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Review article

Developing natural polymers for skin wound healing

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ABSTRACT

Natural polymers are complex organic molecules that occur in the natural environment and have not been subjected to artificial synthesis. They are frequently encountered in various creatures, including mammals, plants, and microbes. The aforementioned polymers are commonly derived from renewable sources, possess a notable level of compatibility with living organisms, and have a limited adverse effect on the environment. As a result, they hold considerable significance in the development of sustainable and environmentally friendly goods. In recent times, there has been notable advancement in the investigation of the potential uses of natural polymers in the field of biomedicine, specifically in relation to natural biomaterials that exhibit antibacterial and antioxidant characteristics. This review provides a comprehensive overview of prevalent natural polymers utilized in the biomedical domain throughout the preceding two decades. In this paper, we present a comprehensive examination of the components and typical methods for the preparation of biomaterials based on natural polymers. Furthermore, we summarize the application of natural polymer materials in each stage of skin wound repair. Finally, we present key findings and insights into the limitations of current natural polymers and elucidate the prospects for their future development in this field.

1. Introduction

Wound refers to the damage or deterioration of normal skin or tissue caused by various stressful events. Generally, wounds are classified into three categories: mechanical trauma resulting from external forces such as war injuries, traffic accidents, and surgical incisions; thermal and chemical trauma caused by temperature and chemical exposure, such as burns and frostbite; and chronic ulcerative wounds [1–8]. Due to the high frequency and prevalence of trauma in society, the regeneration of skin wounds has always been a crucial part of therapeutic treatment. With the advancements in modern medicine, wound healing procedures have become more diversified [9–14]. A wide range of new devices [15–18], clinical medications [19–27], and biological materials [28–38] have emerged, including precision debridement, negative pressure therapy, growth factors, dermal replacements, and various biomedical materials. Among these, suitable biomaterials play a fundamental role in promoting wound healing. Consequently, numerous studies are focused on developing new materials for wound repair, such as hydrogel dressings, bioactive glass, nano-silver gelatin sponges, etc.

Natural polymer materials are polymer compounds derived or synthesized from natural sources such as plants, animals and microorganisms [39–46]. These materials have many advantages, such as renewability, biodegradability and biocompatibility, and are therefore widely used in many biomedical fields, such as tissue engineering, trauma repair, drug delivery and implantable medical devices [47–54]. Due to their biocompatibility, which minimizes the risk of inflammation

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and immunological reaction, these materials are frequently chosen to synthetic materials. They are also biodegradable, which means that these high-molecular compounds can be broken down into smaller molecules by microorganisms, enzymes or other biologically active molecules in the natural environment. They can be metabolized in the body, reducing the risk of long-term side effects. Natural polymers are diverse and suited for a number of medical applications because they may be made from a variety of natural sources and treated in different ways to produce materials with varying physical and chemical characteristics. Various substances, such as sodium alginate, chitosan, collagen, silk fibroin, etc., are currently the subject of research for the production of wound healing biomaterials. Additionally, a growing variety of preparation methods have been developed as a result of science and technological improvement, such as microfluidics, 3D printing, template replication, electric spinning, etc. The multitude of material sources and the variety of preparation techniques enable natural biomedical polymer materials to exhibit rich and exceptional characteristics and highly predictable shapes, allowing them to be used for various wound repairs.

There are several advantages of natural biomedical polymer materials [55–66]: a) Biocompatibility: Natural biomedical polymer materials are biocompatible, meaning they are not harmful to living tissue and do not cause an immune response. This is important for many medical applications, especially in implants or extended-release systems that require long-term presence in the body. In addition, natural polymers typically exhibit better compatibility with surrounding tissues. They are better able to bind and integrate with surrounding tissues when implanted in the body, facilitating the healing and tissue reconstruction process. b) Biodegradability: Degradable natural polymers break down in living organisms into simple metabolites that are usually non-toxic and can be excreted through natural metabolic pathways in the organism. In contrast, synthetic materials may produce harmful metabolites that increase the adverse effects on the organism. In medicine, it is sometimes necessary to use temporary support materials or implants. The use of biodegradable natural polymers avoids the need for secondary surgeries, as these materials gradually degrade after playing their role and do not require additional surgical intervention to remove them. Some natural polymers can be made predictable in the controlled release of drugs or biologically active molecules by adjusting their structure and chemistry. This is useful for therapeutic applications to ensure that drugs are released at the right time and dose. c) Versatility: Natural polymer biomaterials are widely diverse, originating from different organisms and biological processes. Their diversity gives them a rich potential for applications in the biomedical field. d) Sustainability: Natural biomedical polymer materials are often derived from renewable resources, such as plants or animals, making them a more sustainable alternative to synthetic materials. e) Functionalization: Natural biomedical polymer materials can be easily modified to incorporate specific functional groups, allowing for targeted drug delivery, increased biocompatibility, and enhanced mechanical properties. Overall, natural biomedical polymer materials offer a number of advantages over synthetic materials and have become an important component in the development of new medical devices and therapies.

Herein, we provide a comprehensive overview focusing on natural biomedical polymer materials with unique characteristics, composition, preparation methods and their practical applications in wound healing based on their outstanding functions, as shown in Fig. 1. After a cursory introduction to the key elements and representative preparation methods, the design of multifunctional natural biomedical polymer materials in various skin wound repair processes are discussed in depth. Finally, we offer conclusions and perspectives regarding the present limitations and prospective developments of natural polymers.

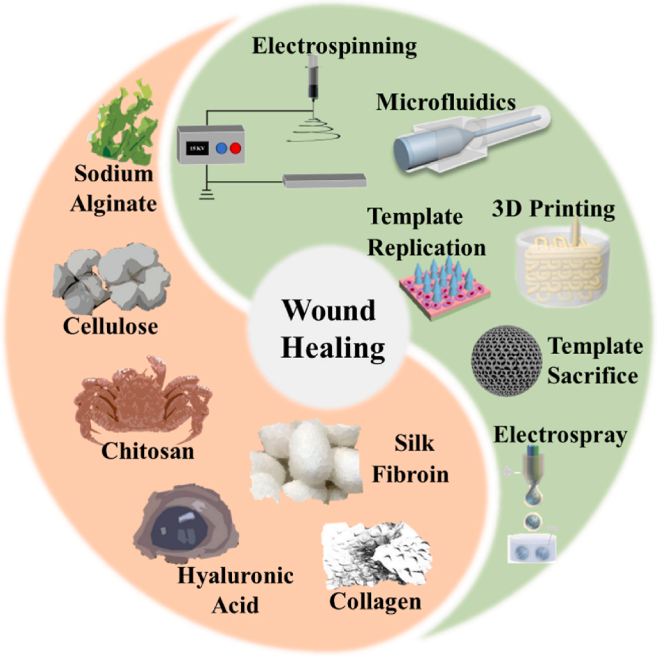

Fig. 1. The components and fabrication strategy of natural polymers.

2. Components of natural polymers

2.1. Natural polysaccharide

Natural polysaccharides are complex carbohydrates composed of long chains of monosaccharide (sugar) units linked together by glycosidic bonds. These biopolymers are found in various natural sources, including plants, animals, and microorganisms. Natural polysaccharides serve a wide range of functions in biological systems and have numerous industrial and commercial applications. Natural polysaccharides are valued for their biodegradability, biocompatibility, and sustainable sourcing. They are widely utilized in the food industry, pharmaceuticals, cosmetics, agriculture, and other sectors, making them an essential class of biopolymers.

2.1.1. Cellulose

Cellulose is the most prevalent organic substance on Earth and a form of carbohydrate [67–70]. It is a complex polysaccharide composed of repeating glucose molecules and is present in the cell walls of all plants and many algae. Cellulose provides structural rigidity and resilience to plants, and is essential for their growth and development. Additionally, it is an essential component of wood, cotton, and other natural fibers. There are numerous industrial applications for cellulose, including the production of paper, textiles, biofuels, and other renewable materials. In some culinary products, it is also used as a low-calorie thickener and stabilizer. Due to its capacity to promote tissue regeneration and lesion closure, cellulose has been used in wound healing. Cellulose-based dressings, when placed to a wound, can provide a moist environment that helps hasten healing and inhibit the growth of germs. Additionally, cellulose dressings can absorb excess wound exudate, thereby reducing inflammation and preventing infections. Certain types of cellulose dressings, such as those manufactured from carboxymethyl cellulose (CMC), can form a gel-like barrier over the incision to promote healing and alleviate pain. Another form of cellulose-based wound dressing is manufactured from bacterial cellulose, which is generated in a manner similar to 3D printing by certain bacteria. This form of dressing has a highly porous structure and can serve as a scaffold for the growth of new tissue and the healing of wounds. Burns, chronic ulcers, and surgical incisions are among the categories of lesions for which cellulose-based

dressings have been shown to be safe and effective in both preclinical and clinical studies [71–73].

Cellulose-based biomaterials can play a beneficial role in skin wound healing. These materials are used in various wound care products and dressings to support the healing process by providing a suitable environment for tissue regeneration. Cellulose-based wound dressings are often designed to maintain a moist environment around the wound. Proper moisture control helps create conditions that are conducive to cell migration, proliferation, and tissue repair. Moist wound healing can promote faster healing and reduce scarring. Wounds often produce exudate, which is a combination of blood, serum, and other fluids. Cellulose-based dressings have high absorption capacity, which helps in managing exudate, preventing it from accumulating around the wound, and reducing the risk of infection [74]. Cellulose-based wound dressings can help prevent biofilm formation on the wound surface. Biofilms are communities of bacteria that can impede the healing process and make wounds more susceptible to infection. Cellulose dressings can create a barrier that inhibits biofilm formation. Some cellulose-based biomaterials, particularly those with 3D structures, can provide a scaffold for the formation of granulation tissue. Granulation tissue is a critical part of the proliferative phase of wound healing and plays a role in wound closure and tissue repair. It's important to note that the effectiveness of cellulose-based wound dressings may vary depending on the specific product, wound type, and individual patient needs. Overall, cellulose-based biomaterials are part of the broader field of biomaterials used in wound care, and they contribute to creating a favorable environment for the body's natural wound healing mechanisms to function optimally.

2.1.2. Chitosan

Chitosan is a naturally occurring polysaccharide derived from the exoskeletons of crustaceans, such as shrimp, crab, and lobster. Biodegradable, non-toxic, and biocompatible, chitosan is a linear polymer composed of randomly distributed -(1–4)-linked D-glucosamine and *N*-acetyl-D-glucosamine units. Chitosan's capacity to adhere to and trap fats and cholesterol in the digestive tract has made it a popular weight loss and cholesterol-lowering dietary supplement [75–78]. It is also used as a biodegradable packaging material and for wound healing and water remediation. Although chitosan has been studied for its potential antibacterial, antifungal, and antitumor properties, additional research is required in these areas. Chitosan's potential to promote wound healing has been investigated. Chitosan, when administered to a wound, can produce a protective film that prevents infection and promotes healing. It is believed that its wound-healing properties result from its ability to stimulate the production of growth factors and promote the formation of new blood vessels, both of which are necessary for the regeneration of damaged tissue [79]. Chitosan can also promote the formation of granulation tissue, a type of tissue that forms during the healing process and is composed of new blood vessels and connective tissue. This can aid in accelerating the healing process and lessen the likelihood of scarring. In addition to promoting wound healing, chitosan possesses antimicrobial properties that can help prevent wound infections. It is also biocompatible, which means that it is non-toxic to living tissue and can be safely used in the body. Chitosan shows promise as a potential treatment for wound healing due to its ability to promote the growth of new tissue and prevent infections; however, additional research is required.

2.1.3. Hyaluronic acid

The body naturally produces hyaluronic acid (HA), which is present in many tissues including the skin, joints, and eyes. It is a glycosaminoglycan, a kind of molecule composed of units of sugar molecules that repeat repeatedly. Hyaluronic acid is crucial for the skin's ability to retain moisture, elasticity, and plumpness. It can store 1000 times its weight in water, preventing dryness and wrinkles while preserving the skin's hydration levels. Dermal fillers, which plump up the skin and minimize the appearance of wrinkles and fine lines, are only one example of how hyaluronic acid is employed in a variety of medicinal and cosmetic purposes [80–84].Additionally, it is used in certain joint injections to lessen discomfort and inflammation in arthritis sufferers. The healing of wounds benefits greatly from hyaluronic acid (HA). The body reacts to a skin injury by creating a blood clot to halt the bleeding, and then it begins to restore the tissue. In this healing process, hyaluronic acid plays various roles. Hyaluronic acid generates a gel-like matrix after an injury that gives new cells a framework to develop into. This matrix aids in the creation of a scaffold for the generation of new tissue. This matrix may aid in preventing scarring by directing the creation of new tissue. Hyaluronic acid promotes cell migration and proliferation by attracting and activating immune cells and other cells vital to the healing of wounds. Additionally, it promotes the growth of fibroblasts, which are cells that create the proteins required for tissue repair, including collagen. Inflammation is a normal component of the healing process for wounds, however excessive inflammation may slow down healing and cause scarring. Hyaluronic acid aids in reducing inflammation. By preventing the synthesis of pro-inflammatory molecules, hyaluronic acid aids in the reduction of inflammation. Because of these methods, hyaluronic acid is a component of various wound dressings and other items intended to speed up the healing process. Burns, diabetic ulcers, and surgical incisions are just a few examples of the acute and chronic wounds that these medicines may help heal more quickly.

2.1.4. Sodium alginate

Brown seaweed is the source of sodium alginate, a natural polymer utilized in a number of sectors including food, medicine, and textiles. It is a salt that dissolves in water and is often used in various culinary items, such as ice cream, salad dressings, and canned goods, as a thickening, stabilizer, and emulsifier [85–88].The food industry uses sodium alginate to produce a gel-like texture that has numerous uses, including the creation of edible films, the encapsulation of flavors or oils, and the production of textured food items like vegetarian meat replacements. It is used as a binder, disintegrant, and viscosity-increasing agent in tablet formulations in the pharmaceutical business, as well as a thickening and sizing agent in the manufacture of textiles in the textile industry. The U.S. Food and Drug Administration (FDA) has typically deemed sodium alginate to be safe, and it is regarded as a natural thickening and stabilizer substitute. Due to its capacity to absorb significant quantities of water and transform it into a gel-like material that may provide a moist wound environment, sodium alginate has been investigated for its possible application in wound healing. This moist environment is believed to hasten wound healing by acting as a barrier of defense and preserving an ideal degree of hydration. Burns, ulcers, and surgical incisions may all be covered and protected by sodium alginate wound dressings, which come in diverse shapes including sheets, gels, and fibers. These dressings are often produced from a mixture of calcium and sodium alginate, which aids in the promotion of clotting and wound healing. According to studies, dressings containing sodium alginate may help to treat wounds more effectively overall, promote wound healing, and lessen pain and inflammation. Additionally, they have shown to be secure and well-tolerated by patients. The use of sodium alginate dressings, nevertheless, must be done so in accordance with a complete wound care plan that may also include other therapies and interventions, and it must be done so under the supervision of a medical expert.

2.1.5. Carrageenan

Carrageenan is a substance extracted from red seaweed (algae) and is used as a thickening or stabilizing agent in various food products. It has been used for centuries in traditional cooking, particularly in Ireland, where a type of red seaweed known as Irish moss is abundant. Carrageenan is valued for its ability to form a gel-like structure, making it useful in a variety of food applications. It is commonly used in the food

industry to improve the texture and stability of products such as dairy products (like ice cream and yogurt), processed meats, salad dressings, and certain beverages. There are different forms of carrageenan, including kappa-carrageenan, iota-carrageenan, and lambda-carrageenan, each with distinct properties that make them suitable for different purposes in food manufacturing. It's important to note that there has been some controversy and debate regarding the safety of carrageenan. Some studies have suggested potential inflammatory effects and digestive issues associated with its consumption, while other studies have found it to be safe. Regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), have generally deemed carrageenan safe for consumption in specified amounts. Some studies have explored the use of carrageenan-based hydrogels for wound healing due to properties like biocompatibility and the ability to release substances that may aid in the healing process. These hydrogels may have features such as controlled drug release or antibacterial properties, which are important considerations in wound care. However, it's essential to note that while research in this area is ongoing, carrageenan-based wound dressings are not yet widely used in clinical practice. Wound care typically involves a range of materials and approaches, including sterile dressings, antimicrobial agents, and advanced wound care products.

2.1.6. Gelatin

Gelatin, a protein derived from collagen obtained from animal tissues, has been explored for its potential applications in wound healing. Collagen is a major component of the extracellular matrix in connective tissues, and it plays a crucial role in tissue repair and regeneration. Gelatin-based dressings or sponges can be used as wound dressings. These materials provide a moist environment, which is conducive to wound healing, and they can also serve as a barrier against microbial infection. The gelatin in these dressings may help promote cell proliferation and tissue repair. Gelatin can be used to create hydrogels, which are water-containing gels that can provide hydration to the wound. Hydrogels are designed to maintain a moist environment, which supports cell migration, angiogenesis (the formation of new blood vessels), and other processes crucial for wound healing. Gelatin can serve as a carrier for the delivery of cells, growth factors, or other bioactive substances to the wound site. This can enhance the regenerative potential and accelerate the healing process. Gelatin-based scaffolds can be created to provide a temporary structural support for tissue regeneration. These scaffolds can be designed to degrade over time as the wound heals, leaving behind regenerated tissue. While gelatin-based wound healing applications show promise, it's important to note that the field of biomaterials for wound care is continually evolving, and research is ongoing. The efficacy of specific gelatin-based products may depend on various factors, including the nature of the wound, the specific formulation of the gelatin product, and individual patient characteristics. As with any wound care approach, it is crucial to consult with healthcare professionals for guidance tailored to the specific circumstances of the wound. Advanced wound care often involves a multidisciplinary approach, and healthcare providers consider various factors when selecting appropriate interventions for optimal wound healing.

2.2. Natural protein

Natural proteins are large, complex molecules that play vital roles in biological processes. They are one of the fundamental classes of biomolecules and are made up of long chains of amino acids. Proteins are essential for the structure, function, and regulation of various components of living organisms. Natural proteins are fundamental biological macromolecules with diverse functions, and they are crucial for the proper functioning of living organisms. They are extensively studied and have a wide range of applications in various fields, including medicine, biotechnology, and scientific research.

2.2.1. Collagen

Collagen is the primary protein found in connective tissue and the most prevalent protein in mammals. It also makes up the majority of the extracellular matrix (ECM), which serves as an essential structural framework for tissue growth, maintenance, and regeneration. Collagen is a kind of structural protein that is made up of three peptide chains arranged in a triple-helix shape. Collagen has strong biocompatibility, biodegradability, and low immunogenicity when it comes to biological qualities. But because of collagen's tight and sturdy helical shape, only under special circumstances can it be broken down by enzymes like collagenase and elastase, which the body may then employ for metabolism or other purposes. Most other proteases can only break side chains of proteins. It is important to note that collagen has beneficial hemostatic qualities that aid in wound healing by encouraging platelet aggregation and plasma coagulation. Collagen is very simple to process and can be made into many other forms, such as films, sponges, and microparticles, making it a popular material in the biomedical industry [89–91]. However, collagen's weak mechanical properties and enzymatic breakdown severely constrained its ability to operate in the body. As a result, several techniques have been used to improve the physicochemical and biological characteristics of collagen, including cross-linking and polymer composition.

2.2.2. Silk fibroin

Natural protein called silk fibroin (SF) has specific physicochemical characteristics and strong biocompatibility, which make it an attractive biomaterial in the biomedical industry, particularly in the creation of drug carriers. There are 18 amino acids in SF, and glycine (Gly), alanine (Ala), and serine (Ser) make up more than 80 % of the total. Three varieties, silk I, silk II, and silk III, are present in the secondary structure of silk fibroin. The liquid form of silk I, which is kept in silkworm glands, has highly -helixed and even haphazard spiral patterns. Additionally, the solid form of silk II that results from spinning has a -sheet crystalline structure that adds to the material's distinctive mechanical capabilities and delayed degradability. At the air/water contact, silk III, in solid form of SF, wins out. By manipulating the SF's internal secondary structures, a variety of attributes like solubility, biodegradability, mechanical, and others may be accurately altered. Crosslinking is often employed to overcome the low mechanical strength of several naturally occurring protein-based polymers used in drug delivery devices, such as collagen and fibrin, while simultaneously raising potential biosafety concerns. Contrarily, the strong -sheet structures of SF allow it to have high mechanical characteristics without the need for any difficult crosslinking processes, which makes SF an excellent material for tissue engineering and drug administration. It is noteworthy that the degumming procedure may further boost the tensile strength of SF, improving its stability, by eliminating sericin, another crucial component of silk [92–94].For its broad application in the realm of medication administration, SF's long-term deterioration is equally significant.

2.2.3. Keratin

Keratin, a fibrous structural protein found in the skin, hair, and nails of humans and other animals, has also been explored for its potential applications in wound healing. Like gelatin, keratin is derived from animal sources and can be used in various forms to aid in the wound healing process. Keratin-based scaffolds can be designed to mimic the natural extracellular matrix, providing a three-dimensional structure that supports cell attachment, migration, and proliferation. These scaffolds may be used in tissue engineering applications to promote the regeneration of damaged tissues. Keratin can be incorporated into wound dressings or films. These dressings can create a protective barrier over the wound, helping to maintain a moist environment that is conducive to healing. Keratin dressings may also have antimicrobial properties, providing additional protection against infection. Similar to gelatin, keratin can serve as a carrier for the delivery of cells or bioactive substances to the wound site. This approach can enhance the

regenerative potential of the wound and accelerate the healing process. Keratin has been investigated for its ability to promote angiogenesis, which is the formation of new blood vessels. Angiogenesis is a critical process in wound healing as it helps ensure an adequate blood supply to the healing tissue. Some studies suggest that keratin may have anti-inflammatory properties, which can be beneficial in the early stages of wound healing to control inflammation and promote a favorable environment for tissue repair.

2.3. Green nanomaterials

Green nanomaterials, often derived from natural sources and processed using eco-friendly methods, have gained interest in various biomedical applications, including wound healing [95–98].These materials are attractive for wound healing applications because they are biocompatible, biodegradable, and often possess unique properties that can aid in the wound healing process. Many green nanomaterials, such as those derived from plant extracts, possess natural antimicrobial properties. They can help prevent wound infections, which can be a significant obstacle to the healing process. Some examples include silver nanoparticles synthesized from plant extracts and nanoparticles derived from essential oils. Green nanomaterials may have anti-inflammatory properties, which can help reduce inflammation at the wound site. This can result in less pain and faster healing. Green nanomaterials can be incorporated into wound dressings or scaffolds. For example, nanocellulose-based wound dressings offer high biocompatibility, good mechanical properties, and can be loaded with bioactive compounds to promote wound healing. Nanomaterials can serve as carriers for drugs and growth factors. This enables controlled release of therapeutic agents at the wound site, promoting tissue regeneration and reducing the need for frequent dressing changes. Some green nanomaterials, like chitosan nanoparticles, have been shown to stimulate the growth of new blood vessels (angiogenesis) and support tissue regeneration. Exosomes are nanoscale vesicles naturally secreted by cells. They contain bioactive molecules and can be harnessed for wound healing. Green nanomaterials can be used to isolate and deliver exosomes to the wound area. The use of green nanomaterials aligns with sustainability goals, as they are typically derived from renewable resources and processed using environmentally friendly methods. It's important to note that research in this field is ongoing, and the specific applications and effectiveness of green nanomaterials in wound healing may vary. The choice of nanomaterial and its formulation depends on the type of wound, the patient's needs, and the intended therapeutic outcome. Additionally, safety and regulatory considerations are crucial when using nanomaterials in medical applications. As such, these materials are subject to rigorous testing and evaluation to ensure their safety and efficacy for wound healing.

3. Fabrication methods

Fabrication methods for natural polymers vary depending on the specific type of polymer and the intended application. Natural polymers can be processed into various forms, such as films, fibers, gels, and scaffolds, to meet the needs of different industries. The choice of fabrication method depends on the desired properties, end-use application, and the specific characteristics of the natural polymer. Natural polymers, with their biocompatibility and biodegradability, find applications in various industries, including medicine, food, agriculture, and cosmetics, and the fabrication methods can be tailored to meet the specific needs of each field.

3.1. Microfluidics

Microfluidics is a field of science and technology that deals with the study, manipulation, and control of fluids and particles that are constrained to small volumes, typically ranging from nanoliters to microliters. It involves the design, fabrication, and operation of devices and systems that can handle, process, and analyze fluids and particles at the microscale level. Microfluidic devices typically consist of microchannels, microvalves, microactuators, and other microstructures that are patterned on a chip or substrate using microfabrication techniques such as photolithography, soft lithography, and microelectromechanical systems (MEMS) technology. These devices can be used for a wide range of applications, including chemical and biological analysis, drug discovery, medical diagnostics, environmental monitoring, and more. The advantages of microfluidics include reduced sample and reagent consumption, rapid and efficient mixing of fluids, precise control over fluid flow and reaction conditions, and the ability to integrate multiple functions on a single chip. These advantages make microfluidics a promising platform for developing miniaturized and portable analytical devices that can be used for point-of-care testing, on-site monitoring, and other applications.

One approach to using microfluidics in wound healing is to create a system that can deliver therapeutic agents to the wound site in a controlled manner. For example, a microfluidic device can be designed to deliver growth factors, stem cells, or other cells to the wound bed, which can accelerate healing and improve tissue regeneration. Another way microfluidics can be used in wound healing is by creating microscale channels or scaffolds that can mimic the extracellular matrix (ECM) of native tissue. The ECM provides structural support and biochemical signals that are essential for proper tissue function and repair. By designing microfluidic channels that mimic the ECM, researchers can create a more physiologically relevant environment for wound healing. Microfluidic devices can also be used for high-throughput screening of potential wound healing compounds. Researchers can use these devices to test different drugs or compounds on cells in a controlled environment, allowing them to quickly screen large numbers of potential treatments. Overall, microfluidics has the potential to revolutionize wound healing research by enabling precise control of the wound microenvironment and allowing for high-throughput screening of potential treatments.

The study, manipulation, and control of fluids and particles that are restricted to tiny volumes, generally ranging from nanoliters to microliters, are the focus of the scientific and technology discipline known as microfluidics [99,100].It entails the creation, maintenance, and use of apparatuses and systems capable of handling, processing, and analyzing fluids and particles at the microscopic size. Microfluidic devices typically consist of microchannels, microvalves, microactuators, and other microstructures that are patterned on a chip or substrate using microfabrication techniques such as photolithography, soft lithography, and microelectromechanical systems (MEMS) technology. Numerous uses for these tools exist, such as chemical and biological analysis, drug discovery, medical diagnostics, environmental monitoring, and more. The advantages of microfluidics include reduced sample and reagent consumption, rapid and efficient mixing of fluids, precise control over fluid flow and reaction conditions, and the ability to integrate multiple functions on a single chip. These advantages make microfluidics a promising platform for developing miniaturized and portable analytical devices that can be used for point-of-care testing, on-site monitoring, and other applications.

Microfluidic microfibers can be continuously prepared with uniform size, and microfibers with different morphologies can be prepared by different microfluidic chips. In Fig. 2a, Yu et al. generated vitamin metal-organic framework (MOF)-laden microfibers with alginate shells and copper- or zinc-vitamin framework cores by using a coaxial capillary microfluidic spinning approach. These microfibers have controllable release features and were explored for their potential in improving tissue wound healing based on the antibiosis and antioxidation of the released vitamins, copper ions, and zinc ions [101]. In another study, self-bonded hydrogel inverse opal particles were developed as a sprayed flexible patch for wound healing. The particles were fabricated by infusing drugs-loaded gelatin and carrageenan pregel into inverse opal scaffolds,

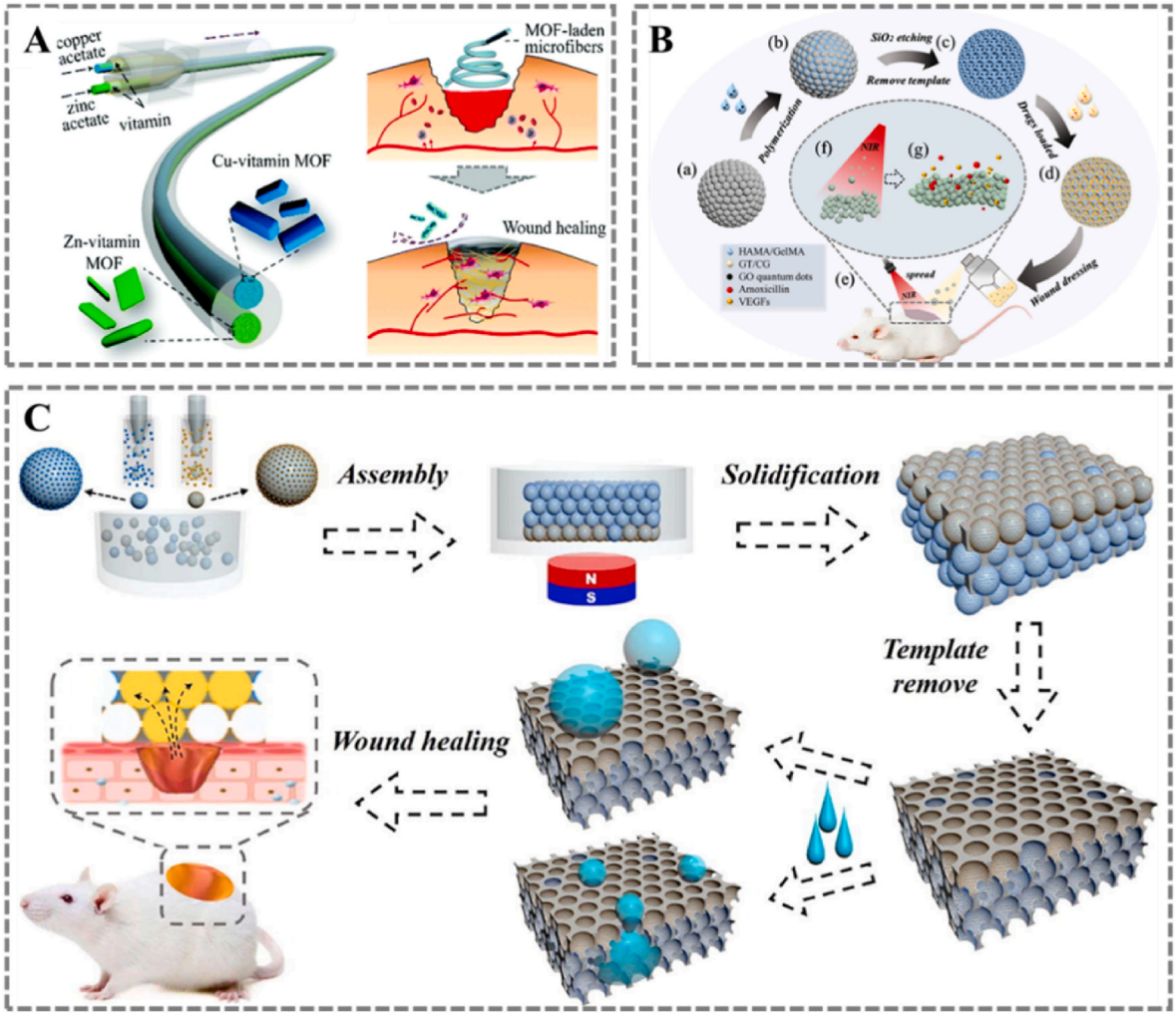

Fig. 2. Natural polymer based-biomaterials prepared by microfluidic technology for wound healing. (a) Microfluidic coaxially spun calcium alginate fibers [101]. (b) Silicon dioxide photonic crystal microspheres prepared by microfluidic technology [102].(c) Porous Janus scaffolds prepared from microfluidic droplet templates [103].

and their photothermal and phase-changing properties allowed them to adhere to each other and form a flexible patch. The particles also enabled controlled drug release and could be used for monitoring drug delivery processes. These results indicated that the self-bonded hydrogel particles have potential value as a multifunctional patch for clinical applications (Fig. 2b). [102] Besides, Chi et al. prepared Janus scaffolds with three-dimensional structure by microfluidic droplet self-assembly in Fig. 2c. Hydrophilic and hydrophobic colloidal particles were prepared using agar and ethoxylated trimethacrylate (ETPTA) mixed with hydrophilic silica nanoparticles and hydrophobic magnetic nanoparticles, respectively. A The two-phase solution was passed through a capillary tube to produce agar droplets coated with the corresponding nanoparticles. The droplet was cooled and solidified to obtain colloidal particles with different surface wettability. Subsequently, the colloidal particles were laminated and assembled under a magnetic field, the voids between them were filled with photocurable waterborne polyurethane acrylate (WPUA) solution and cured with UV light. Finally, the cured agar was removed to obtain bilayer WPUA porous membranes with anisotropic surface wettability. The bilayer WPUA porous membrane exhibits anisotropic surface wettability for unidirectional fluid drainage. The addition of an alkaline polypeptide (AMP) to the membrane provides excellent antimicrobial effects to prevent wound infections. The bilayer porous membrane and AMP integrated with the bilayer porous membrane effectively accelerated wound healing [103].

3.2. Electrostatic spraying

Electrostatic spraying has shown promise as a potential wound healing technology. This technique involves spraying a charged solution onto a wound, which can help promote healing and prevent infection. When an electrostatic spray is used on a wound, the charged particles of the solution are attracted to the surface of the wound, creating a thin and even layer of the solution. This can help to evenly distribute the solution over the wound bed, which can be especially useful for large or irregularly-shaped wounds. In addition to promoting wound healing, electrostatic spraying can also help prevent infection by delivering an antimicrobial solution directly to the wound bed. This can be particularly beneficial in cases where traditional wound dressings may not be effective or practical. In addition, microspheres with various structures, which are loaded with different active ingredients and structures to promote wound repair, are now more commonly prepared using electrostatic spraying [104,105]. Chen et al. created in situ alginate shell-coated nicotinic acid metal-organic skeletons (MOFs) microcapsules and copper/zinc nicotinic acid skeleton cores for wound healing using microfluidic electrospray technology. The nicotinic acid MOFs microcapsules may intelligently, controllably, and programmatically release calcium, copper, and zinc ions depending on the severity of infection since alginate shells are bacterially susceptible to breakdown. The liberated ions also activate copper-zinc superoxide dismutase

(Cu/Zn-SOD), which scavenges oxygen free radicals and protects cells from oxidative stress damage. These actions not only kill the bacteria by disrupting microbial membranes and causing nutrient efflux, but also by activating Cu/Zn-SOD. Niacin's simultaneous release also encourages vasodilation and the uptake of useful metal ions (Fig. 3a). [106] Zhang et al. prepared multifunctional polycaprolactone particles using three-needle coaxial electrospray and a simple non-solvent process. Titanium dioxide-silver nanoparticles and Ganoderma lucidum polysaccharides (GLPs) were encapsulated in the outer shell of the particles as the main antimicrobial and antioxidant components, whereas iron oxide (Fe3O4) nanoparticles were incorporated into the inner core as a photothermite. Based on the c57 mouse burn wound model, the in vivo wound healing effect with special structure and laser-assisted treatment was investigated (Fig. 3b). [107].

3.3. Electrostatic spinning

Electrostatic spinning, sometimes referred to as electrospinning or electrostatic fiber spinning, is a method for creating tiny fibers from a polymer solution or melt by applying electrical charges. An electrostatic field is produced between a charged electrode (usually a metal needle or spinneret) and a grounded collector using a high voltage power source. The polymer melt or solution is then passed past the charged electrode, where it forms a thin fiber and hardens as it approaches the collector under the influence of the electric field. A flexible and popular method for producing fibers with widths ranging from a few nanometers to many micrometers is electrostatic spinning. The resultant fibers may be employed for filtration, tissue engineering, medication delivery, and energy storage. They also have a high surface area to volume ratio. Overall, electrostatic spinning is a strong and adaptable method for creating tiny fibers with predetermined characteristics, making it an important tool in many scientific and technical disciplines.

Electrostatic spinning has shown great promise in the field of wound healing, where it can be used to produce electrospun fibers that promote tissue regeneration and wound closure [108,109]. One approach for using electrospun fibers in wound healing is to incorporate bioactive molecules, such as growth factors or drugs, into the polymer solution prior to spinning. The resulting fibers can then be used to deliver these molecules directly to the wound site, promoting tissue regeneration and reducing inflammation. Electrospun fibers can also be used as a scaffold for cell growth, enabling the formation of new tissue in the wound bed. By controlling the fiber morphology and composition, it is possible to create scaffolds that are highly porous and have a high surface area, facilitating cell attachment and proliferation. In order to speed up the healing of chronic diabetic wounds, Liu et al. created an absorbable nanofiber hydrogel for synergistically regulating the inflammatory milieu. Hyaluronic acid nanofibers electrospun with thioether grafts (FHHA-S/Fe) might be utilized to create nanofibrous hydrogels on-site in the wound bed (Fig. 4a). [110]For the treatment of chronic infected wounds, Li et al. introduced a shape-programmable hierarchical fibrous membrane composite system that was created to synergistically control the inflammatory milieu (Fig. 4b). [111] To rationally direct the care of chronic wounds, the membrane system combines antibacterial activity, controlled medication release in accordance with the demands of wound healing, shape-programmable mechanical modulation, strong adherence, and on-demand desorption from biological tissues. He and colleagues created an asymmetric structure based on electrostatic spinning on the sides of a sponge and a wettable surface modification in order to create an asymmetric composite dressing that was inspired by the structure of the epidermis of the lotus leaf and superhydrophobicity (Fig. 5). [112]By controlling cellular activity, the suggested asymmetric composite dressing successfully prevents bacterial colonization/infection and accelerates wound healing. It does this by combining topological morphology with material qualities. The in vitro findings demonstrated that cell adhesion, proliferation, directed growth, and migration could be successfully encouraged by the aligned nanofiber inner layer. The bionic hydrophobic outer layer of the sponge demonstrates high mechanical capabilities and anti-bacterial adhesion, whilst the sponge has good water absorption and antibacterial qualities. The outcomes of in vivo tests revealed that the composite dressing may greatly speed up the healing of severe burns by reducing inflammation, preventing infection, and accelerating angiogenesis and epithelium regeneration.

3.4. 3D printing

A digital model is used to stack materials sequentially on top of one another to create three-dimensional things via the process of 3D printing, also known as additive manufacturing. By enabling the production of complicated forms and complex geometries that are difficult to generate using conventional manufacturing techniques, 3D printing has completely transformed the manufacturing sector. It has uses in a number of industries, including education, healthcare, aerospace, and architecture. 3D printing is being utilized in the medical field to produce patient-specific models, surgical instruments, implants, and prostheses. The use of live cells in 3D printing to create organs and tissues for transplantation and regenerative medicine is also being studied. With the help of the new 3D printing technology, patients may have scaffolds

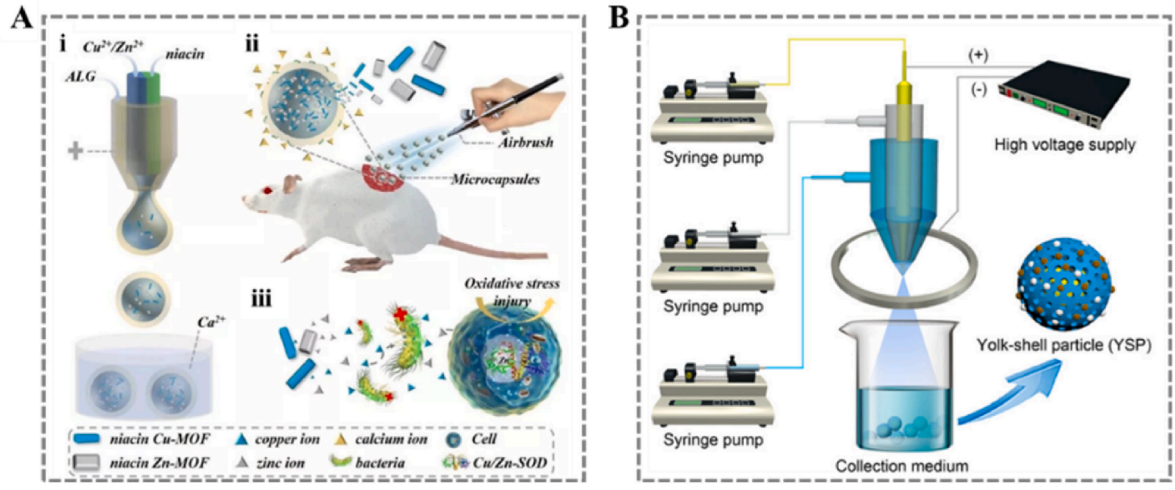

Fig. 3. Natural polymer based-biomaterials prepared by electrostatic spraying for wound healing. (a) MOF-loaded electrospray microspheres used in bacterial infected wounds [106].(b) Coaxial electrospray yolk shell microparticles [107].

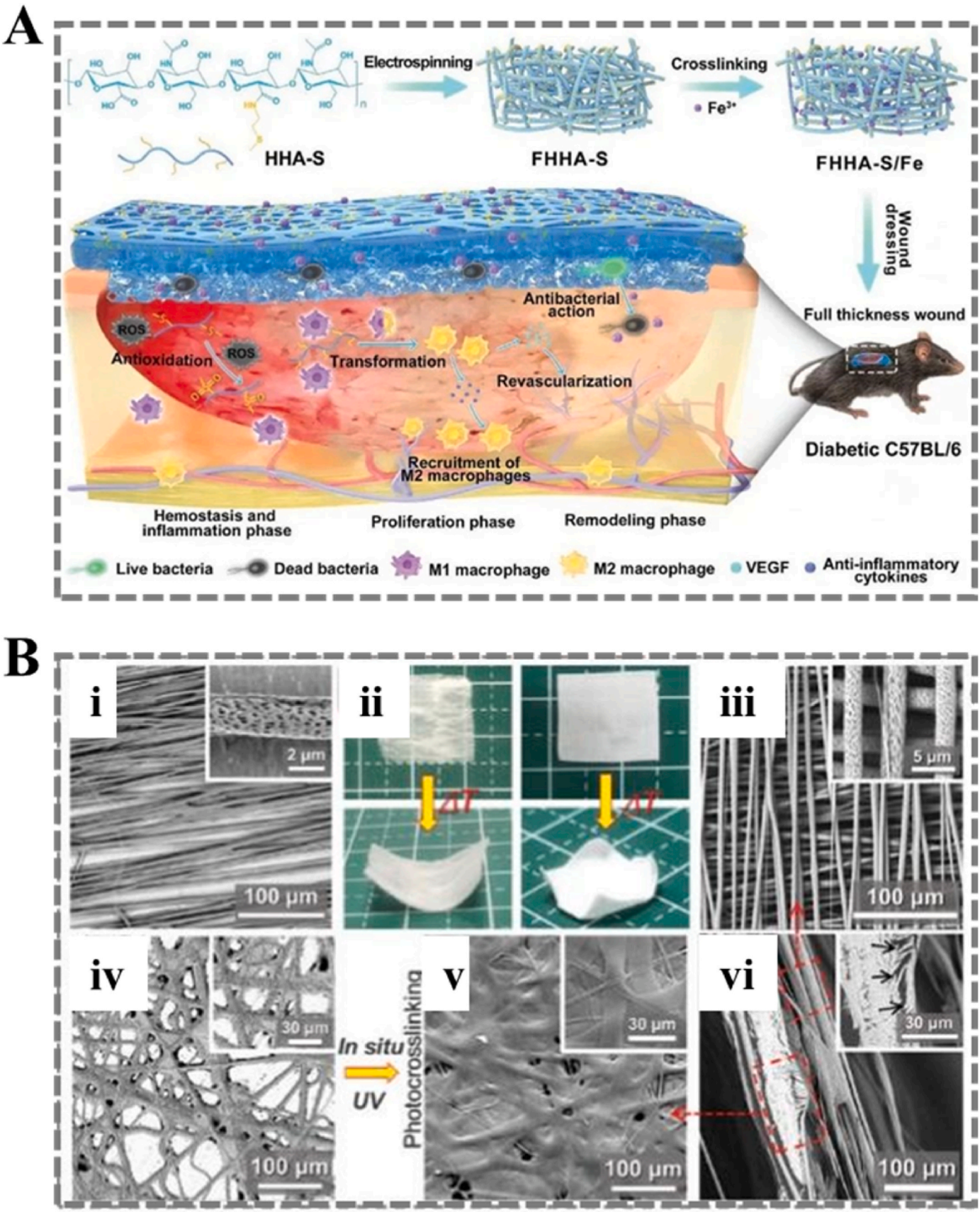

Fig. 4. Natural polymer based-biomaterials prepared by electrostatic spinning for wound healing. (a) Hyaluronic acid nanofibrous hydrogel f to accelerate chronic diabetic wound healing [110]. (b) Hierarchical composite fibrous membrane system [111].

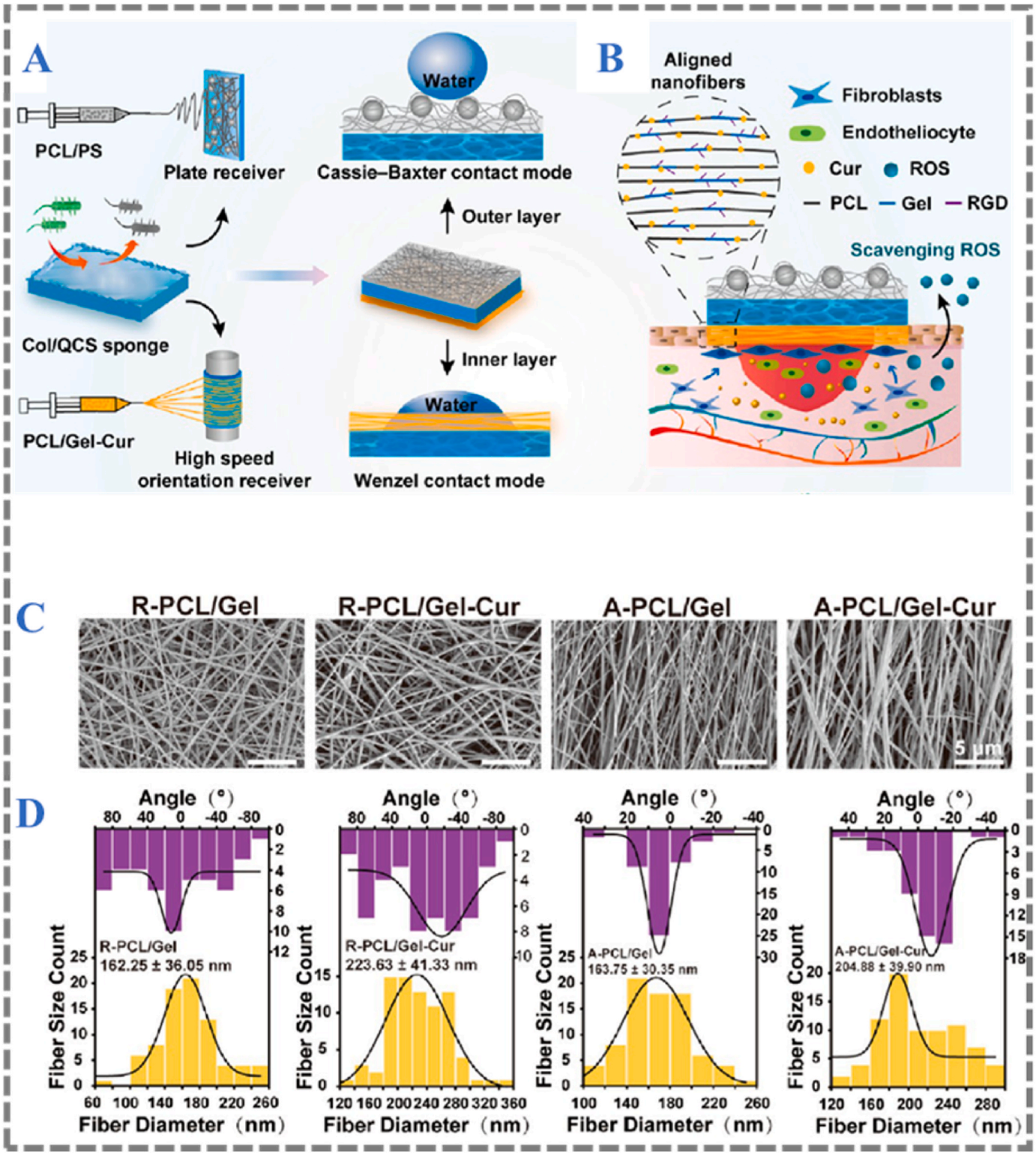

Fig. 5. Natural polymer based-biomaterials prepared by electrostatic spinning for wound healing [112].

and wound dressings that are built specifically for their requirements. It is possible to create scaffolds and wound dressings using 3D printing that will encourage tissue regeneration, lessen inflammation, and enhance wound closure. The capacity to produce complicated geometries that are challenging or impossible to obtain using conventional manufacturing techniques is one of the benefits of 3D printing in wound healing. This makes it possible to make scaffolds and wound dressings that better suit the form of the wound.

Biodegradable hydrogels and polymers may be used to create 3D printed wound dressings, which can also be engineered to release bioactive compounds including growth factors, antimicrobials, and painkillers [113,114]. These bioactive wound dressings may lessen the risk of infection and inflammation while promoting tissue regeneration. In addition to producing wound dressings, 3D printing may be utilized to produce tissue-engineered scaffolds that can be applied to chronic wounds to encourage tissue regeneration. These scaffolds may be

created to replicate the extracellular matrix's natural structure and seeded with cells to encourage tissue development. Overall, 3D printing has the potential to revolutionize the science of wound healing by making it possible to produce individualized scaffolds and wound dressings that can encourage tissue regeneration and enhance wound closure. Even though the technology is still in its infancy, continued research is anticipated to result in more advancements and advances in the usage of 3D printing for applications related to wound healing.

Wang et al. developed a new bio-photosynthetic scaffold to accommodate irregularly shaped wounds and facilitate their healing using an in situ microfluidic-assisted 3D bioprinting technique, which was motivated by the natural symbiotic interaction between salamanders and algae (Fig. 6a). [115] The scaffolds produced by 3D printing can continuously produce oxygen under light thanks to the inclusion of oxygenated photosynthesizing unicellular microalgae (Chlorella pyrenoidosa) in the process. This allows cells to multiply, migrate, and differentiate even in low-oxygen environments. In order to 3D print artificial skin patches with advantages against *Staphylococcus aureus* infections, Zhao et al. developed a novel biophotosynthetic scaffold made of gelatin (Gel), alginate (Alg), and hyaluronic acid (HA). This scaffold is composed of gelatin (Gel), alginate (Alg), and HA (Fig. 6b). [116] A unique ZnO nanoparticle-modified PVDF/sodium alginate (SA) piezoelectric hydrogel scaffold (ZPFSA) was created by Liang et al. using 3D printing. In order to imitate and enhance endogenous bioelectricity to speed wound healing and avoid scarring, the constructed ZPFSA scaffold includes a dual piezoelectric response model dominated by vertical swelling and horizontal friction (Fig. 6c). [117].

3.5. Template sacrifice

Photonic crystals are periodic optical structures that possess bandgaps (photonic bandgaps) and optical properties such as reflection and transmission in different directions [118].Biocomposite inverse opal particles with a variety of cutting-edge features for medication administration and wound healing were demonstrated by Chen et al. (Fig. 7a) [119]Chitosan biomass negatively replicating spherical colloidal crystal templates were used to create nanoparticles. Inverse opal particles may be filled with several active medicinal substances, including fibroblast growth factor, and then covered by a temperature-responsive hydrogel because of their interconnected porous nature. Due to the relatively high temperatures that are brought on by the inflammatory response of the wound, the composite particles are now able to release medications in an intelligent manner. A new photocrosslinked fish gelatin hydrogel-based inverse opal membrane (IOF) patch with advantageous wound healing and dynamic monitoring properties was introduced by Cao et al. (Fig. 7b) [120]Methacryloyl fish gelatin, chitosan, and polyacrylic acid (PAA) were combined to create films with vivid structural colors by replicating colloidal crystal templates. The generated IOFs shown high biocompatibility, low immunogenicity, antibacterial activities, and the encouragement of tissue development and wound healing because the structures of these natural biomolecules were effectively preserved throughout the synthesis process. By using a reverse opal scaffold made of polyacrylamide, polyvinyl alcohol, polyethyleneimine, and lithium chloride (PAM-PVA-PEI-LiCl) and a hydrogel-filled surface made of vascular endothelial growth factor (VEGF) mixed with gelatin methacrylate (GelMA), Wang et al. proposed a structured color ionic hydrogel based on a *trans*-opal scaffold. The VEGF-GelMA surface helps with wound healing by preventing the ionic hydrogel from being

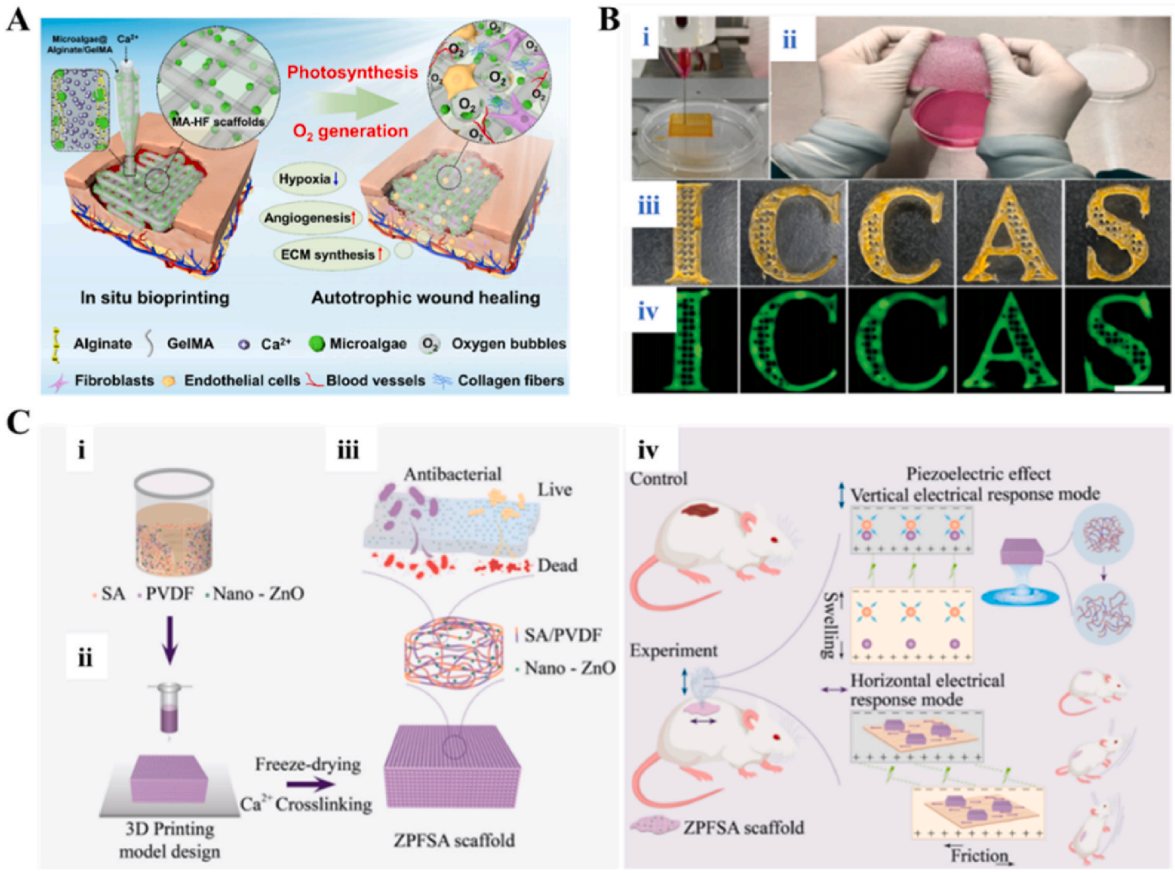

Fig. 6. Natural polymer based-biomaterials prepared by 3D printing for wound healing. (a) The microalgae-laden hollow fibrous (MA-HF) scaffolds [115].(b) 3D architectures printed from the Gel/Alg/HA/PPV ink [116].(c) A novel hydrogel scaffold prepared by 3D printing technology [117].

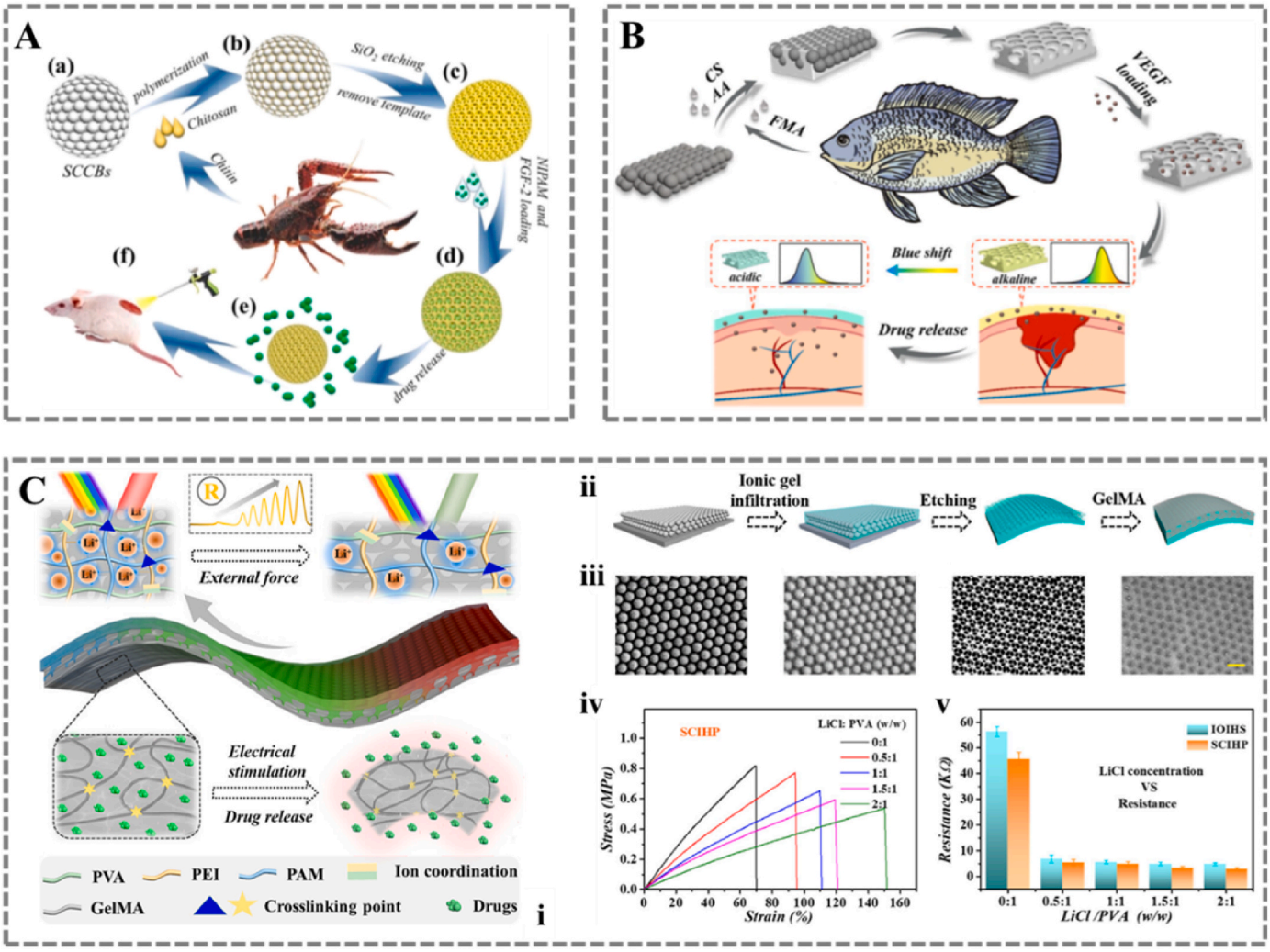

Fig. 7. Natural polymer based-biomaterials prepared by template sacrifice for wound healing. (a) The fabrication process of the biomass inverse opal particles [119] (b)The preparation process of the composite IOF and its application in dynamic pH sensing and wound healing [120].(c) Schematic diagram of the inverse opal scaffold-based SCIHP encapsulating drugs [121].

interfered with by complicated wound conditions. The scaffold gives the composite patch its bright structural color, electrical conductivity, and resistance to frost (Fig. 7c). [121].

3.6. Template replication

Microneedles (MNs), especially tissue-adhesion microneedles inspired by nature, can hold both sides of the wound and tug on both sides of the tissue, acting like sutures, but causing much less tissue damage. This feature brings advantages to the application of microneedles in the field of wound repair. Ferromagnetic fluids are homogeneous, stable colloidal liquids containing nanoscale ferromagnetic particles with 5–20 nm diameters that disperse into small, tapered droplets and form actively tunable, dynamic, magnetically oriented patterns in the presence of a strong magnetic field. By modifying the direction of the external magnetic field, the tapered ferromagnetic fluid particles can be rotated and inclined, thereby creating asymmetric arrays and magnificent mold bodies. On the basis of these ferromagnetic fluid mold bodies, Zhang et al. are able to manufacture biocompatible polymer replicas with serrated microfilament angles of varying diameters and a midline inclination (Fig. 8a). [122] In many mechanical aspects, the replicated angled MN arrays outperform the perpendicular MN arrays, as they remain firmly adhered when the affixed substrate is moved and rotated, despite the presence of external forces. In a different research, the top mold was made via etching, while the negative imprint was made by punching holes into a PP sheet at an angle using triangular pyramid needles. The higher mold and the negative mold were then layered. The pregel for the microneedle material was made by combining PEGDA and HMPP with deionized water. Two hydrogel microneedle pieces joined by gauze made up the microneedle patch. Each microneedle component had an angled end, and the two pieces together created a gripping structure that looked like a claw. In order to prevent the linear wound from dehiscing, the prepared patch might repair and stiffen the epidermis next to it. Additionally, the hybrid patch was able to create a spatial electric field during application since the LM was included into and linked to each microneedle. This allowed for continuous electrical stimulation of the lesion and aided in its healing. The effectiveness of the resulting microneedle patches in treating wounded SD rats in vivo was established, highlighting their promise in wound healing and other relevant biomedical fields (Fig. 8b). [123] Ice templating is one common processing technique used to introduce unique architectures into porous scaffolds. Solute particles continue to cluster around the forming ice crystals as the cooled substance freezes, until the sample is completely frozen. The ice is subsequently eliminated by sublimation or thawing, leaving a pore morphology that is a negative imprint of the original ice crystals. In a typical study, using a designed cold-plate electrostatic spinning and autonomous magnet stirring system, a layer of ice crystals up to 6 mm thick was accumulated on

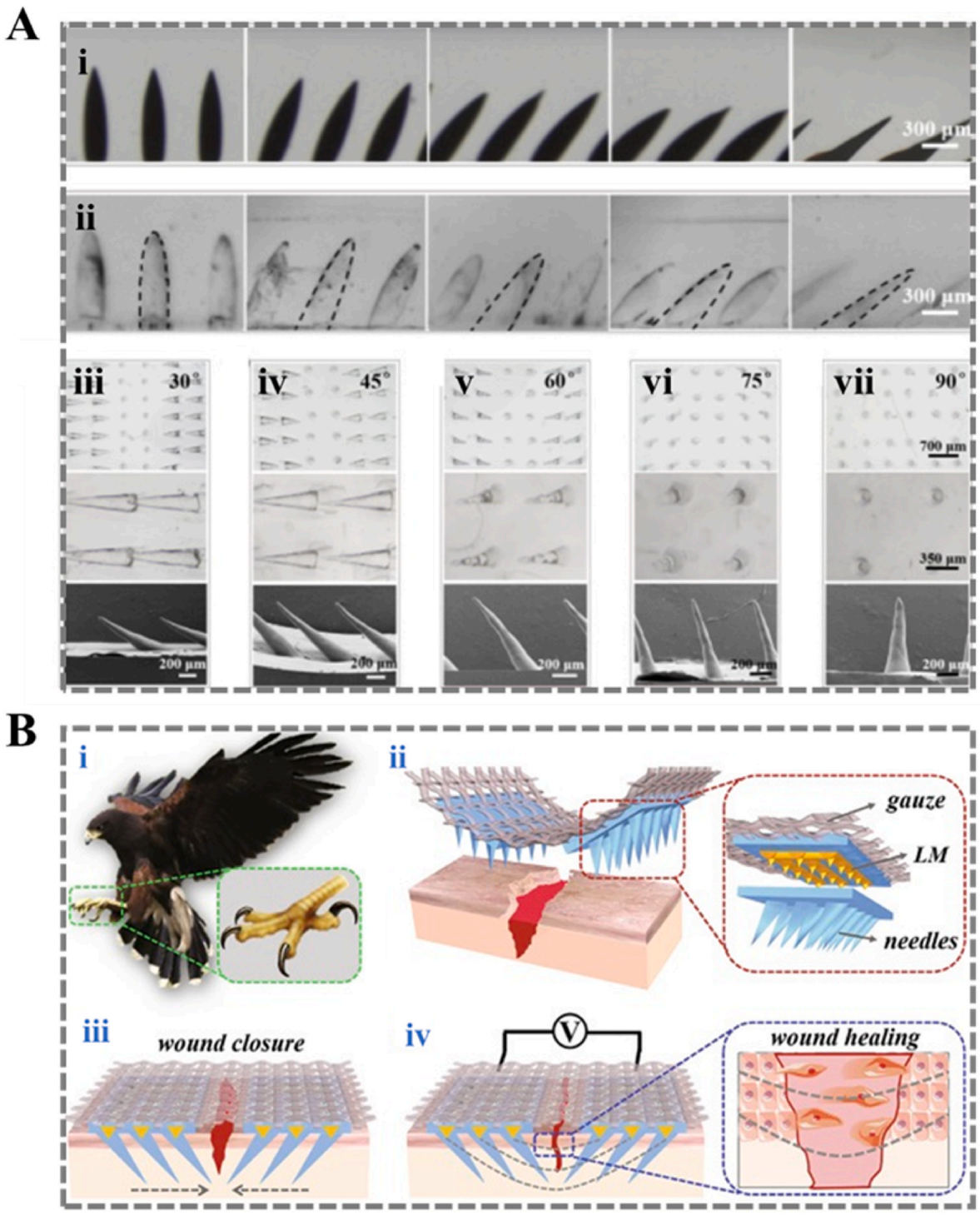

Fig. 8. Natural polymer based-biomaterials prepared by template replication for wound healing. (a) Magnetic fluid template replication microneedles [122]. (b) Eagle claw-inspired template replication microneedles [123].

Polycaprolactone (PCL) nanofibers modified on the surface of SF particles [124]. The sacrificial ice crystals developed interconnecting macropores ranging in size from tens to hundreds of meters. The increased pore size and porosity of the interconnection induced more and deeper cell infiltration and significant collagen deposition, which further improved the wound healing speed.

4. Functional natural polymers in skin wound healing

Natural polymers play significant roles in different skin wound healing processes, contributing to the overall effectiveness of wound management and tissue repair. In the early inflammation phase of wound healing, natural polymers such as chitosan and hyaluronic acid can help reduce inflammation. Chitosan, with its anti-inflammatory properties, can minimize the inflammatory response, while hyaluronic acid contributes to a balanced immune response, potentially reducing excessive inflammation. Natural polymers like collagen, chitosan, and keratin provide a scaffold for cell migration and proliferation. Collagen-based dressings act as a structural framework for cells to move into the wound area and stimulate cell division, promoting the formation of

granulation tissue. Collagen, as a primary component of the extracellular matrix, facilitates the formation of this supportive network. It guides fibroblasts to synthesize new collagen, helping reestablish tissue integrity. Natural polymers, including hyaluronic acid and alginate, maintain a moist wound environment that is conducive to cell proliferation and migration. This moist environment also helps prevent the formation of scabs, promoting faster healing. Natural polymers like collagen and gelatin contribute to collagen deposition and organization during the remodeling phase. Collagen-based dressings and scaffolds help ensure the proper alignment and bundling of collagen fibers, improving the tensile strength of the healing tissue. Certain natural polymers, such as keratin, have been found to minimize scarring and promote a more natural appearance of healed tissue. This is particularly valuable in aesthetic areas or where scar formation could impair function. Natural polymers like chitosan have inherent antimicrobial properties, helping prevent infections in the wound area. Chitosan dressings can inhibit the growth of bacteria, making them suitable for wounds at risk of infection. Alginate dressings, composed of seaweed-derived alginic acid, absorb excess exudate from the wound. This not only maintains a moist environment but also helps prevent bacterial proliferation in overly moist conditions. Some natural polymers, when used as carriers for growth factors, can enhance their bioavailability and activity. This can further stimulate cell proliferation and tissue regeneration. For instance, hyaluronic acid can act as a carrier for growth factors like epidermal growth factor (EGF). Natural polymers can stimulate angiogenesis (the formation of new blood vessels) through their influence on growth factors and cell behavior. This is vital for ensuring adequate blood supply to the healing tissue. Polymers like pectin, which can be used in wound dressings, create a protective barrier over the wound while allowing for oxygen and nutrient exchange. This can help prevent external contaminants from entering the wound. In summary, natural polymers play multifaceted roles in different phases of skin wound healing. They support and optimize the processes of inflammation, proliferation, and tissue remodeling, promote a favorable wound environment, reduce inflammation, prevent infections, and enhance tissue regeneration. Their biocompatibility and biodegradability make them valuable components of wound care strategies, with applications in various types of skin wounds, ranging from acute injuries to chronic ulcers and surgical incisions.

4.1. Hemostasis

The physiological mechanism known as hemostasis prevents bleeding from broken blood vessels. The interplay of platelets, blood proteins known as clotting factors, and blood artery walls makes it a complicated process. The process of hemostasis is essential for the prevention of excessive bleeding and is crucial in maintaining normal blood flow and circulation.

There are three basic stages to the hemostatic process. Vasoconstriction: Blood arteries that have been damaged close in order to lessen blood flow to the area of harm. The release of many vasoconstrictor chemicals, including thromboxane A2, mediates this constriction. Formation of platelet plugs: Small, disk-shaped cells called platelets travel through the circulation. When a blood artery is injured, platelets gather around the wound, bond with one another, and form a plug that closes the hole. A number of signaling molecules, including thrombin, which stimulates platelets, are released during this process, mediating it. Coagulation is the process by which a blood clot, a network of fibrin fibers that fortifies the platelet plug and stabilizes the broken vessel, forms. A number of coagulation factors, including thrombin, factors VIII, XI, and X, influence this process.

Wang et al. utilized -(2,3-epoxypropoxy)propyltrimethoxysilane (KH560) as a cross-linking agent to construct a capillary-type composite hemostatic sponge (CCK) with a low-density, interconnected microchannel structure, suitable mechanical strength, high elasticity, and exceptional fluid absorption capacity (Fig. 9a). [125]Composite hemostatic sponge (CCK) has a low-density linked microchannel structure, adequate mechanical strength, high elasticity, and exceptional liquid absorption capacity. The addition of numerous hydrophilic carboxymethyl functional groups and the formation of a capillary-like structure by the ice separation-induced self-assembly (ISISA) process provided the CCK sponges with an exceptional capacity for liquid absorption, which substantially enhanced the material's hemostatic properties. Preman et al. demonstrated that supramolecular hydrogel (SMTH) based on sodium alginate/poly (*n*-vinylcaprolactam) is biodegradable and temperature-pH dual sensitive (Fig. 9b). [126]Molecular hydrogel

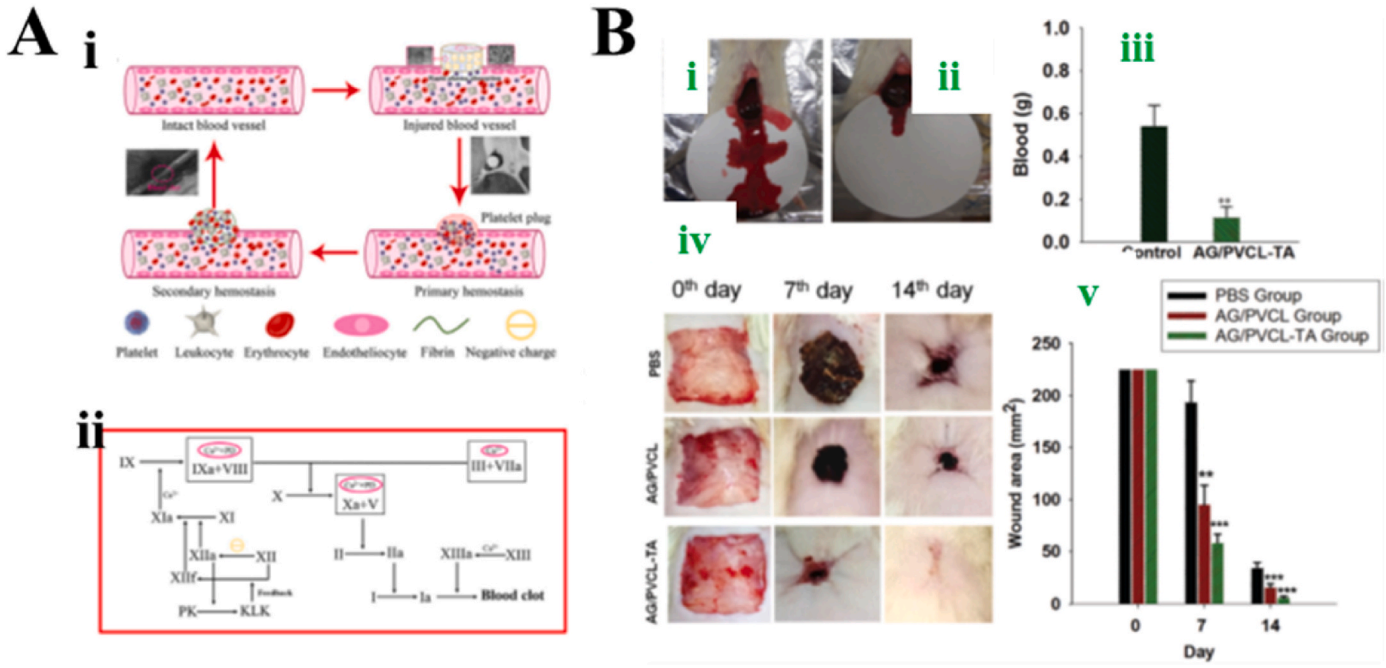

Fig. 9. Natural polymer based-biomaterials with hemostasis property for wound healing. (a) The diagram showing the hemostasis process of the CCK sponge [125] (b) Demonstration of the hemostatic performance of the AG/PVCL-TA hydrogel [126].

(SHG) scaffolds are produced by radical polymerization followed by chemical and ionic cross-linking. Tannic acid (TA)- SHG (AG/PVCL-TA) was also synthesized and its hemostatic and wound-healing properties were investigated. Wang et al. created hybrid hyaluronic acid-polyurethane (HA-PU) cryogel by perylene bonding oxidized hyaluronic acid (OHA) with dihydrazide-modified aqueous biodegradable polyurethane emulsion (PU-ADH) at −20° Celsius. Within minutes, the desiccated cryogel can assimilate water or blood to approximately 22 and 16 times its dry weight, respectively, and has a highly compressed volume and stable fixation. This immediate capacity to restore form in minimally invasive techniques enables rapid hemostasis (Fig. 10). [127].

4.2. Antibacterial

The risk of infection increases when the skin is wounded because the epidermal barrier is compromised, allowing germs to enter the body, particularly in unhygienic or dirty environments outside. Antimicrobial medication coatings, antimicrobial gauze or dressings, and the use of medical tapes containing antimicrobial agents are a few examples of antimicrobial wound healing techniques. To aid in the healing of wounds, Chi et al. created a patch called the biomass-energetic chitosan microneedle array (CSMNA) (Fig. 11a). [128]Due to its exceptional qualities, including its inherent antibacterial capabilities, chitosan is often utilized for wound healing. Additionally, the microstructure of the microneedle helps to prevent excessive skin and patch adherence while still delivering the drug-carrying agent to the target location. In the meanwhile, the vascular endothelial growth factor (VEGF) is wrapped in the CSMNA micropore by the temperature-sensitive hydrogel. As a consequence, the temperature rise brought on by the inflammatory response of the wound may be exploited to regulate the release of smart drugs. Biomass CSMNA patches have been proven in studies to support tissue regeneration, angiogenesis, collagen synthesis, and inflammatory control during wound healing. Therefore, this multifunctional CSMNA patch may be useful for clinical applications such as wound healing. For the release of drugs and the healing of wounds, Zhang et al. suggested a novel class of controlled responsive particles made of various natural polymeric materials (Fig. 11b). [129]These hybrid particles were made up of black phosphorus quantum dots (BPQDs) that had been loaded with growth stimulants and antimicrobial peptides, gelatin, agarose, and

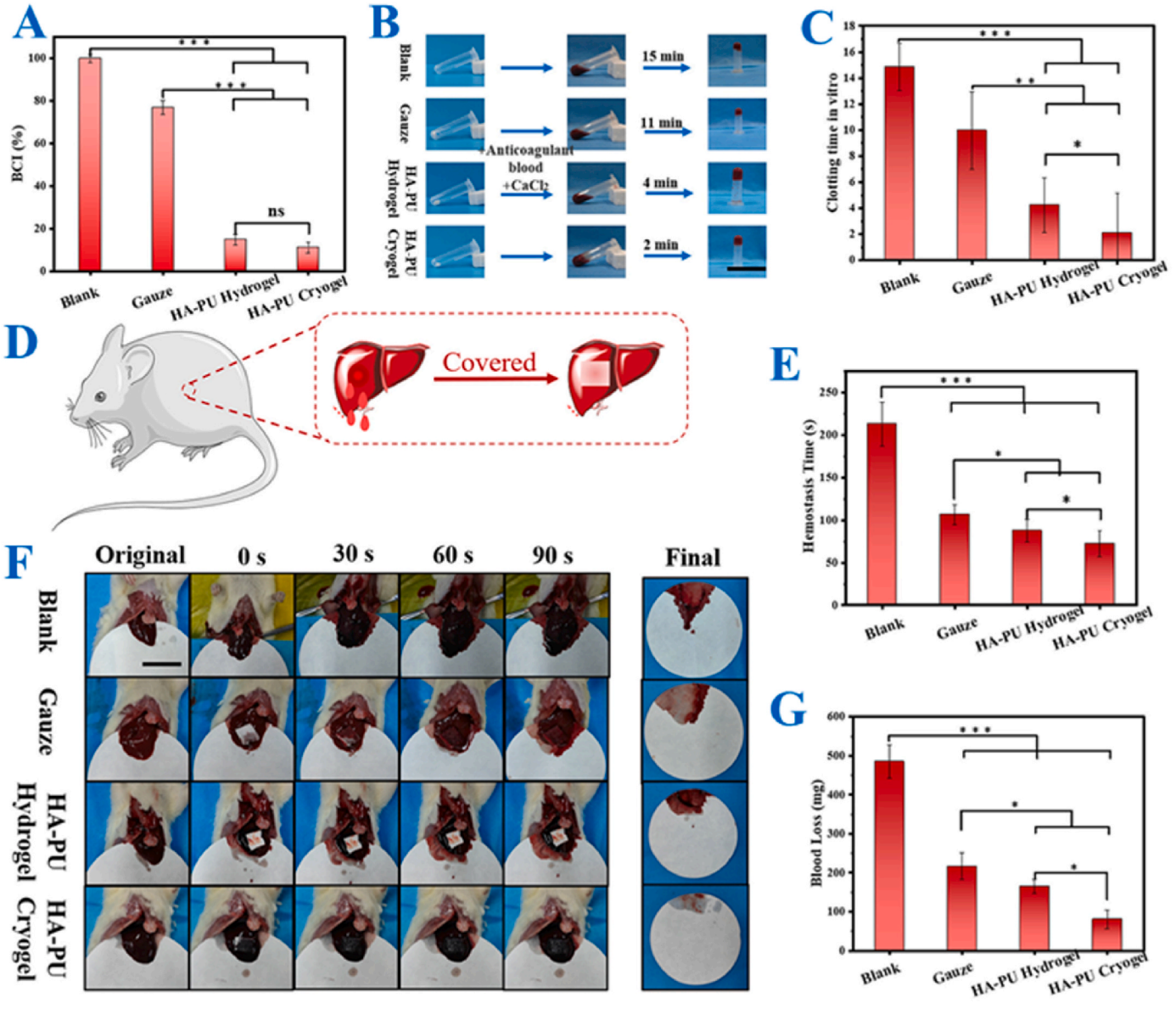

Fig. 10. Hemostatic properties. Blood coagulation index (BCI) [127].

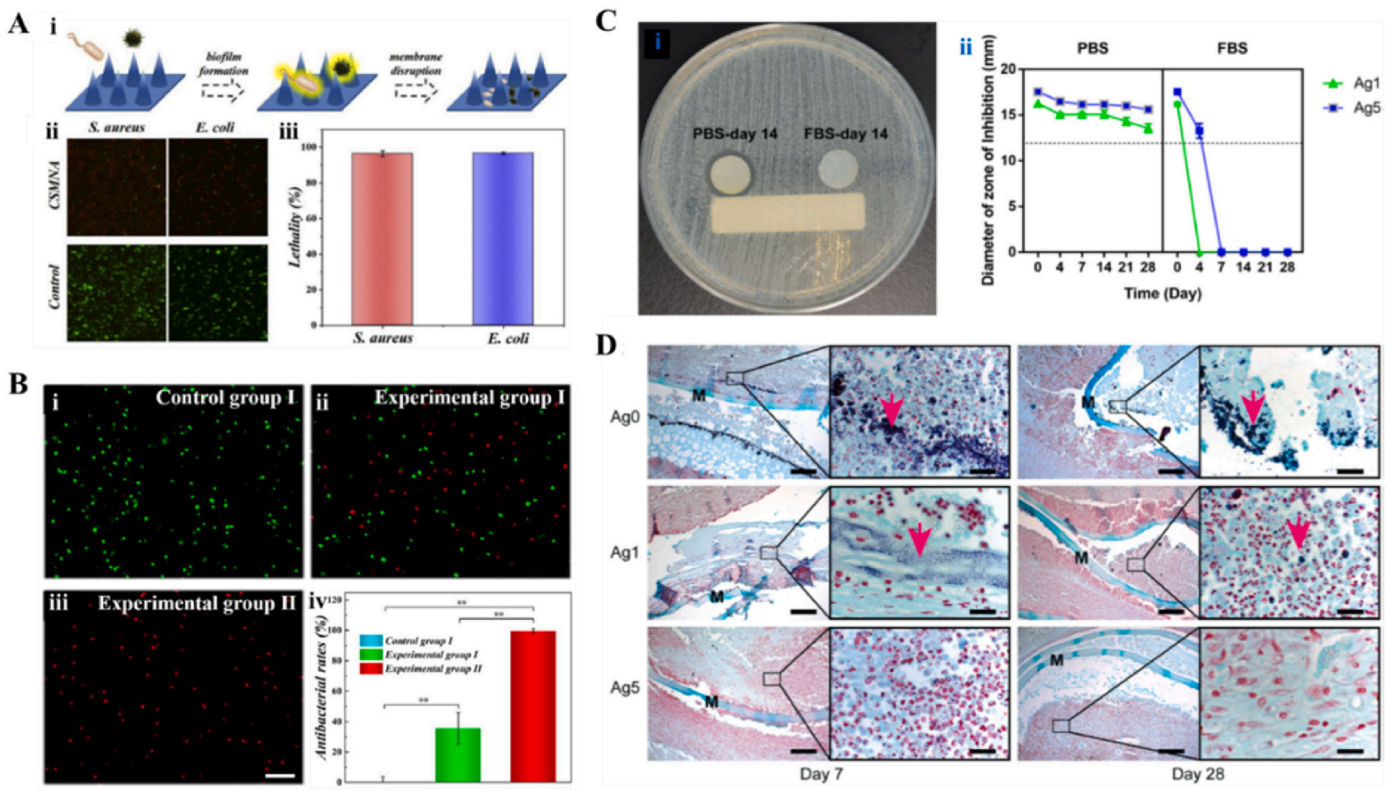

Fig. 11. Natural polymer based-biomaterials with antibacterial property for wound healing. (a) Antibacterial property of the CSMNA [128].(b) Confocal laser scanning images of the *E. coli* [129].(c) A representative ZOI test photo of the samples (d) The Gram staining of sections after wound healing [130].

filipin protein. The BPQDs absorb near infrared (NIR) light and elevate the temperature of the particles to gelatin's melting point when exposed to NIR radiation. The reversible phase change that occurs when the gelatin begins to melt causes the medications that are enclosed to gradually liberate. BPQD-loaded particles with NIR-responsive characteristics have shown in vitro and in vivo investigations that they may accomplish the necessary regulated release of growth factors, hence encouraging neovascularization. The particles were also antibacterial throughout storage and usage because the antimicrobial peptide was combined with a secondary hydrogel and enclosed in the scaffold. Due to these characteristics, BPQD-loaded natural protein hybrid particles are excellent for both medication delivery and wound healing. When making medical products like wound dressings more antibacterial, silver nanoparticles (AgNPs) are often employed. However, there is no agreement regarding the efficacy and safety of AgNPs. To establish the antibacterial impact of nanosilver in vivo and to assess the wound healing capacity of nanosilver-doped chitosan membranes, Shao et al. clarified the effects of proteins and inorganic ions on the antimicrobial characteristics of nanosilver. Through in vitro interactions with phosphate buffer or serum, their antibacterial qualities and silver release patterns were assessed. To evaluate their antibacterial efficacy and wound healing capacity, in vivo tests were conducted. The findings demonstrated that the biological environment has a significant impact on silver release: proteins act as a barrier to prevent silver release whereas inorganic ions cause delayed silver release. In order to achieve the in vivo antibacterial action, a high quantity of silver nanoparticles must be included. Additionally, the inclusion of silver nanoparticles had no impact on the pace of tissue response or wound healing. It can be concluded that AgNP incorporation enhances the antimicrobial effect of biomaterials without modifying the wound-healing capacity of chitosan-based membranes (Fig. 11c and d). [130].

4.3. Anti-inflammation

Inflammation is the body's natural response to injury or infection, and it plays a crucial role in the early phases of wound healing. However, prolonged or excessive inflammation can impede the healing process. Therefore, effective inflammation management is essential for optimal wound healing. There are numerous methods for addressing inflammation during wound recovery. Various anti-inflammatory topical agents can be administered directly to the lesion in order to reduce inflammation. These include corticosteroids, which can help reduce localized inflammation. However, their use in wound recovery is typically restricted to specific circumstances and under medical supervision. Anti-Inflammatory Natural Compounds: Numerous natural compounds have anti-inflammatory properties and can be used to treat wounds. Aloe vera gel, turmeric, honey, and chamomile, for instance, have been traditionally utilized for their anti-inflammatory properties. These natural substances can be applied topically to wounds to reduce inflammation and promote healing. As mentioned previously, certain dressings comprised of natural polymers, such as alginate, collagen, and hyaluronic acid, have inherent anti-inflammatory properties.

Wu et al. obtained rapidly crosslinked medical adhesives by a simple and efficient method utilizing natural plant polyphenol tannins (TA) and hydrogen bonding interactions with citrate-based mussel-inspired mastic (iCMBA) prepolymers, avoiding the use of traditional toxic and strong oxidizing agents, which both endowed the adhesives with excellent self-repairing properties and sufficiently superimposed TA and iCMBA prepolymers' The antioxidant, anti-inflammatory and antibacterial tannin crosslinked mussel biomimetic medical adhesives (3 A-TCMBAs) were obtained (Fig. 12a). [131]3 A-TCMBAs' excellent biotissue adhesion, self-repairing properties, and good elasticity and mechanical properties make it easy to be applied to a variety of wounds or traumas without the need for additional fixation devices, such as sutures. 3 A-TCMBAs have good biocompatibility, antioxidant, and

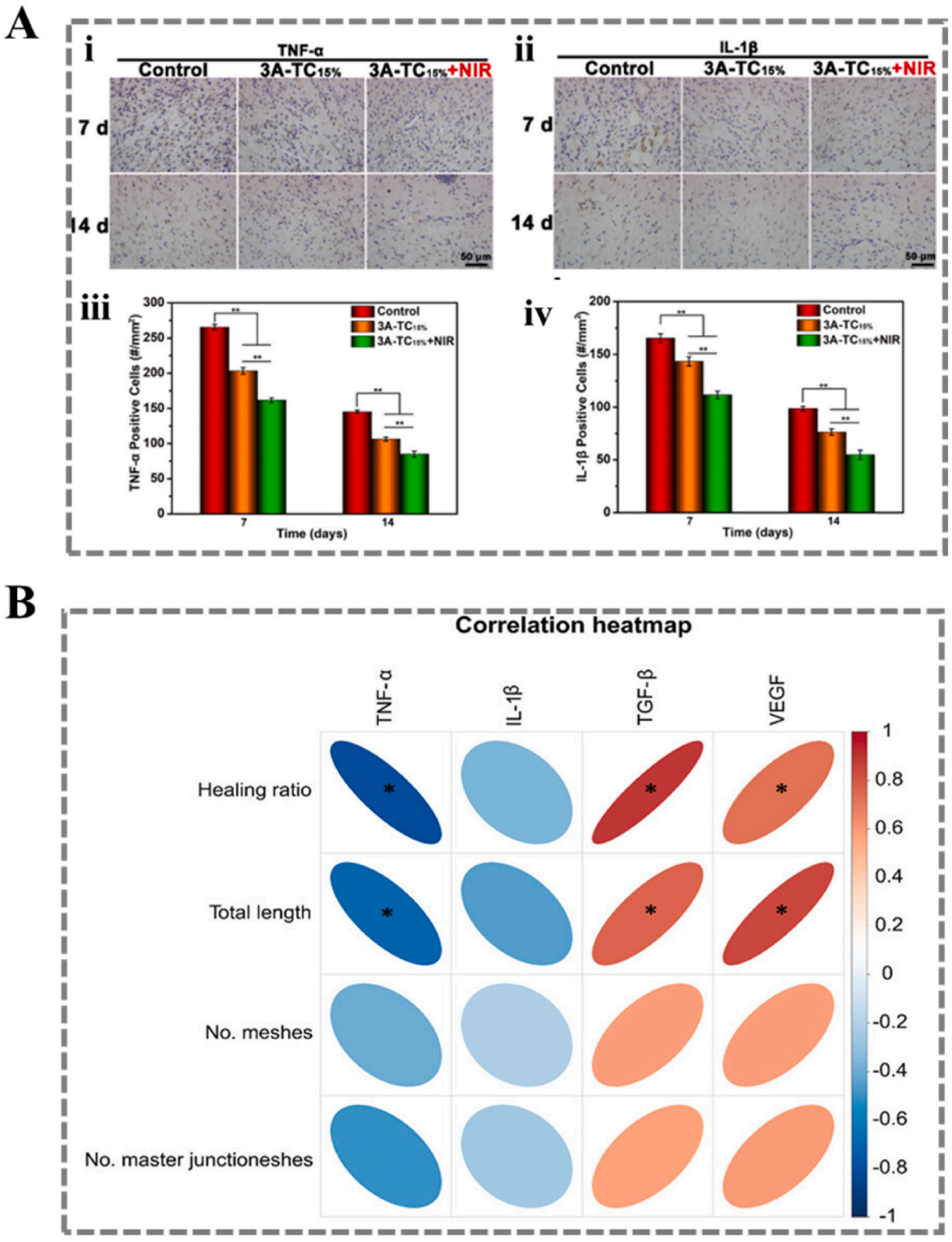

Fig. 12. Natural polymer based-biomaterials with anti-inflammation property for wound healing. (a) Characteristic inflammatory factor characterization [131]. (b) Heat map of growth factors after healing with anti-infective material [132].

photocompatibility properties, and they are suitable for use in a variety of wounds or trauma. Compatibility, antioxidant and photothermal sterilization (assisted by near infrared light (NIR)) properties. In an infected rat whole skin wound model, 3 A-TCMBA + NIR treatment promotes wound closure and facilitates wound healing through sustained anti-inflammation. Due to the protracted inflammatory period and the accumulation of M1 macrophages, diabetic lesions are difficult to repair. Therefore, hydrogel dressings with the ability to regulate macrophage heterogeneity have a promising clinical application in promoting the healing of diabetic wounds. The accurate conversion of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages via a simple and biosafe method remains a formidable obstacle. In this study, Zhao et al. developed an all-natural hydrogel capable of modulating macrophage heterogeneity in order to promote angiogenesis

and diabetic wound repair. The protocatechuic aldehyde-hybridized collagen-based natural hydrogel possesses excellent bioadhesion, antimicrobial properties, and the capacity to scavenge reactive oxygen species. Importantly, the hydrogel can transform M1 macrophages into M2 macrophages without the need for additional constituents or external intervention. This straightforward and safe immunomodulation technique has tremendous potential for use in reducing the inflammatory phase and accelerating wound healing in diabetic lesions (Fig. 12b). [132].

4.4. Angiogenesis

The formation of new blood vessels from existing vessels is angiogenesis. This process is essential for the growth and development of the tissues and organs of the body, as well as for wound healing and tissue repair. Xie et al. developed a nanoparticle-nanofiber system for wound healing that releases two growth factors (Fig. 13a). [133]The nanofibers were infused with vascular endothelial growth factor (VEGF) to expedite angiogenesis. In vitro studies demonstrated that nanofiber complexes swiftly delivered VEGF and PDGF-BB, supported fibroblast proliferation, and displayed antimicrobial activity. In vivo studies conducted on a normal rat whole skin wound model demonstrated that the nanofiber/nanoparticle scaffold substantially accelerated the wound healing process by promoting angiogenesis, increasing re-epithelialization, and controlling granulation tissue formation. In the later phases of healing, there was also evidence of faster collagen deposition and earlier remodeling at the site of injury when compared to commercial Hydrofera Blue wound dressings, resulting in a quicker regeneration of the entire skin layer. During wound healing, the hypoxia-inducible factor 1-(HIF-1a) pathway plays a crucial role in regulating angiogenesis. However, the diabetic state precludes stabilization of HIF-1a, thereby inhibiting subsequent angiogenesis, while impaired macrophage function and phenotypic transformation in the diabetic state result in a chronic, long-lasting inflammatory response. Inhibition of angiogenesis and inflammatory dysfunction pose a significant clinical challenge for diabetic wound healing. Pang et al. synthesized borosilicate (BS), a novel bioceramic with an interconnected coupling network of BO3 and SiO4 that permits the incorporation of therapeutic ions, such as Cu2+, and with filipinin (SF), a bioceramic material with a composition and structure similar to that of natural extracellular matrix (ECM), a composite system was obtained, which was converted into SF-MA-BS hydrogel (Fig. 13b). [134] The composite system can diffuse to the entire wound surface and undergo in situ photocrosslinking during application, forming a complete SF-MA-BS hydrogel that adheres firmly to the wound surface, protects the wound surface from external contamination, and promotes wound regeneration spontaneously by releasing therapeutic ions. In streptozotocin-induced diabetic rat wound repair, SF-MA-BS substantially promoted wound healing, and curiously, interaction with Cu2+ restored the HIF-1a pathway, thereby promoting angiogenesis. In the meantime, SF-MA-BS could effectively regulate inflammation and prevent long-term inflammation damage. These findings indicate that SF-MA-BS hydrogel has a reparative effect on diabetic ulcers and warrants further clinical testing. For the treatment of infected diabetic ulcers, Yao et al. developed a dual dynamic bond crosslinked hydrogel with excellent injectability, biocompatibility, adhesion, and antimicrobial activity. In vitro, the hydrogels produced by cross-linking histidine with Zn2+ and SA through reversible ligand and hydrogen bonds not only promote migration and angiogenesis of skin-associated cells, but also have excellent adhesion and antimicrobial properties (Fig. 13c). [135].

4.5. Anti-cicatricial

Scars are normal connective fibrous tissue produced by the body as it restores and repairs damage caused by trauma, inflammation, or burning. In some instances, however, the evolution of scars is not ideal and may result in depressions, protrusions, hypertrophy, erythema, or pigmentation, and some scars may even develop into hyperplastic scars or keloid tumors, which have a severe aesthetic impact. Hypertrophic scars and keloids have the greatest impact on appearance and are prone to erythema, edema, and irritation during healing. Clinical investigations have demonstrated the efficacy of silicone gel for these

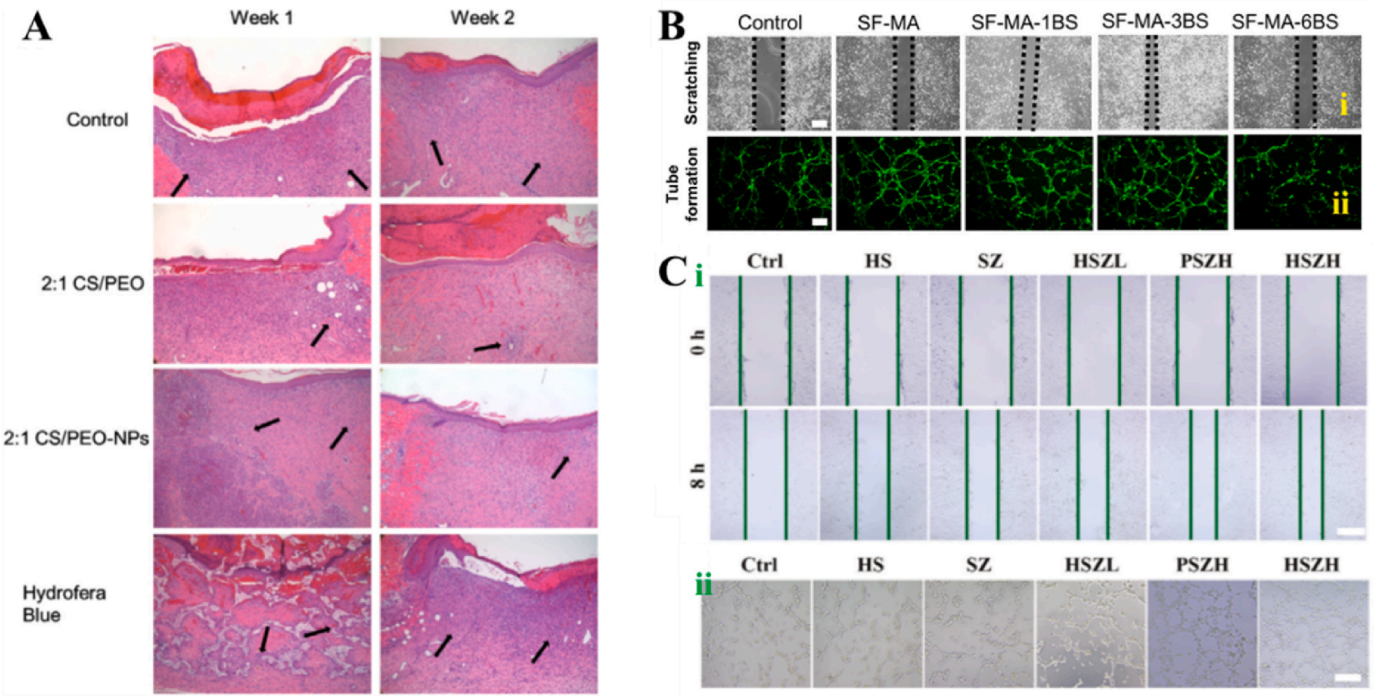

Fig. 13. Natural polymer based-biomaterials with angiogenesis-promoted property for wound healing. (a) Histological evaluation of wounds treated by CS/PEO-NP meshes. H&E staining for skin wound samples [133]. (b) Migration (upper row) and tube formation (lower row) of HUVECs [134]. (c) Scratch assay of NIH3T3 cells with the hydrogels and tube formation of HUVECs co-culturing with different hydrogels for 24 h [135].

aberrant wounds. By applying the silicone material to the incision, it prevents excessive transepithelial water loss from newly generated epithelial tissue that has not yet normalized, thereby inhibiting the aberrant proliferation of fibroblasts that produce excessive collagen and result in a raised visible scar. Therefore, scar gel products disclosed in U. S. patents typically contain silicone fluid with viscosities ranging from thousands to tens of thousands of centipoise (cP) to provide scar moisturizing effect; silicone solvent with low viscosity and easy evaporation to provide quick-drying effect; and fumigant silicone to provide quick-drying effect. And fumed silica as a thickener to facilitate the application of the scar gel. However, scar gel products containing fumed silica as a thickening agent have a tendency to stratify in the oil phase over time, so when extruded in use, the clear, low-viscosity silicone solvent will be extruded first instead of the uniform phase of the scar gel, resulting in an unattractive appearance. Moreover, the production process for burnt silicone is burdensome, and the energy cost of the apparatus required for its production is still excessive. Moreover, the scar gel products on the market are prone to white powder precipitation during use, which is simple to detect and has an aesthetic impact.

Zhou et al. have devised a single-preparation hybrid dual-network polydopamine-HA (PDA-HA) hydrogel with substantially greater adhesion than HA hydrogels (Fig. 14a). [136]In addition to their simple fabrication and enhanced efficacy, PDA-HA hydrogels can be vacuum-dried into patches, which facilitates their storage and distribution. PDA-HA patches swiftly rehydrate wounds by absorbing exudate and adhere firmly to wounds when applied. In 14 days, mice whose lesions were treated with the PDA-HA patch demonstrated increased healing rates and complete epithelialization in animal experiments. During wound repair, fibroblasts induced -smooth muscle actin-positive myofibroblasts (-SMA+) to secrete large quantities of extracellular matrix (ECM) to facilitate wound contraction. However, the persistent presence of myofibroblasts resulted in an excess of ECM production, which can result in significant scar formation. Significantly less -SMA + area fraction was observed in the PDA-HA patch group, indicating that the PDA-HA patch inhibited scar formation.

Asiaticoside, which is extracted from the umbelliferae plant has the function of promoting fibroblast proliferation and collagen synthesis, so it can be used to promote wound healing and repair scars. Lv et al. used silk protein nanofibers as a carrier to load asiaticoside, which were transferred to the aqueous-phase gel system using the special hydrophobicity of silk protein nanofibers (Fig. 14b). [137] In vivo experiments in animals demonstrated that silk protein gels loaded with asiaticoside increased the rate of wound healing, promoted granulation tissue formation, approximated new epidermis and dermis to normal skin, and effectively inhibited scar formation. The study of vascularization and inflammatory response during the healing process showed that the drug-loaded gel increased the healing rate by regulating the polarization of macrophages to anti-inflammatory macrophages, stimulating VEGF secretion and promoting angiogenesis during the early stage of wound proliferation, while it reduced the level of vascularization and scar formation by decreasing VEGF secretion and inhibiting endothelial cell assembly during the wound remodeling stage.

5. Perspective

It is necessary to select the type of wound dressing and its material based on the type of wound, as skin injuries are characterized by a variety of factors including burns, abrasions, ruptures, and diseases. Few natural polymer-based wound dressings have reached the commercialization stage despite extensive research on their use in wound recovery. In this paper, we examine the structure, composition, and properties of natural polymers, including proteins and carbohydrates, as well as their

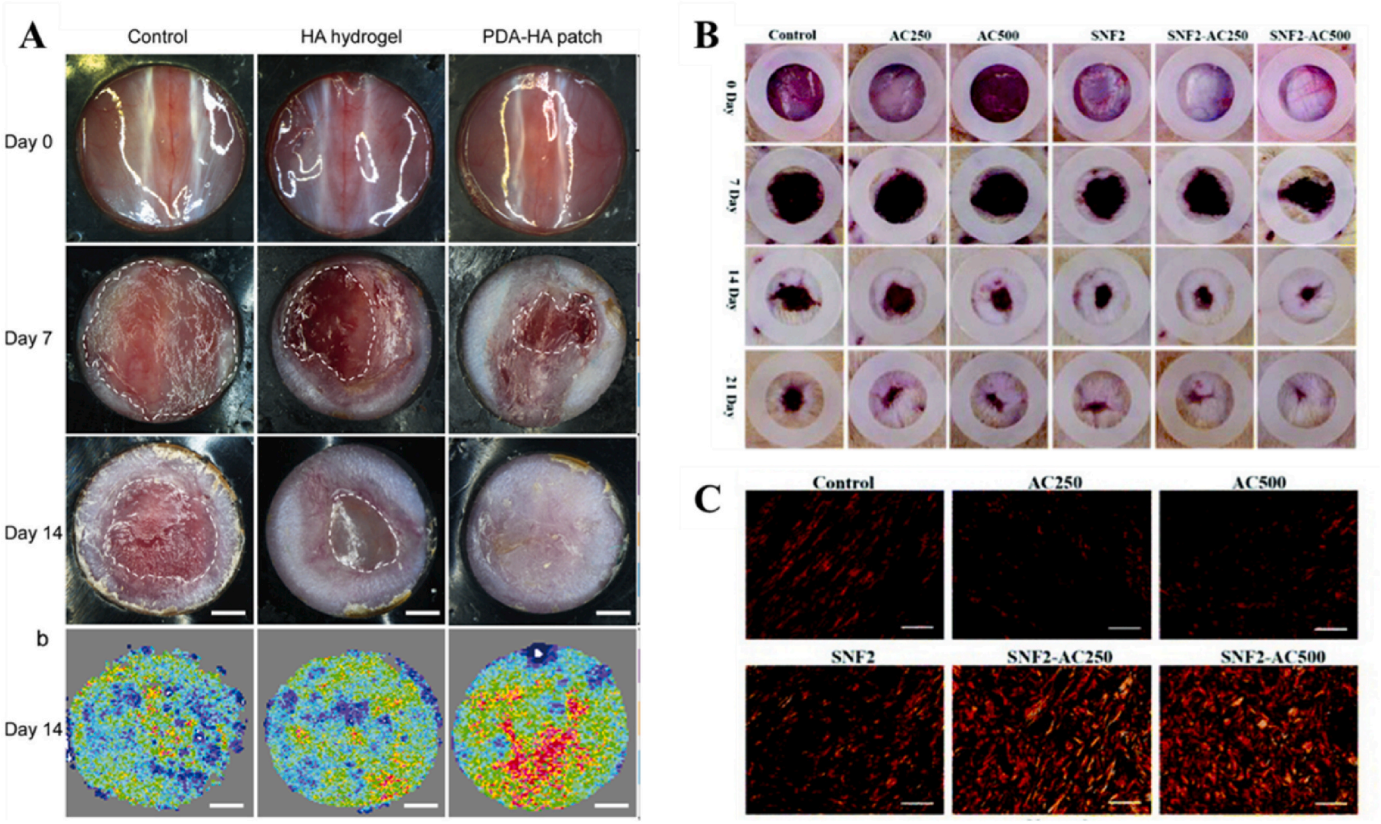

Fig. 14. Natural polymer based-biomaterials with anti-cicatricial property for wound healing. (a) Effects of the PDA-HA patch on wound healing. Representative images of wounds [136]. (b) Representative digital photographs of wounds at 0, 7, 14 and 21 days post-operation (c) Picrosirius red stained images of wounds at day 21 after surgery [137].

composition and structure. Clinically, chitosan is the most prevalent and effective carbohydrate due to its wide availability, low cost, bacterial resistance, and positive clinical outcomes. Gelatin sponges infused with nanosilver are another common hemostatic dressing used in the operating room; however, they are more expensive and cannot be used on large incisions. And the current natural polymer wound dressing consists of hydrogel film, porous sponge, etc., which must be trimmed and applied to various incisions.

Individualized or patient-specific wound dressings may be a future therapeutic goal based on each type of wound, the patient's age, gender, and health status, as well as environmental factors, and unique wound dressings are needed for appropriate treatment. The versatility of natural polymers makes them amenable to many preparation methods. Three-dimensional structured 3-dimensional dressings can be obtained by 3D printing technology as scaffolds for wound filling. The material can also be programmed to give different infiltration properties, making the dressing more functional. Handheld electrostatic spinning equipment has been introduced, which can spray directly on the trauma, and various types of active factors can be added to the solution to personalize the trauma dressing. In addition, microspheres based on various types of natural polymers have been intensively studied, and the high specific surface area of porous natural polymer microspheres can load more drugs to achieve good therapeutic effects.

6. Conclusion

The challenges of wound healing are particularly pronounced in the case of diabetic, burn, chronic, and ulcerative wounds, where the regeneration of healthy skin tissues presents significant hurdles in clinical practice. In this context, the utilization of natural biomedical polymers emerges as an exceedingly effective technique to address these challenges and expedite the healing process. This paper aims to provide a comprehensive review of the pivotal roles played by various natural polymers in the repair and regeneration of cutaneous wounds. Natural hydrogels, such as chitosan and alginate, have garnered substantial attention in the realm of wound care. One of their foremost advantages lies in their complete biodegradability, which not only aids in the ecological sustainability of wound management but also obviates the need for subsequent removal procedures. These hydrogels excel in preventing secondary infections of incisions, a critical aspect of wound healing, as they form a protective barrier that inhibits microbial ingress. Furthermore, these hydrogels exhibit remarkable potential as drug delivery vehicles, facilitating the controlled release of therapeutic agents to the wound site, thereby promoting a more efficient and targeted healing process. However, it is important to acknowledge that natural polymer hydrogels are not without their limitations. Notably, they may possess inherent weaknesses in terms of physical strength and moisture retention. To address these limitations and further enhance their efficacy in wound healing and tissue engineering applications, strategies involving the crosslinking and copolymerization of natural hydrogels with other complementary natural polymers have gained prominence. These collaborative approaches harness the unique strengths of various natural polymers, such as gelatin, collagen, hyaluronic acid (HA), pectin, and fibronectin, to collectively improve the performance of hydrogels. This fusion of natural polymers serves multiple purposes. It not only bolsters the physical integrity of the hydrogel, rendering it more resilient and better equipped to withstand the dynamic conditions of a healing wound but also enhances its moisture retention capacity, ensuring the provision of an optimal microenvironment for the wound. Moreover, the incorporation of these additional natural polymers can impart specific bioactive properties to the hydrogel, such as enhanced cell adhesion, proliferation, and differentiation, further accelerating the tissue regeneration process. In conclusion, the utilization of natural biomedical polymers holds immense promise in the context of wound healing, particularly in challenging scenarios where standard clinical practices face formidable obstacles. The symbiotic integration of natural polymers, such as chitosan and alginate, along with collaborative crosslinking and copolymerization with other natural polymers, represents a forward-looking strategy that not only addresses the limitations of individual components but also harnesses their collective potential to drive innovation in wound care and tissue engineering applications.

Ethics approval and consent to participate

The manuscript is a review article. The authors declare no experimentation on human or animals were designed.

CRediT authorship contribution statement

Han Zhang: Formal analysis, Writing – original draft, Writing – review & editing. **Xiang Lin:** Writing – review & editing. **Xinyue Cao:** Writing – review & editing. **Yu Wang:** Writing – review & editing. **Jinglin Wang:** Writing – review & editing. **Yuanjin Zhao:** Conceptualization, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Please declare any financial interests/personal relationships which may be considered as potential competing interests here.

Yuanjin Zhao is an editorial board member for Bioactive Materials and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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