. aureus* [66]. This finding underscores the suitability of GA-loaded CA mats for wound dressing applications.

In a similar study, Wahab et al. fabricated polyurethane nanofiber-based nanofibers containing silver/zinc oxide nanoparticles (PUZnAg), which were obtained to ensure long-term efficacy in antibacterial wound dressing applications [67].

In a recent study, Augustine et al. [68] utilized the electrospinning technique to prepare nanofibers, employing polycaprolactone (PCL) as the base material for the production of membranes. These membranes were then combined with biosynthesized AgNPs, aiming to explore their potential for wound dressing applications. The resultant PCL/AgNPs exhibited noteworthy mechanical properties, suggesting their potential for use in wound management. Furthermore, the material demonstrated a substantial antibacterial effect against both *E. coli* and *S. aureus*, indicating its efficacy in preventing bacterial infections. This finding underscores the importance of enhancing the fabricated material's capacity to protect wounds and promote healing. The study demonstrated that the quantity of Ag nanoparticles employed should be minimal, as this led to an enhancement in the mechanical and biological properties of the PCL/AgNP nanofibers. The nanocomposite scaffolds exhibited remarkable antimicrobial activity against *S. aureus*, *E. coli*, and *C. albicans*. Furthermore, the cell viability, cell attachment, and proliferation on the nanocomposite scaffolds were demonstrated to be cytocompatible. Consequently, biosynthesized Ag nanoparticle membranes composed of a polycaprolactone (PCL) could serve as promising candidates for wound dressings. In a related study, Sajedeh Khorshidi et al. investigated the antibacterial activity of a wound dressing comprising graphene oxide (GO). They found that silk fibroin was a suitable polymer for fabricating SF/GO nanocomposite fibers. The nanocomposite material, produced through the strategic distribution of GO nanoparticles within the fibroin matrix, exhibited enhanced physicochemical properties, cell compatibility, and noteworthy antibacterial activity [69]. In a related study, Sadeghianmaryan et al. [70] utilized the electrospinning method to prepare polyurethane (PU)/graphene oxide (GO) nanofibers, demonstrating that the incorporation of GO provided substantial benefits to the mechanical properties of nanofibers [71]. In addition, PU/GO nanofibers exhibited potent antibacterial and antifungal properties, underscoring their potential as wound dressing materials [70].

As stated in the study by Mohammadi et al. [72], electrospun scaffolds containing a novel Gum tragacanth (GT) and PVA were fabricated for use as wound dressings. The PVA/GT scaffolds had many advantages for use in wound dressing applications, such as the biodegradability, non-toxicity, and biocompatibility of gum tragacanth, which facilitate fibroblast cell adhesion and proliferation.

Aydogdu et al. prepared bacterial cellulose/polycaprolactone nanofibrous scaffolds for wound dressing applications, and the prepared nanofibers showed that the biocompatibility of the scaffold [73]. Ghavami Nejad et al. fabricated nanofibers containing poly(dopamine methacrylamide-co-methyl methacrylate) (MADO) and silver nanoparticles (AgNPs) to use in wound dressing applications. The antibacterial effect of the fabricated nanofibers was evaluated using bacterial strains of *E. coli*, *S. aureus*, and *P. aeruginosa*. The results demonstrated that MADO/AgNPs nanofibers exhibited antibacterial activity against all three bacterial strains, indicating their potential for wound dressing applications [74].

Membrane

In a recent study, Farrukh Altaf et al. [75] fabricated polyvinyl alcohol (PVA)/starch hydrogel membranes, employing glutaraldehyde as a cross-linker to form the hydrogel. These PVA/St hydrogel membranes demonstrated both antibacterial activity and mechanical strength. In summary, the PVA/St hydrogel membrane's advantageous properties, including its effectiveness against bacteria, its mechanical strength, and its physical characteristics, make it a suitable material for use in wound dressing applications. In a related study, Ahmed et al. [76] prepared a PVA/starch composite membrane that was combined with an antibacterial agent, silver, to enhance its antibacterial activity. This composite membrane exhibited efficient porosity and oxygen permeability. The fabricated hydrogel membranes exhibited enhanced healing properties in comparison with conventional wound dressings composed of cotton gauze. These findings suggest that the fabricated hydrogel membranes have the potential to be utilized as a wound dressing. In a related study, Cai et al. [77] developed nanofiber membranes that incorporate iron oxide nanoparticles (Fe_3O_4 NPs), chitosan (Chi), and gelatin (GE) through the process of electrospinning. The Fe_3O_4/CS/GE nanofiber membranes exhibited remarkable properties, including elevated mechanical strength, augmented toughness, and potent antibacterial action against *S. aureus* and *E. coli*. Consequently, the Fe_3O_4/CS/GE nanofiber membranes, endowed with their exceptional mechanical and antibacterial characteristics, emerge as promising materials for wound dressing applications.

Lin et al. [78] fabricated hydroxypropyl cellulose, chitosan, polyethylene oxide, and graphene nanofiber membranes by electrospinning, and the characterization showed that the membranes were not toxic. The membranes also had the potential to become superior antibacterial wound dressings. Mimosa pudica plant extract was used for the synthesis of silver nanoparticles, and PVA membranes were developed with biosynthesized Ag nanoparticles. The fabricated PVA/Ag membranes exhibited antibacterial activity against both *S. aureus* and *E. coli*, indicating their capacity to impede bacterial colonization when wounds were covered with the membranes.

The presence of Ag in the membranes promoted cell proliferation and migration of epithelial cells, while supporting wound closure. The collective findings suggest that PVA/Ag membranes have potential for utilization in the development of antibacterial wound dressings [79].

Biofunctional wound dressings

Liang et al. developed a novel class of self-regulating/anti-adhesive alginate hydrogels with enhanced moisture retention properties, achieved by incorporating propanediol. These hydrogels have been shown to regulate moisture levels, thereby promoting wound healing. In addition, alginate-based hydrogels have demonstrated superior healing and inflammatory properties in wound dressing applications. Specifically, hydrogels with self-regulatory and anti-adhesive properties have been shown to be beneficial for the healing of burn wounds in wound care applications [80].

In a related study, Chen et al. improved the ultra-tough, self-healing, and tissue-adhesive hydrogels for wound dressing. Sodium alginate was combined with polyacrylamide to create a hydrogel with these properties. The dopamine-grafted oxidized sodium alginate and polyacrylamide were used to enhance the mechanical and biological properties of the composite hydrogel, which was shown to accelerate wound healing. Consequently, the hydrogel exhibited both tissue regeneration support and wound healing acceleration, making it a suitable and promising biomaterial for wound dressing applications [81]. Mostafa Saberian et al. obtained hydrogels containing alginate and chitosan polymers. This composite polymer is considered to be among the most effective polymeric combinations due to its ability to promote wound healing. Aloe vera and honey are two biomaterials that have been utilized in wound dressing applications. The addition of aloe vera and honey to the Alg/Chi composite hydrogel resulted in the development of a biocompatible and mechanically suitable material, which has prompted further studies to explore its potential in wound repair [82].

In a recent study, Muhammad Umar Aslam Khan and colleagues developed a novel hydrogel for wound dressing applications. This biocompatible and biodegradable material was fabricated using natural polymers, namely arabinoxylan (ARX) and guar gum (GG). In addition to its biocompatible and biodegradable properties, the material exhibited notable antibacterial activity. These hydrogels have the potential to serve as high-quality materials for various applications, including wound healing, wound protection, wound dressing, and the control of drug delivery systems [83].

The double network was fabricated with gelatin/sodium alginate (G/SA) fibers and gelatin/sodium alginate/sodium hyaluronate (G/SA/HA) fibers that were contained hyaluronic acid solution in the gelatin-sodium alginate matrix. As a result of the studies, it has been obtained that Aloe vera-based sponges have high biocompatibility and high antibacterial activity. Consequently, aloe vera was incorporated into the gelatin/sodium alginate/sodium hyaluronate matrix as a

bioactive agent, yielding aloe vera-based G/SA/HA sponges with substantial pores that facilitate high interconnectivity for wound dressing applications [84].

In a separate study, Sathiyaseelan et al. [85] obtained polyvinyl alcohol/chitosan composite scaffolds using Pinus densiflora (PD) and iron oxide nanoparticles (FeONPs). The obtained sponge scaffolds showed less porosity than polyvinyl alcohol/chitosan sponge scaffolds. In addition, the added materials improved the proliferation of cells on the scaffold. The CS/PVA/PD/FeONPs sponges have been demonstrated as a promising candidate for utilization in wound dressings.

Tamer et al. developed a sponge-based wound dressing, utilizing a blend of PVA and Kaolin. The antibacterial properties and blood coagulation index of this sponge were examined, revealing a substantial enhancement in blood coagulation upon contact with the PVA/Kaolin mixture. Concurrently, the antibacterial activities exhibited a decline with the incorporation of Kaolin into the PVA matrix. These remarkable properties endow the PVA/Kaolin sponge with the potential to serve as a multifunctional wound dressing [86]. In a related study, Ribeiro et al. [87] fabricated nanofibers utilizing a combination of chitosan (CS), poly(ethylene oxide) (PEO), cellulose nanocrystals (CNC), and acacia plant extract through the electrospinning method. The CS/PEO/CNC composite material exhibited a substantial antibacterial effect, with the ability to enhance the antifungal activity of certain fungi, thereby demonstrating a broad-spectrum effect against various microorganisms. This feature renders the material suitable for utilization in wound dressing applications aimed at preventing or treating infections. Furthermore, the acacia extract was subjected to oscillatory motion for a duration of 24 h, thereby demonstrating the material's capacity for a prolonged effect, which in turn reduces the frequency of dressing changes.

Li [88] developed a multifunctional scaffold material that was loaded with mupirocin and lidocaine, aiming to enhance its utility in wound dressing. This scaffold comprised two layers: PCL in the first layer and CHi in the second. Fabricated nanofibers exhibited high antibacterial activity and were non-toxic when used with fibroblasts, suggesting the potential of the multifunctional scaffold material for use in wound dressing applications.

The combination of biopolymers and synthetic polymers in the production of wound dressings has been shown to yield a number of desirable properties, including good biocompatibility, good biodegradation, good mechanical properties, and antimicrobial effects, which collectively promote tissue regeneration. A notable study in this area was conducted by Shirin Rafieian et al. [89], who fabricated PVA/Chi/AV films through the use of electrospinning. The mechanical properties of the resulting nanofibers were attributed to the incorporation of PVA polymer. Subsequent to ascertaining the most efficient amount of PVA in terms of mechanical properties, it was maintained constant and optimized by altering the amounts of aloe vera and chitosan. It has been observed that as the amount of aloe vera and chitosan in the produced material is increased, product costs decrease and biocompatibility increases. According to the results, this combination of natural and synthetic polymers could be used for wound dressing applications due to their affordability, biocompatibility, and flexibility.

The fabrication of ceftazidime (CTZ)-loaded silk fibroin/gelatin (SF/GT) nanofibers (NFs) was accomplished by electrospinning, a method that has been employed to produce a range of nanofibers [90]. The SF/GT/CTZ nanofibers exhibited noteworthy antibacterial activity, underscoring their potential as a wound dressing material. These nanofibers demonstrated efficacy in preventing post-surgical adhesions and infections, highlighting their biocompatibility and antibacterial properties.

In a related study, Sofi et al. [91] fabricated a composite wound dressing nanofiber comprising polyurethane (PU), lavender oil, and silver nanoparticles, processed by electrospinning. The hydrophilicity of the nanofibers was enhanced through the incorporation of silver nanoparticles and lavender oil, and no toxic effects were observed on cultured fibroblast cells in vitro in the dressings. These findings suggest that the material has potential as a composite nanofiber for wound dressing applications.

Liao et al. [92] fabricated a potential material for wound dressing applications that contained carbon nanotubes (CNTs)/polyvinyl alcohol (PVA)/epidermal growth factor (EGF) by electrospinning. The bioactively released EGF supported the growth of fibroblasts and showed their potential in wound dressing applications. The results showed that the EGF positively influenced the produced dressing materials in in vitro and in vivo assays. The PVA/CNTs/EGF composite material has the potential to serve as an effective wound dressing, capable of impeding foreign agents and promoting tissue regeneration. Merrell et al. developed curcumin-loaded PCL nanofibers for use as a wound dressing, exhibiting antioxidant, anti-infective, and anti-inflammatory properties. These properties endow the Cur/PCL nanofibers with considerable promise for utilization in wound dressing applications [93]. In a related study, Nasef et al. [94] prepared a polyvinyl alcohol (PVA)- and chitosan (Chi) hydrogel membrane. The membrane was loaded with the drug and vitamin E after preparation. To ascertain the mechanical and biological properties of PVA/Chi/Ag, a series of tests were conducted on the material. The composite membrane of PVA/chitosan/AgNO3/vitamin E hydrogel manifested significant properties as a wound dressing material, and the PVA/Chi/Ag membrane demonstrated effective antimicrobial properties against S. mutans due to the presence of AgNPs.

Monteiro et al. prepared a mesh of nanofibers composed of chitosan, which was loaded with gentamicin and liposomes immobilized at the surface of the nanofibers. This approach was taken to enhance the antibacterial activity of electrospun membranes. The results of the tests demonstrated that the NFM nanofibers were capable of inhibiting the growth of *E. coli*, *P. aeruginosa*, and *S. aureus* [95].

In a separate study, Fajardo et al. developed a chitosan-based film containing CHI and silver sulfadiazine (AgSD) for wound dressing applications. The CHI/Chi/AgSD films demonstrated effective antibacterial activity against *P. aeruginosa* and *S. aureus* [96].

The adhesion of the dressing to the wound surface is often associated with discomfort and challenges in removal. To address this challenge, a lipid component was incorporated into the polymer matrix membranes to enhance the dressing's performance. To further improve the dressing's adhesion to the wound and ease its application, lipid nanoparticles were added to membranes containing PLGA and Aloe vera. The resultant material shows promise for the treatment

of chronic wounds [97]. Another wound dressing material was prepared by Archana et al. [98] using a solution casting method, incorporating chitosan, TiO_2, and pectin. The tensile strength of the material was enhanced by increasing the amount of TiO_2 nanoparticles and decreasing the amount of pectin. The fabricated material exhibited numerous advantages, including excellent antibacterial properties, high swelling properties, good hydrophilic nature, biocompatibility, and wound closure rate, making it a promising candidate for wound dressing applications. It has been observed that similar results can be achieved by using PVP instead of pectin.

In a recent study, Mahmoud et al. prepared two types of scaffolds for wound treatment, each loaded with a distinct antibiotic drug. The first scaffold comprised collagen and low-molecular-weight chitosan, while the second utilized collagen in conjunction with high-molecular-weight chitosan. The latter was selected to enhance the mechanical properties of the scaffold. Both scaffolds exhibited favorable biodegradability and exhibited almost complete release of the antibiotic drug. In vivo studies demonstrated the potential of these materials for wound dressing applications due to their rapid tissue regeneration properties [99]. PCL, CS, and CS-caffeic acid conjugate (CSCA) were utilized to treat wounds, and their combination resulted in the fabrication of nanofibrous materials for wound dressing applications. The investigation focused on the exploration of the potential of these nanofibrous materials in wound healing applications. The study revealed that the PCL/CS/CSCA fibrous mat exhibited superior cell attachment and cell proliferation properties, along with more effective antimicrobial activity compared to the PCL/CS. Notably, the PCL/CS/CSCA fibrous mat demonstrated no toxicity toward cells. Consequently, the PCL/CSCA fibrous mat emerges as a promising material for wound dressing applications [100]. To enhance the antibacterial activity of the PCL/PVA/CS mats, the mats were loaded with Eugenol (EUG) for wound dressing applications. The antibacterial effect of the CL/PVA/CS/EUG mats was evaluated against *S. aureus* and *P. aeruginosa*. The findings of these tests demonstrated that the CL/PVA/CS/EUG mats exhibited substantial antibacterial activity, while also failing to elicit any toxic effects on human dermal fibroblasts. Consequently, based on the collective outcomes of these assessments, it can be concluded that the CL/PVA/CS/EUG mats possess the potential to serve as a suitable material for wound dressing applications [66].

Curcumin (Cur) is a suitable substance for investigating wound healing properties. Curcumin exhibits favorable antibacterial and antioxidant properties in wound dressing applications. Duan et al. prepared Cur/hyaluronic acid/pullulan (Cur/HA/PU) films, and Huang et al. prepared PCL/CS/Cur composite material to investigate the controlled release of curcumin [101].

In a separate study, the combination of hyaluronic acid with propolis ethanolic extract (EEP) and cornstarch (CSt) was investigated for its potential to enhance wound dressing efficacy. The resultant HA/EEP/CSt films were identified as a promising candidate for the development of films with antibacterial and wound healing properties. The addition of EEP led to a reduction in swelling values and degradation rates when compared to CSt and CSt/HA films [102].

In a separate study, Lamarra et al. prepared composite films by using solutions functionalized with cabreuva essential oil, with PVA and chitosan (CE-PVA). Their characterization results reported their potential to treat burns or minor wounds in wound dressing applications [103]. Shah et al. prepared wound dressing films that contained CS and Ser with moxifloxacin (Mox)-loaded AgNPs. The composite films exhibited a strong burn wound healing capacity with fibrosis, collagen reorganization, neovascularization, and epidermal regeneration [104].

Bharathi et al. [105] prepared polymeric mats by electrospinning, incorporating polyethylene oxide (PEO)/graphene oxide (GO) with cerium oxide (CeO_2) and peppermint oil (PM oil). The incorporation of CeO_2 and PM oil into the mats was enabled by the surface charge properties of these components, resulting in a sustained antibacterial effect. The mats exhibited minimal toxicity toward fibroblast cells, while the PEO/GO/CeO_2/PM oil composite mats demonstrated wound healing activity. The study revealed that the nanofibrous mat composite facilitated wound contraction, collagen deposition, and re-epithelialization, thereby accelerating the healing process. The incorporation of these mats in wound dressing applications resulted in enhanced wound healing. These antibacterial mats hold promise for use as wound dressing materials in biomedical applications. Abhishek et al. prepared bacterial cellulose (BC)-based hydrogel with silver nanoparticles. To obtain silver nanoparticles, an aqueous curcumin/hydroxypropyl-β-cyclodextrin complex (CUR:HPβCD) was used, and the characterization results showed that the silver nanoparticles were synthesized successfully by a green chemistry approach. Consequently, AgNPs can be utilized in conjunction with BC to formulate hydrogels for wound dressing applications. The BC/AgNPs hydrogels demonstrated remarkable antimicrobial properties, attributable to their antioxidant characteristics. Furthermore, the hydrogels exhibited cytocompatibility with the employed cell lines. The BC/AgNPs material possesses the potential to facilitate the healing of chronic wounds, attributable to its high moisture content, substantial transparency, and effective microbial effect [106].

The study on pH control with an electrical voltage, as conducted by Kiaee et al. [107], involves the fabrication of a dressing composed of poly(ethylene glycol)-diacrylate/laponite, encased within a drug-loaded chitosan capsule. This study utilizes a direct current applied to the wound dressing through the anode and cathode tips, resulting in an increase in the pH level near the anode. The presence of an alkaline environment leads to the shrinkage and deprotonation of the chitosan. The interaction between the dressing and the polymer leads to a weakening of the polymer, facilitating drug release. These wound dressings have the capacity to regulate the pH of the environment, thereby enabling precise drug release at specific times. However, achieving optimal pH levels for effective drug release requires very high values. In addition to the development of pH-sensitive wound dressings, studies are underway to create dressings that are sensitive to local pH changes, responding to low acid values or basic environments. A notable example of such studies is the carboxylated agarose/tannic acid hydrogel developed by Ninan et al. [108]. This hydrogel exhibits sensitivity to low pH and is formed through physical crosslinking of carboxylated agarose at a temperature decrease from 70 to 4 °C. The decrease in pH leads to cross-link deterioration. The release of the antibacterial tannic acid,

a result of this deterioration, prevents the formation of infection in the wound area. Although the antibacterial properties of tannic acid used in this study have a significant effect on wound protection, the hydrogel used has some deficiencies in its effects on wound healing.

Another study that employed NIPAM in the developed hydrogel was conducted by Lin et al. [109]. In these studies, NIPAM was utilized to form a hydrogel in conjunction with fibroblast growth factor (bFGF). The distinctive property of this hydrogel is its capacity for sustained release of the encapsulated drug and other factors over time. The LCST (low critical solution temperature) value of the hydrogel formed with NIPAM is approximately 33 °C, and temperatures higher than this value will facilitate the release of the drug in the capsule and protect the wound from infection. As the wound temperature will be lower than the LCST value of NIPAM during the closure and post-healing period, bFGF release will be induced and angiogenesis will be supported. This dressing constitutes an alternative treatment option for infected wounds, as it facilitates drug release in a regulated manner and is sensitive to heat. However, the variation in temperatures across different body regions necessitates direct contact with the wound to accurately perceive the temperature, thereby rendering the wound dressing insensitive to heat.

An illustration of this phenomenon can be seen in the study by Li et al. [110], which produced hollow CuS/bicarbonate nanoparticles capable of releasing CO2 through NIR light therapy when exposed to temperatures of 42 °C. The study noted that the photothermal conversion efficiency of CuS nanoparticles was enhanced by their color and the ability to adsorb NIR light. This dressing, when applied as a solution to the wound area, can produce CO_2 when NIR irradiation is applied. The CO_2 produced can treat microcirculation and promote NO angiogenesis by increasing the regional oxygen level. Although in vivo studies show that this solution provides significant improvements in wound healing, concerns have been raised about leakage or leakage of the solution.

Smart wound dressings

Chitosan–polyethylene oxide (CS–PEO) nanocomposite fibers have the potential to serve as an effective replacement for conventional bandages. The CS–PEO nanofibers, comprising berberine, a natural anti-parasitic agent, were fabricated through the electrospinning method. The outcomes demonstrated that the nanofiber scaffolds exhibited optimal characteristics, including regularity, absence of beads, and non-toxicity, fostering robust growth and proliferation of fibroblast cells. The high porosity of the produced nanofibers indicates their potential for use as a wound dressing, offering anti-parasitic properties that could aid in the treatment of wounds caused by Leishmania major [111]. Furthermore, the study demonstrated that Jucá extract, when used in conjunction with polymeric materials, exhibited an anti-inflammatory effect [112]. The incorporation of juca extract with polymers in the formulation of wound dressings has been shown to impede the adhesion of new re-epithelialization cells to the dressing, thereby facilitating their removal during the wound healing process. This study underscores the potential of biocompatible

polymers and juca fruit extracts as wound dressing materials, owing to their fluid management capabilities and extract release profiles [113].

A smart wound dressing was formulated with carrageenan (κC), locust bean gum (LBG), and cranberry extract (CB) to observe bacterial wound infections. The resulting hydrogels demonstrated the capacity to serve as a visual system for monitoring bacterial wound infections by exhibiting color changes that corresponded to pH shifts during bacterial growth. The incorporation of CB not only facilitated the observation of pH changes but also served to impede bacterial adhesion on the surface of the hydrogels. Consequently, a biocompatible wound dressing was developed, representing a valuable material for the early detection of bacterial wound infections [114].

As stated by numerous researchers in their studies, the aqueous extract of Moringa oleifera (MO) leaves exhibits healing activity. However, the plant aqueous extract demonstrates suboptimal wound healing properties. To address this limitation, the phytosome complex was successfully obtained with MO aqueous extract, thereby enhancing its therapeutic potential. The complex has been identified as a promising candidate for use as a drug-loaded biofunctional wound dressing [115].

In another study, a multifunctional wound dressing was developed by combining chitosan-based hydrogels with red cabbage extract (RCE). This dressing exhibited the capacity to protect, cure, and indicate the healing process. The RCE, comprising bioactive composites, has been shown to possess a variety of properties, including antioxidant, anti-inflammatory, anti-carcinogenic, bactericidal, antifungal, and antiviral activities. These properties have led to its utilization as a natural pH-sensitive indicator in wound healing processes. The encapsulation of RCE within a chitosan-based hydrogel has been shown to enhance the development of a smart, therapeutic pH-sensitive wound dressing. The colorimetric properties of RCE have enabled the observation of color changes in the chitosan/RCE hydrogels in both acidic and basic environments. This multifaceted hydrogel has not only served as a pH indicator in bacterial media but has also demonstrated a therapeutic effect on wounds when employed as a wound dressing [116].

Jellyfish (JF) swarms have found practical applications in the Asian food industry due to their biocompatibility and biodegradability, which stem from their biomass comprising a variety of biological materials, including mucin glycoprotein and collagen. In this study, the fabrication of nanometric "core–shell"-type fibers by electrospinning utilized jellyfish. The fabricated nanofiber scaffolds exhibited the capacity to enhance the growth of cardiac cells, and the incorporation of silver nanoparticles (AgNPs) into the fabricated nanofibers demonstrated antibacterial activity on these scaffolds. Animal testing results indicated that the fabricated JF scaffolds with AgNPs exhibited excellent wound healing [117]. Curcuma Longa extract (CLE), a pH-sensitive natural dye, was utilized as a pH-sensitive indicator. The CLE-loaded hydrogels, composed of hydroxyethyl cellulose (HC) and itaconic acid (IA), were developed as a pH-sensitive wound dressing. The prepared CLE-loaded HC/IA hydrogels were subjected to various pH buffer solutions to assess their color change responses. Upon exposure to these buffer solutions, the hydrogels underwent a discernible color shift, transitioning from a yellow hue to a dark red shade. These results demonstrated that the CLE-loaded HC/IA hydrogels functioned

not only as a wound dressing but also as a pH indicator, offering a multifaceted approach to wound management [118].

In the present study, a multilayer wound dressing was prepared, consisting of a polyvinyl alcohol (PVA) foam and electrospun sodium carboxymethylcellulose (CMC) surface mesh. The antimicrobial drug stearyl trimethyl ammonium chloride (STAC) was loaded into the PVA foam for infection control, and the material demonstrated hemostatic function. Furthermore, the laser photodynamic response potential and its effect on increasing bacterial inhibition of the wound dressing were investigated by loading methylene blue (MB). Antibacterial drug and laser photodynamic therapy (PDT) were applied in conjunction against *S. aureus* and *E. coli* bacteria. MB's unique color-changing ability enabled real-time bacterial infection monitoring of the wound dressing. The prepared material exhibited an ideal combination and excellent biofunctional multilayer. Consequently, the ideal wound dressing obtained could be a promising candidate for wound dressing materials in the healthcare industry [119].

This study successfully identified a suitable hydrogel for use as a wound dressing. Polyvinyl alcohol (PVA) was utilized as the polymeric base for the hydrogel, and the PVA polymer was loaded with Cyanine3 (Cy3)- and Cyanine5 (Cy5)-modified silica nanoparticles (SNP-Cy3/Cy5). These nanoparticles were then cross-linked with an ultraviolet (UV)-degradable polyprodrug (GS-Linker-MPEG). Initially, the presence of Cy3 and Cy5 within the smart hydrogel enabled the monitoring of bacterial infections through pH-responsive fluorescence resonance energy transfer (FRET). Subsequently, the smart hydrogel facilitated the treatment of infections through the use of near-infrared (NIR) light-triggered antibiotic release. The incorporation of up-conversion nanoparticles (UCNP) into the hydrogel served to trigger the release of GS. The UCNP exhibited a property that supported the antibacterial activity by converting NIR light to UV light, and after irradiating the hydrogels with NIR light, the UCNP converted NIR light to UV light, enabling GS release for antibacterial treatment. The prepared hydrogels exhibited good water absorption ability, good biocompatibility, and excellent mechanical properties, which are important properties for smart hydrogels [120].

In a separate study, Satureja cuneifolia plant extract (SC) was combined with sodium alginate (SA) and polyethylene glycol (PEG) scaffolds to treat diabetic ulcer wounds by 3D printing. The antimicrobial effect showed good activity against Escherichia coli and *Staphylococcus aureus* strains, and the SA/PEG/SC scaffolds prevented infection and accelerated wound healing. Therefore, it was shown to be a promising candidate for diabetic wound healing and against bacterial infections [121].

Researchers prepared a composite nanofibrous mat (CNM) using a combination of three materials: chitosan, gelatin, and shape memory polyurethane (SMPU), along with a silver nitrate solution. The prepared CNMs exhibited a shape memory effect and several advantageous characteristics, including optimal water/vapor transmission, wettability, biological properties, antibacterial activity against bacteria, cytocompatibility on fibroblast, and hemostatic properties. The shape memory effect of the CNMs enables their use in a pre-programmed, fixation-assisted wound closure process. Additionally, the potential of CNMs as a wound

healing treatment and smart wound dressing is promising. This study demonstrates the efficacy of multifunctional composites in wound therapy, combining synthetic functional polymers, natural proteins, and polysaccharides [122].

Observation of wound infection is crucial for the treatment of chronic wounds. The change in pH is an indicator of wound infection, and in this study, the anthocyanin in Clitoria ternatea (CT) flowers was extracted to serve as a pH indicator. The color change of the CT extract can indicate the status of wound healing due to the anthocyanins present in the extract, which are pigments that exhibit different pH values, allowing for observation of wound healing with the naked eye. The CT extract exhibited notable antibacterial activity against various bacterial strains, including *S. aureus*, *E. coli*, *P. aeruginosa*, and *S. epidermidis*. Furthermore, the toxicity of the CT extract to cells was not observed in the conducted tests. Consequently, the natural dyes derived from CT flowers have the potential to serve as a wound dressing due to their antibacterial properties and the ability to detect pH changes associated with wound infection [123].

In a related study, Hamedi et al. produced a novel wound dressing composed of a thyme oil nanoemulsion (TM-PEC)-loaded alginate-chitosan film. This innovative wound dressing exhibited potent antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* bacteria, as well as the ability to impede bacterial growth. These findings suggest that TM-PEC-loaded alginate-chitosan films have significant potential as a wound dressing [124].

In the study by Flores et al., two types of hydrogel were prepared: TTO nanocapsule (TTO-NC) and nanoemulsions (TTO-NE). TTO has been shown to possess antimicrobial and anti-inflammatory properties, which aid in collagen regeneration. The study demonstrated that both TTO-NC and TTO-NE hydrogels enhanced the treatment of inflammatory disorders and promoted wound healing. Notably, the TTO-NC hydrogel exhibited accelerated wound healing compared to the TTO-NE hydrogel. The study concluded that both TTO-NC and TTO-NE hydrogels enhanced wound healing when used as a wound dressing [125]. In a separate study, Sadri et al. formulated a green tea (GT) extract from the leaf of Camellia sinensis in a composite of chitosan/polyethylene oxide (Chi/PEO) nanofibers to determine the wound healing effect of GT. The composite, Chi/PEO/GT nanofiber, was prepared to heal wounds as a wound dressing. The incorporation of green tea into the chitosan-based scaffolds resulted in enhanced wound surface moisture retention, reduced inflammation, and accelerated recovery and healing properties. In addition to these advantages, green tea leaf extract possesses properties such as anti-inflammatory, antibacterial, and antioxidative effects. Consequently, green tea leaf extract was incorporated into the obtained scaffolds as an antibacterial agent to augment the therapeutic efficacy of the chitosan-based nanofiber scaffolds. The Chi/PEO/GT nanofiber scaffolds demonstrated notable stability and swelling properties. The higher swelling property of the obtained scaffold indicated that it could hold more moisture, thus preventing the wound dressing from sticking to the wound surface, which was wet. The oxygen permeability of the Chi/PEO/GT nanofiber scaffolds was also high, and these properties contributed to wound healing and recovery. Furthermore, the Chi/PEO/GT nanofiber scaffolds exhibited antibacterial activities against both gram-positive and gram-negative bacteria. Furthermore,

the results of animal tests indicated that the healing efficacy and speed of wound recovery of the chi/PEO/GT nanofiber scaffold were superior to those of the chi/PEO scaffold without green tea leaf extract. Consequently, these results suggest that the chi/PEO/GT nanofiber scaffold could be a promising wound dressing, with the potential to facilitate faster and more effective wound healing [126]. In addition, Zataria multiflora (ZM) essential oil, a natural antimicrobial agent, was incorporated into polymeric nanofiber mats to prepare a promising wound dressing. The incorporation of ZM essential oil into the CS/PVA/Gel/ZM nanofiber mats resulted in a pronounced antimicrobial effect against bacterial strains, while maintaining non-toxic and biocompatible properties. The results of this study indicate that the CS/PVA/Gel/ZM nanofiber mats have the potential to serve as a promising candidate for wound dressings in surgical and burn wounds due to their biocompatible, antimicrobial, and mechanical properties [127].

The nanofiber mats were fabricated using a blend of antibacterial poly(ε-caprolactone) (PCL)-gelatin (GEL) and clove essential oil (CLV). The antibacterial and biological activity of the CLV-loaded PCL-GEL nanofiber mats in wound dressings was subsequently assessed. The CLV-loaded PCL-GEL nanofiber mats exhibited not only antibacterial properties but also enhanced wound healing. Consequently, these mats have the potential to serve as a suitable material for antibiotic-free wound healing applications [128]. The objective of this study was to develop antimicrobial wound dressings coated with silver nanoparticles, sodium alginate, and various essential oils (e.g., mandarin, clove, and niaouli) to prevent wound infection and biofilm formation. The results demonstrated that the fabricated wound dressings exhibited enhanced antimicrobial and antibiofilm properties. The study demonstrated that the fabricated wound dressings could be used to treat infections and be evaluated for antibiotics for wound healing. The use of sodium alginate and essential oils with silver nanoparticles resulted in the development of wound dressings that could benefit wound healing by avoiding infection [129].

The essential oil from Zingiber cassumunar Roxb. (Plai) has been utilized in herbal remedies for treating inflammation, pain, sprains, and wounds. In this study, the essential oil was incorporated into poly(lactic acid) and poly(ethylene oxide) fibrous membranes for application as an analgesic and antibacterial in wound dressings. The hydrophilicity and water absorption capacity of the material were enhanced to ensure moisture balance, thereby accelerating wound healing. The produced wound dressing demonstrated an antibacterial effect against *S. aureus* and *E. coli*, exhibiting no toxicity to human fibroblast and keratinocyte cells. These findings indicate that the produced materials are suitable for use as analgesic and antibacterial wound dressings [130]. The objective of this study was to prepare a gelatin-based hydrogel with essential oil extracted from the Eupatorium adenophorum Spreng plant (Crofton weed). The emulsion-loaded hydrogel pads demonstrated notable antibacterial activity against various pathogens, suggesting that hydrogels have the potential to serve as effective antibacterial wound dressings [131].

Smooth, flexible wound dressings that can act as delivery vehicles were obtained by using cabreuva essential oil (CEO) (Myrocarpus fastigiatus), a natural compound with antimicrobial capacity, and chitosan-poly(vinyl alcohol) (PVA)

polymers. The addition of CEO into the chitosan-PVA nanofibers showed good mechanical properties such as water affinity and gas permeability. The produced materials demonstrated an antibacterial effect against various microorganisms and were non-toxic to cells. The enhanced material can be utilized in superficial burns or minor wounds due to the controlled release property of the cabreuva essential oil [132]. The objective of this study was to produce nanofibers with zein/cinnamon oil for application as a wound dressing. The produced zein/cinnamon oil nanofibers exhibited an antibacterial effect against *E. coli* and *S. aureus* bacteria. The nanofibers produced in this study exhibited a web-like morphology, with the capacity to accumulate at the wound site as an antibacterial wound dressing. These fibers demonstrated gas permeability, facilitating gas exchange following deposition at the wound site. These multifaceted properties of the nanofibers contributed to their ability to promote wound healing [104]. Poly(ethylene glycol) (PEG) has been shown to exhibit good biocompatibility and low toxicity. PEG was used to obtain polyurethane-urea (PUU) films, and in this study, PUU films that were degradable by reactive oxygen species (ROS) were obtained. The hydrogel films showed some mechanical and thermal properties, good water uptake, and low toxicity. The hydrogel films were degradable by a ROS-mediated cleavage process with visible light. The films were loaded with silver sulfadiazine (AgSD), a drug that enhances antibacterial activity. The study demonstrated that the produced hydrogel films have the potential to improve wound dressings, particularly for the treatment of burn wounds [133].

Membranes that release nitrofurazone in response to changes in acidity were produced, with the active agent being released only at pH values greater than 7. To this end, the nanomaterials were fabricated with polymers that exhibit selective solubility at pH values greater than 7. It was hypothesized that the manufactured dressings would selectively provide an antibiotic treatment according to the pH of the wound, in cases where there are natural signs of infection. To assess the efficacy of the membranes, they were evaluated in various pH media. The pH-sensitive nanofiber drug carriers produced were recommended as ideal smart wound dressings for burns or chronic wounds, with the potential to enhance the therapeutic effects in the treatment of damaged skin tissues [134]. The membranes were fabricated using a combination of Chitosan (CS), Arabinoxylan (ARX), and reduced graphene oxide (rGO), which were crosslinked using tetraethyl orthosilicate (TEOS). This combination was used to fabricate composite hydrogels for wound dressing, and the prepared composite hydrogel exhibited a good antibacterial effect against pathogens that cause skin diseases. In addition, MC3 T3-E1 cells adhered, proliferated, and differentiated well on the composite hydrogels, and the prepared composite hydrogel showed non-toxic properties on cells. Therefore, the ARX/CS/rGO composite hydrogel could be a promising candidate as a wound dressing to treat and care for skin wounds [135].

In this study, poly(vinyl alcohol) (PVA) fibers doped with upconverting nanoparticles (UCNPs) and UV-cleavable levofloxacin were utilized to examine the treatment of wounds. Under near-infrared (NIR) light stimulation, the UCNPs were activated, emitting UV light to disband levofloxacin conjugates, thereby facilitating the regulated release of the drug. In addition, the nanofibers exhibited

an antibacterial effect against *Escherichia coli* and *Staphylococcus aureus*. The improvement of antibacterial fibrous fibers with the release of drugs is an essential strategy for the treatment of wound infections, and this strategy has become an important material to be used in wound dressings and biomedical applications [136].

The study involved the preparation of a nanofiber membrane using polyvinyl alcohol (PVA) nanofibers, incorporating chitosan nanoparticles (CSNP), and drug-loaded graphene oxide–magnetite (GO–Fe_3O_4) nanocomposites. This membrane was developed for the purpose of smart wound dressings, particularly for burns and diabetes wounds. The test results of the drug-containing membranes demonstrated that the incorporation of chitosan and GO–Fe_3O_4 as carriers facilitated regulated drug release within the membranes. The release of the drug could be adjusted by the presence of the CSNP. According to the tests, the produced membranes exhibited good antimicrobial activity against bacteria [137]. Also, the nanofiber membranes exhibited good compatibility because of the mechanical properties of the GO [138]. Therefore, the produced membranes could be a candidate for both wound dressing and drug delivery [137].

In the study by Jayesh et al. [139], Nisin was utilized due to its noteworthy antibacterial properties in the preparation of a wound dressing. The researchers fabricated composite nanofibers comprising polylactic acid (PLA), polyethylene oxide (PEO), and DHBA, a natural phenolic acid present in various fruits and vegetables. Following one day of incubation with the composite nanofibers, a substantial reduction in methicillin-resistant strain *S. aureus* (MRSA) biofilm formation capabilities was observed. Furthermore, it was observed that an increase in iron concentration led to a decrease in biofilm formation. The study concluded that the composite nanofibers have potential for use as a dressing for antibiotic-resistant bacteria (ARB)-infected wounds, with the ability to inhibit biofilm formation and control infection. In a subsequent study, nanofibers based on zinc oxide nanostructures and orange oil (ZnO/OO) were obtained. The nanocomposite coatings exhibited superior antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* in comparison to ZnO nanofibers. The coated wound dressings demonstrated notable resistance to microbial colonization of *S. aureus* and biofilm formation. The findings of this study indicate that the produced wound dressings coated with ZnO/OO have the potential to serve as a novel material for the fabrication of bioactive wound dressings and bioactive coatings. The wound dressings thus produced were found to be a promising candidate with anti-infective properties and a functional coating for medical devices [140].

In this study, a smart dressing was fabricated for the theranostics of diabetic wounds. Theranostics is the collection of therapeutic agents and diagnostic agents on a single platform. The fabrication of the smart dressing involved the use of graphene quantum dots (GQDs), luminescent porous silicon (PSi), chitosan (Chi), and a peptide. The GQDs-decorated PSi, which was loaded with a peptide and embedded in Chi film, was fabricated as a smart wound dressing. The GQDs/PSi with efficient fluorescence resonance energy transfer (FRET) effect leads to fluorescence changing and drug releasing. Also, the use of GQDs with PSi remarkably increased the loading capacity for peptide drugs including epidermal growth factor and insulin, which can support diabetic wound healing. The fabricated dressing exhibited stimuli-responsive drug release, with the degradation of Chi in the GQDs/PSi film

in the acidic and oxidation medium against acid and oxidative conditions in diabetic wounds. The results demonstrate that the dressing exhibited fluorescent color change in real time, indicating the healing of diabetic wounds. Therefore, the fabricated smart dressings could be an excellent material to treat diabetic wounds [141].

The study demonstrated that infections can lead to a rapid increase in the wound pH, which can impede the healing process. The investigation presented a smart wound dressing that employed a combination of hydroxypropyl methylcellulose (HPMC) and epigallocatechin- 3-gallate (EGCG) through the formation of hydrogen bonds and hydrophobic interactions. The prepared complex film exhibited stimulus-sensitive, self-assembled, and multi-layered characteristics. The combination of these elements led to a decrease in the hydrophilicity of HPMC and an enhancement in the mechanical strength, antioxidant activity, and light barrier properties of the resulting film. The regulation of EGCG release was facilitated by the EGCG/HPMC complex film through the modulation of the pH or temperature of the surrounding medium. Furthermore, the incorporation of CuS nanoparticles into the fabricated film enabled the controlled release of EGCG through near-infrared (NIR) exposure. The inhibitory effect of EGCG release on bacterial infection was a notable finding. The fabricated complex films exhibited a color change in response to bacterial growth, indicative of the structural changes in EGCG. These films not only detected bacterial growth but also exhibited bactericidal properties. The UV protective effect of the complex film effectively shielded β-carotene from UV-induced photodegradation. These fabricated films hold great promise for use in dressing applications, offering the potential to achieve optimal wound healing through their wound healing properties and their ability to detect and inhibit bacterial infection by color change [142].

In this study, polylactic acid (PLA)-based composite fibers were fabricated using a combination of electrospinning and CA/β-CD encapsulation. CA/β-CD was formed through the encapsulation of cinnamaldehyde (CA) in β-cyclodextrin (β-CD). The incorporation of CA/β-CD into the PLA led to the development of antibacterial properties in the composite fibers, which exhibited effectiveness against *Escherichia coli* and *Staphylococcus aureus*. Consequently, the utilization of PLA/CA/β-CD fibers holds promise for applications in wound dressing and other biomedical contexts [143]. In a related study, a PEGDA/Laponite hydrogel was prepared with embedded chitosan drug nanocarriers. The hydrogel was equipped with an electronic driver and microelectrodes fabricated on a flexible substrate. The application of voltage to the electrodes resulted in a change in the pH of the applied field. The pH regulation provided by the electric field was ideal for controlling drug delivery, and cell viability tests showed the biocompatibility of the electronic wound dressing. The results demonstrated the function and efficacy of the pH-sensitive electronic dressing for the treatment of chronic wounds [144].

The objective of this study was to develop poly (butylene-adipate-co-terephthalate) (PBAT)/poly (ε-caprolactone) (PCL) electrospun fibers containing propolis by the electrospinning method. PBAT/PCL nanofibers incorporated propolis, which possesses antimicrobial and anti-inflammatory properties, thereby promoting antimicrobial activity and wound healing. Consequently, the PBAT/PCL/propolis

nanofibers emerged as a promising candidate for utilization as a cutaneous wound dressing [145].

Günnur et al. fabricated poly (lactic-co-glycolic acid) (PLGA) membrane nanofibers with carboxyl groups on the surface, and embedded the antibacterial peptide RW/KRF on the membrane surface by crosslinking agents EDC/NHS. The PLGA/peptide inhibited bacteria and reduced toxicity, and also demonstrated good cell compatibility. Consequently, the fabricated membranes hold promise as a potential candidate for wound dressing due to their positive effects on the wound healing process [146].

A flexible smart bandage was produced with wireless control of drug delivery by three-dimensional (3D) printing. The fabricated flexible and stretchable bandage consists of two separate parts, one for drug delivery and the other for electronics. The drug delivery is performed using thermo-responsive drug carriers, which are activated by temperature changes. The temperature change was induced by a heater that was controlled wirelessly (i.e., Bluetooth) and programmed based on the treatment strategy. The components of the bandage, such as the heater, hydrogel, and 3D structure, had to be flexible to allow for a suitable and wearable bandage. The bandage exhibited an efficient wound healing process using wireless electronics for on-demand drug delivery [147].

Bilayer wound dressing

In this study by Marjan et al., a bilayer dressing was fabricated via electrospinning, consisting of a nanofibrous healing-promoting bottom layer (BL) with pectin, soy protein isolate, and pomegranate peel extract, and a cellulose microfiber top layer (TL) for protection and monitoring. Scanning electron microscopy confirmed its thin bilayer structure, and the dressing lost 60. 05% of its mass in seven days in a phosphate-buffered solution. The dressing exhibited antibacterial activity, releasing SPI and phenolic compounds. The dressing was biocompatible, promoting cell adhesion, migration, angiogenesis, and tissue regeneration. In vivo experiments demonstrated accelerated epidermal formation, blood vessel growth, collagen deposition, and enhanced wound healing, suggesting the Cel/Pec-SPI-P bilayer dressing as a promising approach for clinical wound treatment [42].

In this study, a bilayer scaffold (BS) was developed with a 3D-printed hydrogel top layer (Pec/PAA/PRF) and a nanofibrous bottom layer (Pec/PAA/SIM). The use of biodegradable polymers, cross-linked via galacturonate linkage and Ca^{2+} activation, was investigated. The results showed that PRF and SIM promoted angiogenesis and neovascularization. The 3D printing process ensured the uniform distribution of PRF, and the nanofiber layer exhibited an average diameter of 96. 71 $\pm$18.14 nm. The BS demonstrated a Young's modulus of 6. 02 $\pm$0.31 MPa and an elongation at break of 30.16 $\pm$2.70%. The gradual release of growth factors over a period of seven days resulted in enhanced cell viability and accelerated wound healing, as evidenced by a closure rate of 95.80 $\pm$3.47% after 14 days. BS promoted collagen deposition and re-epithelialization, indicating its potential for skin tissue regeneration [45].

Future aspect of wound dressing (conclusion outlook)

This review discusses recent advancements in multifunctional wound dressings, emphasizing their antibacterial, antimicrobial, adhesion, anti-inflammatory, antioxidant, substance migration, self-healing, accelerated healing, and stimulus-responsive capabilities. The integration of innovative materials, such as nanofibrous layers, platelet-rich fibrin (PRF), and 3D-printed scaffolds, has led to significant improvements in the therapeutic potential of modern wound dressings.

The primary objective of advanced wound dressings is to promote rapid healing while minimizing scar formation and replicating the natural extracellular matrix (ECM) to enhance tissue regeneration. The selection of biomaterials constitutes a pivotal aspect in the development of effective wound dressings, as these materials must exhibit biocompatibility, biodegradability, and functional responsiveness to the wound environment [45].

Recent research has emphasized the importance of nanofibrous sublayers in wound healing, as they closely mimic the ECM and provide an optimal scaffold for cell proliferation and migration. Electrospun nanofiber dressings have demonstrated superior wound healing efficiency by maintaining moisture balance, enhancing gas exchange, and facilitating controlled drug release [44]. Furthermore, PRF-based wound dressings have been shown to facilitate sustained growth factor release, thereby promoting angiogenesis and fibroblast activity, thus underscoring their potential as a valuable addition to biofunctional wound care strategies [47].

The potential of composite materials in wound healing has been a subject of extensive research. Studies have demonstrated that hybrid biomaterials, which integrate natural and synthetic polymers with bioactive agents such as silver nanoparticles, curcumin, and essential oils, exhibit robust antibacterial properties and facilitate enhanced wound closure rates. Polymer-based dressings, including hydrogels, foams, and sponges, have exhibited optimal mechanical strength, flexibility, and cost-effectiveness, rendering them suitable for diverse clinical applications [45].

A significant breakthrough in wound dressing development is the application of "3D-printed scaffolds", which enable precise control over structural properties and material composition. These scaffolds, composed of materials like gelatin methacryloyl (GelMA), alginate, and polycaprolactone (PCL), facilitate cell adhesion and tissue regeneration [45]]. Furthermore, the combination of 3D bioprinting with bioinks containing stem cells and growth factors has opened new avenues for personalized wound healing approaches [47].

The integration of 'sensor technology into wound dressings' is another promising advancement. Smart dressings capable of monitoring pH, temperature, humidity, and infection levels have been developed, enabling real-time assessment of wound conditions. These systems can trigger drug release in response to environmental changes, improving treatment efficacy and reducing the need

Table 1 Applications of multifunctional wound dressings

Type of dressing	Polymer composites	Effects	References
Hydrogel	SA/NIPAM/PVA	Anti-inflammatory drug was released at different temperature values for wound healing	[34]
	Alg/Gel/agNPs	Showed antibacterial activity	[49]
	PVA/Cs/CeO_2 NPs	Reduced wound infections without the use of antibiotics	[51]
	Cs/PPG/TiO_2	Showed antimicrobial efficacy	[52]
	HA/ZnO	Showed good biodegradability and swelling and improved antibacterial activity and blood coagulation	[55]
	Alg/propanediol	Self-regulating/anti-adhesive alginate hydrogels and exhibited better healing, inflammatory properties	[80]
	SA/PAA/GO/dopamine	Increase the mechanical and biological properties also supported tissue regeneration and accelerated wound healing	[81]
	GG/ARX	Showed good antibacterial properties	[83]
	PVA/Cs/$AgNO_3$/Vit. E	Showed effective antimicrobial properties against s. Mutans	[94]
	LBG/CB/κC	Monitored bacterial wound infections and prevented the adhesion of bacteria	[114]
	Cs/RCE	Helped to protect, cure and indicate the healing	[116]
	PEGDA/Laponite	Ph regulation provided by the electric field to control drug delivery showed the biocompatibility	[144]
	HC/IA/CLE	An indicator to observe the ph of the wound	[118]
	BC/AgNPs/Cur/HPβCD	Exhibited an excellent antimicrobial activity and cytocompatibility	[106]
	PEG/Cs/diacrylate-laponite	Control the ph of the environment at the right time for drug release	[107]
	NIPAM/bFGF	Released the drug in the capsule and protected the wound from infection	[109]
	Cs/ARX/rGO	Exhibited a good antibacterial effect against pathogens that cause skin diseases	[135]

Table 1 (continued)

Type of dressing	Polymer composites	Effects	References
Sponge	Cs/PEG	Accelerated re-epithelialization, the boost in vascularization, and remodeling of granulation tissue	[57]
	Gel/GA/ZnO	High mechanical and biological properties and good antimicrobial properties	[58]
	PVA/GO	Showed the blood compatibility and antibacterial effect	[60]
	Gel/SA/SH/AA	Exhibited high biocompatibility and high antibacterial activity, large pores providing high interconnectivity	[84]
	PVA/Kaolin	Excellent antibacterial activity and blood coagulation	[126]
Nanofibers	PVA/Cs/AgNPs	Showed resistance to *E. coli*	[66]
	Cs/PEO/TE	Environment-friendly material exhibited antibacterial activity	[101]
	PVA/Cs/TCH	Exhibited influential antibacterial activity and cytocompatibility	[65]
	GA-loaded CA	Showed antibacterial activity against *S. aureus*	[66]
	PU/ZnAg	Used in antibacterial wound dressing applications	[67]
	PCL/AgNPs	Showed excellent mechanical properties and protected to avoid bacterial infection	[68]
	SF/GO	Showed superior physicochemical properties, cell compatibility, and good antibacterial activity	[69]
	PU/GO	A strong inhibition ability for antibacterial and antifungal activity	[70]
	PVA/GT	Biodegradability, non-toxicity, and biocompatibility	[72]
	PVP/TiO_2	Showed excellent antimicrobial effect and biocompatibility on cells	[98]
	Cs/PEO/CNC/AP	Produced a sufficient antibacterial effect, a long-lasting effect, reducing the frequency of dressing changes	[87]
	PCL/Cs- mupirocin/lidocaine	Exhibited high antibacterial activity	[88]
	SF/Gel/CTZ	Showed good antibacterial activity	[90]
	PU/AgNP/lavender oil	Increased hydrophilicity, showed non-toxic effects	[91]
	CNT/PVA/EGF	Egf supported the growth of fibroblasts, provided inhibit foreign agents and encouraged the regeneration of tissues	[92]

Table 1 (continued)

Type of dressing	Polymer composites	Effects	References
	Cur/PCL	Showed nti-oxidant, anti-infective, and anti-inflammatory properties released curcumin molecules to rapid wound closure	[93]
	Cs-gentamicin/liposome	Inhibited *E. coli*, *P. aeruginosa*, and *S. aureus* growth	[95]
	Alg/PEO/Lavender	The antibacterial and anti-inflammatory effects on the healing of burn wounds	[18]
	PCL/CND	Fluorescent nanofiber for monitoring to enhance full-thickness wound dressing to wound recovery	[148]
	PLA/PEO/DHBA/Nisin	Reduced mrsa biofilm formation and effected on antibiotic-resistant bacteria	[139]
	ZnO/OO	Showed higher antibacterial activity and high resistance to microbial colonization and less biofilm formation	[140]
	PLA/CA/β-CD	Developed the antibacterial effects of the composite fibers against *E. coli* and *st. aureus*	[143]
	PBAT/PCL/propolis	Promoted antimicrobial activity and wounds healing	[145]
	Cs/PEO/GT	Exhibited an antibacterial effect against *E. coli* and *st. Aureus*	[126]
	Cs/PVA/CEO	Showed good water affinity and gas permeability	[132]
	PVA/UCNPs/levofloxacin	Exhibited an antibacterial effect and released of drugs for the treatment	[136]

Table 1 (continued)

Type of dressing	Polymer composites	Effects	References
Film	GG/TiO_2NPs	Showed good mechanical properties and swelling capacity also exhibited antimicrobial activity and healing properties	[24]
	PVA/St/Gl/CA	Higher swelling potential, better solubility, lower elastic modulus, excellent in vitro degradation, and antibacterial activity	[23]
	PLA/PEG/TA	Exhibited biodegradability and good antibacterial effect	[29]
	Cur/HA/pullulan	Exhibited good antibacterial and antioxidant properties	[101]
	HA/EEP/CSt	Developed films with antibacterial and wound healing properties	[102]
	CHI/Cs/AgSD	Exhibited a good antibacterial effect against to *P. aeruginosa* and *S. aureus*	[96]
	PVA/Cs/AV	Improved affordability, biocompatibility, and flexibility	[89]
	PVA/Cs/CE	To treat burns or minor wounds	[103]
	Cs/Ser/AgNP/Mox	Exhibited a strong burn wound healing capacity	[104]
	Cs/Alg/TM-PEC	Inhibition of the growth of bacteria	[124]
	GQDs/Psi/Cs/peptide	Showed the healing of diabetic wounds in real time with fluorescent color change	[140]
	HPMC/EGCG	Showed not only detect the growth of bacteria but also inhibit bacterial infection	[142]
	PEG/PUU/AgSD	Showed good water uptake and low cytotoxicity and antibacterial activity	[96]
hydrogel film	Cs/PPG/TiO_2	Exhibited excellent antimicrobial activity and used for biomedical applications	[52]

Table 1 (continued)

Type of dressing	Polymer composites	Effects	References
Membrane	PVA/St	Exhibited antibacterial activity and mechanical strength	[75]
	PVA/starch/Ag	Improved antibacterial activity, efficient porosity and oxygen permeability	[76]
	Fe_3O_4/Cs/Gel	Showed high mechanical strength, improvement in toughness, and high antibacterial activity	[77]
	Cs/pectin/TiO_2	Exhibited excellent antibacterial properties, swelling properties, hydrophilic nature, biocompatibility, and wound closure rate	[98]
	CAL/Gel/Cs	Showed bioactive, biodegradable, and non-toxic properties	[21]
	PVA/CsNP/GO/Fe_3O_4	Good antimicrobial activity against bacteria and exhibited good compatibility	[138]
	PLGA/RW/KRF	Inhibited bacteria and reduced cytotoxicity, showed good cell compatibility	[146]
	PLA/PEO/plai	Improved the hydrophilicity and water absorption ability exhibited an antibacterial effect and no toxicity	[130]
Scaffolds	SF/chitin/AgNPs	Biodegradable and biocompatible properties, increased the tensile strength	[15]
	Cs/PVA/PD/FeONPs	Improved the proliferation of cells on the scaffold	[85]
	PCL/Gel/AV	Showed good antimicrobial activity, biocompatibility, and biodegradability	[149]
	SA/PEG/SC	Exhibited good antimicrobial effect and cell viability, prevented infection and accelerate wound healing	[121]
	JF/AgNPs	Showed good antibacterial activity and excellent healing of wounds	[117]
	Chi/PEO/Berberine	Helped to heal and recover wounds and showed antibacterial activities	[111]
Mats	PCL/PVA/Cs-eugenol	Demonstrated a good antibacterial activity and no toxic effect on human dermal fibroblasts	[66]
	PEO/GO/CeO_2/peppermint oil	Exhibited low cytotoxicity, a fast-healing mechanism thanks to facilitating wound contraction	[105]
	PVA/CMC/STAC/MB	Color-changing ability enabled real-time bacterial infection monitoring	[117]
	Cs/PVA/Gel/ZM	Showed an antimicrobial effect and biocompatible, antimicrobial and mechanical properties	[127]
	PCL/Gel/CLV	Showed both antibacterial effects and improved wound healing	[129]
Fibrous mat	PCL/Cs/CsCA	Exhibited good cell attachment and cell proliferation and effective antimicrobial activity	[100]

Table 1 (continued)

Type of dressing	Polymer composites	Effects	References
Nanofiber gel	Arg/Cs	Improved the wound healing process including wound closure	[150]
	CuS/bicarbonate	Caused effective photothermal transduction due to their color and adsorbed nir	[110]
	Thyme/oregano essential oils/collagen	Showed good antimicrobial activity	[151]
	Cs/PVA/Cur/GO/AgNP	Pegylated graphene oxide	[28]

for frequent dressing changes [45]. This innovation represents a paradigm shift toward personalized, stimulus-responsive wound management solutions.

While the development of biofunctional and smart wound dressings has advanced significantly, challenges remain in optimizing these materials for chronic wound treatment and ensuring their economic and clinical viability. Future research should focus on improving large-scale production techniques, enhancing the affordability of advanced biomaterials, and validating their long-term efficacy through extensive clinical trials [44].

In conclusion, the future of wound dressing technology lies in the continuous integration of biomaterials, nanotechnology, and sensor-based monitoring systems. These advancements have the potential to revolutionize wound care by providing multifunctional, adaptive, and patient-specific solutions. The insights presented in this review serve as a valuable reference for the design, selection, and application of next-generation wound dressings (Table 1).

Author contribution All authors contributed equally.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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