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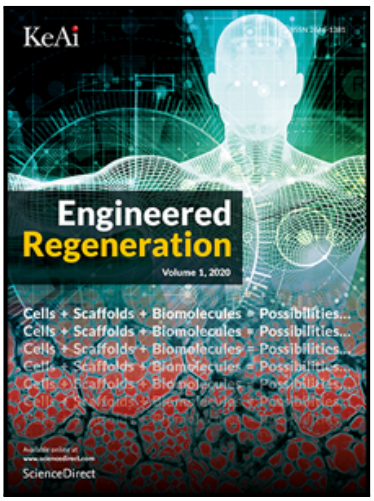

Engineered Microneedles Arrays for Wound Healing

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Highlights

- The advances of engineered microneedles arrays for wound healing were reviewed.
- The design strategies, advanced applications and advantages of engineered microneedles arrays were summarized.
- The challenges, further orientations and prospects were discussed.

Engineered Microneedles Arrays for Wound Healing

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Wound healing is the regenerative process of original skin structure after destructing by different damage sources. Due to their transdermal delivery capability and high specific surface area, microneedles arrays (MAs) have been recognized as encouraging biomaterials for wound healing. In this review, we have outlined the engineered MAs used for tissue regeneration and wound healing. Engineered MAs was first classified by design methodologies such as bionic design, intelligent-responsive design, actively-triggered design, matrix materials innovation, and composite smart design. Then, the MAs were divided into two categories based on the different loading substances: drug-loaded MAs and living component-loaded MAs. Finally, we have summed up the important elements of the preceding discussions and forecasted their future evolution.

Keywords: Engineered design, Microneedles arrays, Wound healing

1. Introduction

Our skin is easily injured by numerous stimuli in the ambient environment since it is exposed to the outermost layer of the body[1, 2]. Skin damage caused by trauma, fire, hazardous chemicals, hereditary illnesses, and systemic diseases poses a serious threat to people's lives and health. Wound healing is a complex and multifaceted process involving hemostasis, inflammation, granulation, and remodeling. Failures in any link may cause delayed healing. Biomaterials are designed to interact with biological systems, allowing them to exert their healing capacity to stimulate the regeneration of tissues or organs[3]. Skin biomaterials with outstanding biocompatibility and regenerative capability have been developed in response to the rising demands for wound healing[4-7]. Microneedles arrays (MAs) are novel types of transdermal delivery biomaterials that may penetrate the stratum corneum to the dermis selectively for vaccination, percutaneous diagnostics, and cosmetic applications[8-10]. MAs are also widely used in wound healing due to its painless and minimally invasive properties[11]. Thanks to their engineering design and intelligent administration strategy, MAs can penetrate the unfavorable environment on the wound surface, such as vascular neuropathy, immunological dysfunction, nutritional imbalance, and infection, to accomplish more active therapeutic goals[12, 13].Furthermore, superior biocompatibility and customizable microstructure endow MAs with the ability to transport a variety of medications or cells. As a result, innovative dressings based on MAs are likely to become more commonly employed in wound healing in the future[14].

In this work, we have reviewed the most recent developments in MAs for wound healing. We focus on medical MAs design and material innovation, and hope to stimulate the development of a new generation of intelligent MAs for wound healing. Briefly, we begin with the engineered design strategy for the fabrication of medical MAs, including bionic design, wound-responsive design, actively-triggered design, material innovation, and composite smart design. Then, we categorize the various forms of medical MAs, such as chemical drug-loaded MAs, cell-loaded MAs, protein-loaded MAs, nucleic acid-loaded MAs, and so on. With this, we endeavor to emphasize that the optimal medical MAs scheme can be achieved through engineered

design for the purpose of restoration and regeneration of complicated wounds. Finally, we have outlined major problems for future research based on the literatures in this review, highlighting uncertainties and challenges in this field.

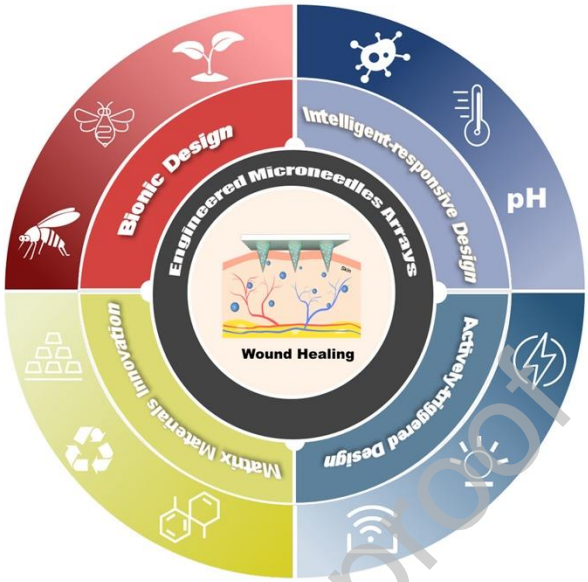

Figure 1. Schematic illustration of the design strategies of engineered MAs for wound healing.

2. Engineered design for fabricating medical MAs

The preparation strategies of engineered MAs are mainly divided into mold-based fabrication and mold-free fabrication. Mold-based fabrication is the most commonly used production method, with several benefits including high precision and reusability. During the preparation process, the needle tips can be filled by means of vacuuming, centrifuging, imprinting, infiltration and so on[15]. Mold-free fabrication methods, such as 3D printing[16], drawing lithography[17], droplet blowing[18], have lately been intensively studied. These preparation methods provide technical support for designing more complex structures, higher drug loadings, and more integrated MAs.

2.1 Bionic design

The stratum corneum is a natural protective layer of skin that regulates skin metabolism and protection functions[19-21]. The insertion and fracture forces of MAs must be enhanced in order to penetrate the stratum corneum without destroying the needle structure. Researchers have been looking to nature for inspiration to increase

the puncture impact of MAs in recent years[22-26]. For example, Jeon et al. created a double-layer sticky microneedles array (MA) to mimic endoparasites that enlarge their proboscis to immobilize on the intestines of their hosts **(Figure 2a)**[27]. The shell of such a MA was composed of expandable mussel adhesive protein (MAP) and the core was made of non-expanding silk fibroin (SF), allowing it to cling to the skin surface and develop entanglement with the tissue to accelerate wound healing. Wang et al. created a unique MA by stretching silicone rubber (Ecoflex) molds and laser engraving, which was inspired by the form of mosquito mouthparts **(Figure 2b)**[28, 29]. Due to its ultra-fine needle tips and diverse pattern design, such MA can be administered precisely and painlessly. In addition, N-isopropylacrylamide (NIPAM) hydrogel was integrated into needle-tips to achieve smart temperature-responsive drug release. The highlighted wound healing performance has been validated by animal experiment. In another example, Zhang et al. designed a conductive MA with a claw-like shape inspired by hawk claws **(Figure 2c)**[30]. The MA was held securely to the skin surface by the claw clamping mechanism, which also aligned the linear wounds to prevent secondary dehiscence. The bionic MA was also embedded with liquid metal, which connected the needle-tips to an external power supply, allowing the MA to create a spatial electric field surrounding the wound to direct cell migration and encourage cell proliferation. Its finest healing-promoting capacity was verified *in vivo* studies. In addition to insects and animals, ice may be used to inspire MAs patterns. Zhang et al. designed a frozen MA that can be loaded with multiple active substances using a freezing template strategy since freezing does not degrade the activity of biologically active compounds**(Figure 2d)**[31]. Results indicated that *Bacillus subtilis* was loaded into frozen MA to treat cutaneous fungal infections. Driven by advances in micro/nanofabrication technology, materials science, and 3D printing, more complicated bionic MAs for wound management can be realized[32].

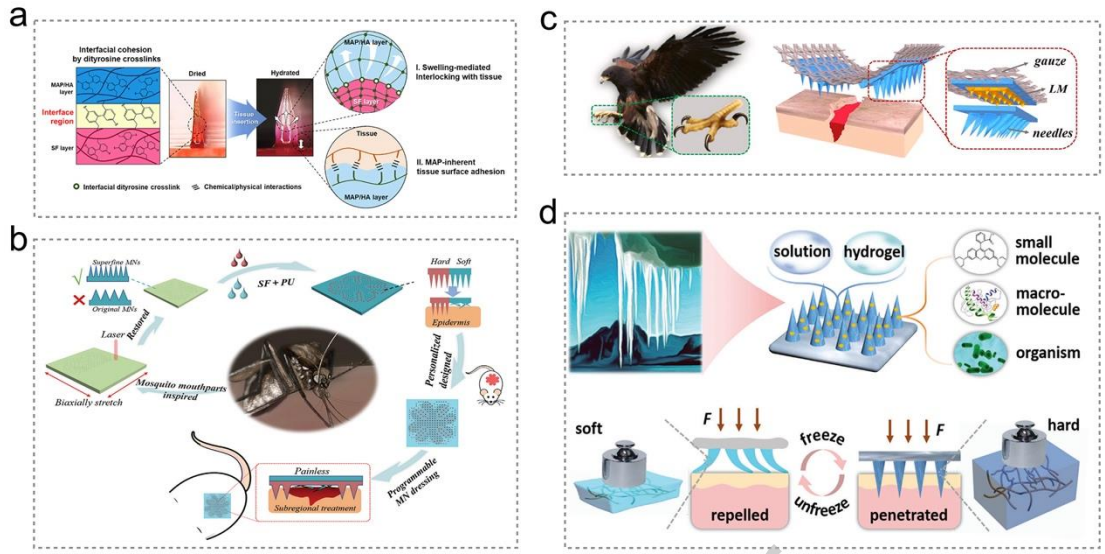

Figure 2. (a) Endoparasites-inspired MA adhere to skin through the adhesion of mussel adhesive protein and the physical interlocking characteristics of needle tips. (reprinted with permission from [27]) (b) Mosquito mouthpart-inspired MA for painless administration and wound management. (reprinted with permission from [28]) (c) Claw-inspired MA with liquid metal encapsulation to prevent linear wounds from cracking. (reprinted with permission from [30]) (d) Ice-inspired MA for the treatment of cutaneous fungal infections. (reprinted with permission from [31])

2.2 Intelligent-responsive design

The wound microenvironment, such as temperature, pH, humidity, and infection state, reflects healing status. To improve the repair effectiveness, a tailored therapy method is required. The use of dressings with microsensors allows for effective biomarker monitoring in the wound environment, enabling treatment choices to be adjusted autonomously[33-36]. Permana et al. explored the application of silver nanoparticles synthesized from green tea extract as bacteria-responsive anti-biofilm agents **(Figure 3a)**[37]. They confirmed that the amount of silver nanoparticles released from MA increased by 9 times in the presence of bacteria, indicating the selective release of such agents. *In vitro* anti-biofilm results indicated that 100% of the bacteria in rat skin were eradicated after 60 hours' administration of the system. Xu et al. incorporated chloramphenicol (CAM) inside gelatin supramolecules and

integrated them into MA to intelligently respond to the gelatinase generated by bacteria **(Figure 3b)**[38]. With the rapid dissolution of MA, gelatinase produced by microorganisms led to the release of encapsulated CAM into the Vibrio vulnificus biofilm matrix, showing more effective therapy for rapid sterilization. Temperature and pH variations can also function as triggers for intelligent responses. The pH-sensitive polymer Eudragit S100 is dissolvable in alkaline tissue fluid. To prevent medication leakage, Ullah et al. employed Eudragit S100 as the covering layer of needle-tips. When exposed to an alkaline wound microenvironment (pH>7), Eudragit S100 quickly dissolved and released therapeutic agent from the MA **(Figure 3c)**[39]. ROS, which may exceed 500 μM in inflammatory tissues, is a major actor in a variety of pathological processes[40]. Gu et al. prepared an anti-acne MA based on ROS-responsive polyvinyl alcohol (RR-PVA) **(Figure 3d)**[41]. The RR-PVA gel rapidly degrades and releases the drug in high concentrations of H_2O_2, resulting in extremely efficient antibacterial actions on *Propionibacterium acnes* (*P. acnes*)-infected hair follicles. Despite the efficacy of these approaches, their usage in wound healing is still in the early stage. More intelligent MAs are likely to incorporate electrochemical sensors and luminescence approaches in the future.

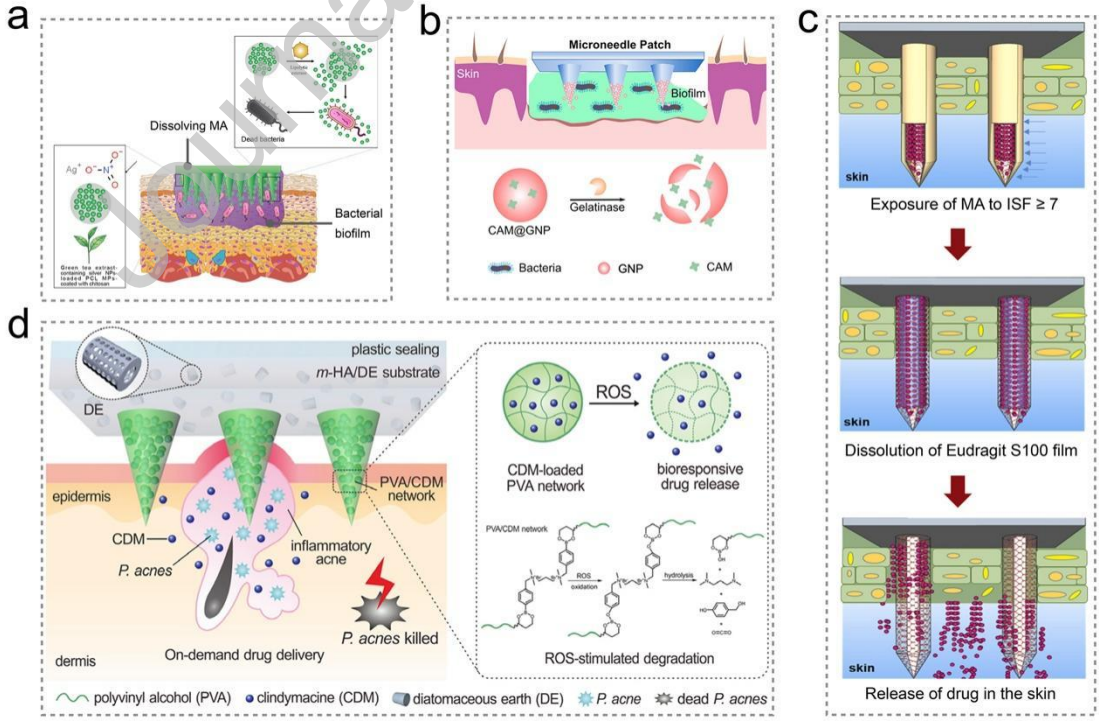

Figure 3. (a) Schematic diagram of dissolvable MA loaded with bacterial responsive microparticles. (reprinted with permission from [37]) (b) Bacterial gelatinase sensitive chloramphenicol (CAM) MA for biofilm treatment. (reprinted with permission from [38]) (c) Wound pH-responsive coating MA for wound administration. (reprinted with permission from [39]) (d) ROS-responsive MA for the treatment of *P. acnes*-infected hair follicles. (reprinted with permission from [41])

2.3 Actively-triggered design

Actively-triggered designs are able to respond to external stimuli, allowing for precise medication release[30, 42-48]. Photodynamic antimicrobial chemotherapy (PACT) is a brand-new antibacterial treatment. When photosensitizers are applied to a wound surface and exposed to light, the resultant free radicals interact with numerous biological components, causing microorganisms destruction. As an example, Salvador et al. encapsulated the photosensitizer methylene blue into MA to activate methylene blue by the external light source, producing active radicals that killed bacteria **(Figure 4a)**[49]. PACT's bactericidal activity against *C.albicans*, *S.aureus*, and *E.coli* exceeded 96% in this study. Photothermal therapy (PTT) employs efficient photothermal agents to absorb heat from near-infrared (NIR) irradiation. Sun et al. designed a smart MA liquid band-aid triggered by NIR for wound healing **(Figure 4b)**[50]. The porphyrin-like metal centers nanoparticles (PMCS) loaded in MA possessed photothermal conversion and nanozyme properties. Under the activation of NIR, results showed that hydrogen peroxide can be decomposed into hydroxyl radicals by PMCS, resulting in the elimination of inflammation and effective antibacterial action. Such design is expected to become a new strategy of infection wound management. Similarly, Lei et al. developed a MA functionalized with biomineralized melanin nanoparticle for ROS scavenging[51]. It is capable of treating melanoma by PTT and promoting wound regeneration significantly. In addition to conventional drugs, NIR can also be used to control therapeutic gases. Zhang et al. employed black phosphorus as photothermal agent to control the oxygen release from hemoglobin under NIR **(Figure 4c)**[52]. The efficacy of the oxygen-loaded MA to

improve diabetic wound healing was demonstrated. In another example, N-diazeniumdiolates (NONOates) group were encapsulated inside MA and decomposed by NIR irradiation to produce nitric oxide to speed diabetic wound healing, according to Yao et al. **(Figure 4d)**[53]. Electro Magnetic Theory (EMT) is involved in various physiological and pathological processes, including wound healing, tumor metastasis, and embryonic development. Gaware et al. prepared a conductive chitosan-porous carbon MA, which was characterized by electric-field-triggered drug release **(Figure 4e)**[44]. Under the condition of voltage 5 V and pH 4, MA showed maximum cephalexin release amount to exert maximize antibacterial properties. Moreover, the conductive MA did not cause chromosome aberration in mouse bone marrow cells, showing superior biocompatibility. Despite significant advances, further integration and optimization of EMT, NIR, ultrasonic, and plasma should be taken into consideration for designing better actively-triggered MAs.

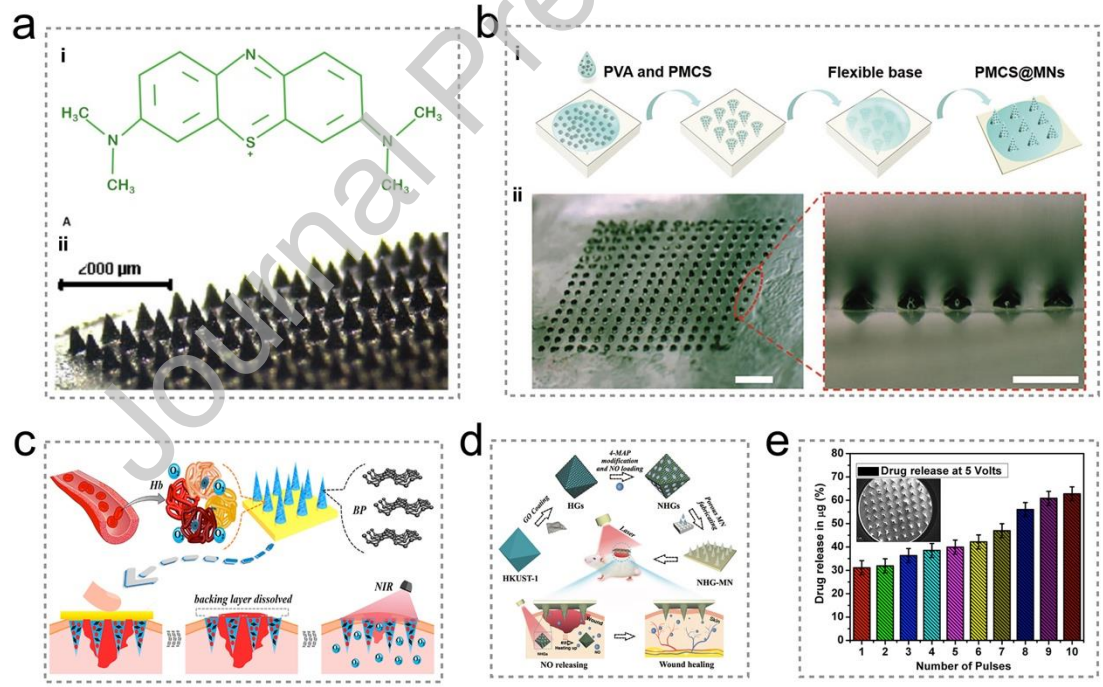

Figure 4. (a) Methylene blue-loaded dissolving MA: Chemical structure of photosensitising methylene blue (i) and corresponding optical images of the needle-tips (ii). (reprinted with permission from [49]) (b) Fabrication process of the soluble NIR triggered-MA (i) and their corresponding optical images (ii). (reprinted with permission from [50]) (c) Black phosphorus (BP)

loaded MA for photothermal-responsive oxygen release. (reprinted with permission from [52]) (d) MOF-loaded MA for photothermal-responsive nitric oxide release. (e) Drug release profile of carbon nanocomposite MA triggered by electrical pulses (Inset: optical images of MA). (reprinted with permission from [44])

2.4 Matrix materials innovation

As the cornerstone of innovation, body-friendly and effective matrix materials are constantly being developed[54-64]. Polymeric MAs with excellent biocompatibility are widely employed in the delivery of controlled-release drugs through minimally invasive methods. For example, a novel coordination polymer nanodots (PNDs)-integrated MA was designed for wound healing **(Figure 5a)**[65]. The generated FNDs were synthesized from gallic acid, polyvinylpyrrolidone (PVP), and Fe ions, showing great pH-dependent catalytic activity and ROS scavenging properties. Experimental results showed that the polymeric MA exhibited excellent antibacterial performances as well as pH and H_2O_2-dependent color change, making it a viable novel material for wound management. Hydrogel has always been a hotspot in research due to their outstanding biocompatibility and superior mechanical qualities. Larrañeta et al. prepared a novel hyaluronic acid (HA)-based hydrogel crosslinked with poly(methyl vinyl ether-alt-maleic acid) **(Figure 5b)**[66]. Such hydrogel preparation can be deemed pollution-free due to the lack of organic solvents or potentially harmful compounds in the synthesis process. Following tests revealed that the generated hydrogel MA kept anti-infective characteristics and could release the model medicine continuously for 48 hr. In another attempt, Sun et al. designed a photothermal responsive hydrogel MA employing a boronate- and MXene-mixed hydrogel to achieve the controllable delivery of adenosine **(Figure 5c)**[45]. *In vivo* experiments revealed that adenosine-encapsulated MA can aid wound healing by promoting angiogenesis. Natural products have long been a valuable source of medication development due to their potent therapeutic properties and low risk of adverse effects. Honey is a natural substance with antibacterial and antioxidant qualities that has been used to treat wounds since ancient times. Frydman et al. used

Manuka honey as the major component of MA for methicillin-resistant staphylococcus aureus (MARA) antibacterial and wound repair evaluation **(Figure 5d)**[67, 68]. It was found that honey with a concentration of more than 10% showed great bactericidal action against MRSA, although the high temperature may weaken the antibacterial and wound-healing characteristics. However, this study just evaluated the bactericidal effect within 24 hr and lacked the mechanical characterization of honey MA. Despite advancements in matrix materials, MAs that can control bleeding rapidly with good adhesion properties are still needed to respond to the varied environment of different wounds.

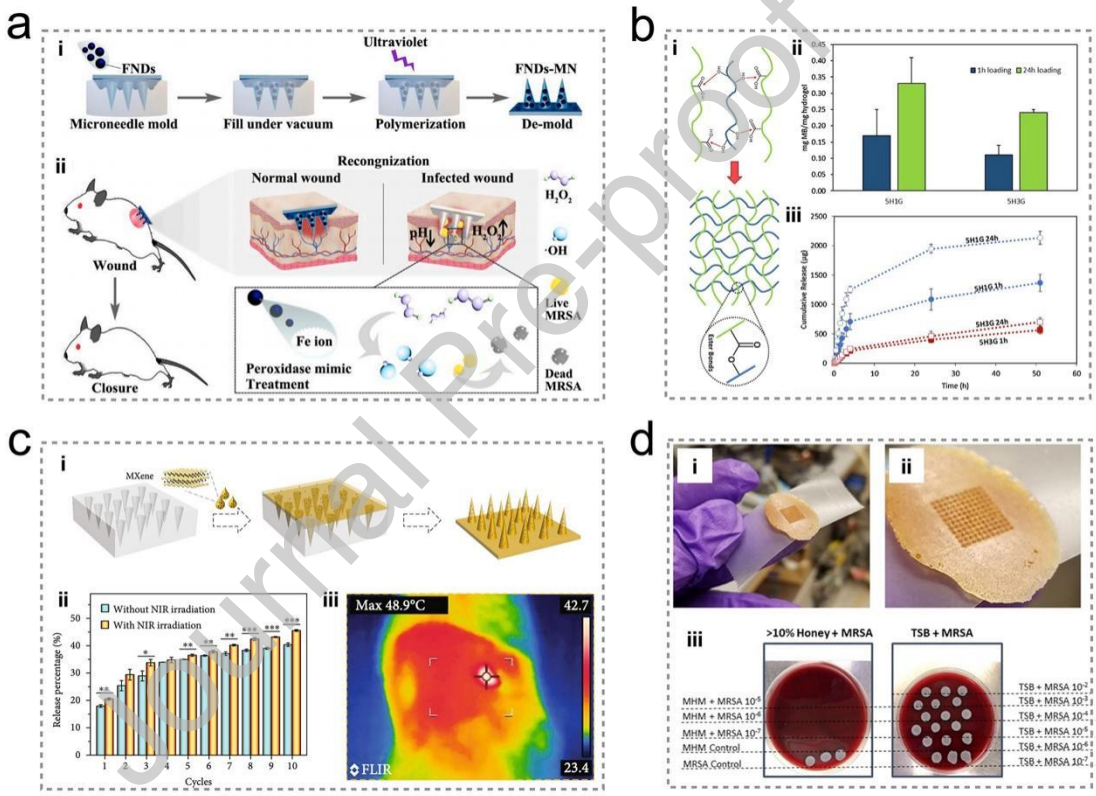

Figure 5. (a) Fabrication process of PNDs-integrated MA (i) and their application for infected wound management (ii). (b) Diagram of chemical cross-linking process between Gantrez ® S97 and sodium hyaluronate (i) as well as the cumulative drug loading (ii) and release amount profiles (iii). (c) Fabrication process of the MXene-integrated MA (i) and the photothermal drug release curve (ii) with the corresponding skin thermal images (iii). (d) Photographs of Meluca honey MA (i-ii) and its antibacterial effect on MRSA (iii).

2.5 Composite smart design for wound monitoring and treatment

During wound healing process, a large amount of secretions will be generated, and their properties are strongly related to wound recovery state. At present, several studies have focused on designing devices that can simultaneously monitor the wound environment and promote healing. In a typical example, Gao et al. proposed a double-sided integrated MA (i-SMD), which can not only monitor the physiology of wounds but also release drugs in accordance with the epidermal environment to achieve the best therapeutic effect **(Figure 6a)**[69]. On one side of MA, microelectronic circuits can sense the movement of the wound area. On the other side, the cross-shaped microfluidic channel formed a pattern for the fluorescence detection of inflammation biomarkers. Furthermore, by using NIPAM hydrogel as a temperature-responsive system, regulated medication release may be achieved, resulting in excellent diabetic wound healing performance. Similarly, Guo et al. created a unique multifunctional smart MA by combining microfluidic channels, patterned electronics, and inverse opal (IO) photonic crystal (PC) structures **(Figure 6b)**[25]. Owing to the fluorescence enhancement effect of IO PC structures, microfluidic channels could accurately analyze inflammatory factors (IL-6, lactic acid, calprotectin) in the wound bed. Patterned MXene electronic devices can perform real-time analysis of wound movement to prevent unconscious strenuous stretching on wounds. By filling temperature-controlled hydrogel with pharmaceuticals, the IO PC structure in MA was able to accomplish controlled drug release for the healing of stripe-shaped and circular wounds. As a result, such composite smart MA is expected to carry out precise management for wound monitoring and treatment[70-75].

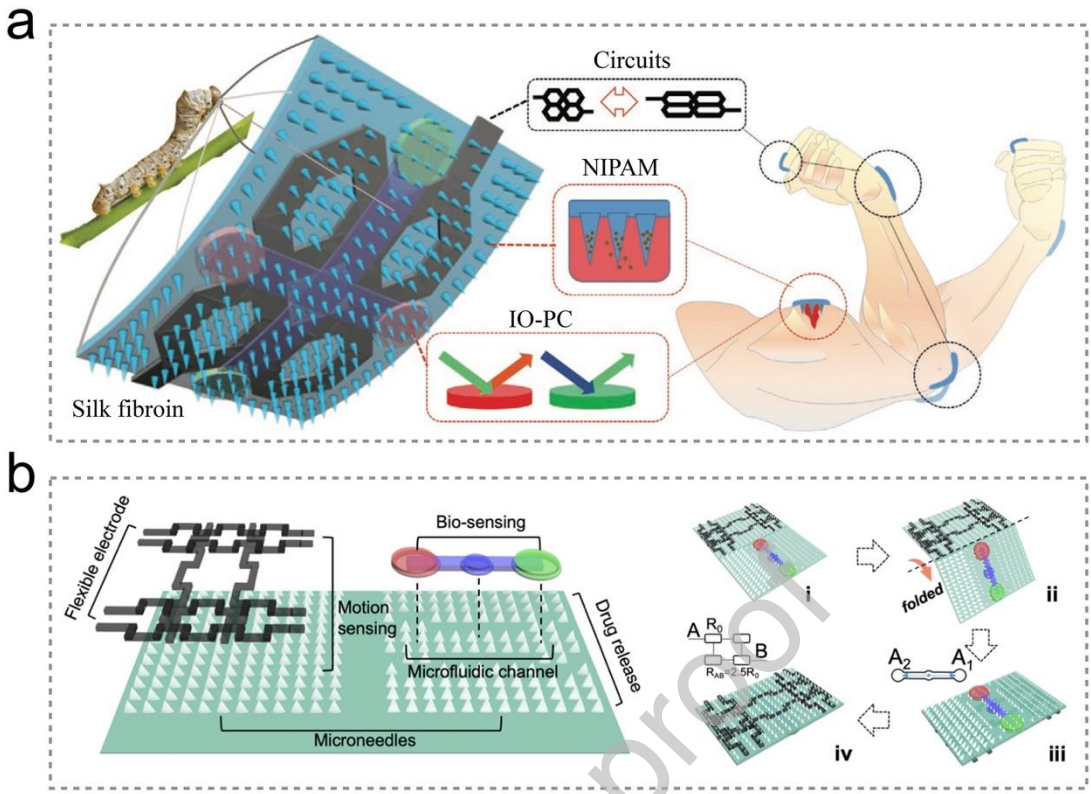

Figure 6. Schematic diagram of intelligent i-SMD (a) and shark tooth-inspired MAs (b) for biochemical analysis, motion sensing, and wound healing. (reprinted with permission from [25] [69])

3. Advanced applications for wound repair and regeneration

3.1. Drug-loaded MAs for antibiosis

MRSA infection usually causes wound ulceration and delayed recovery, posing a significant societal cost. Intravenous injection of vancomycin (VAN) is usually the preferred treatment to prevent bacterial proliferation. However, systemic exposure to VAN can lead to noticeable side effects and even bacterial resistance. To solve the problem, Ziesmer et al. developed a VAN-loaded MA for the precise subcutaneous administration to combat MRSA infection **(Figure 7a)**[76]. The VAN-loaded needle-tips can be properly penetrated to the subcutaneous tissue depending on the solid shell of MA, effectively reducing MRSA's growth *in vitro* and *in vivo*. Metal ions are effective antibacterial agents in addition to antibiotics[77-82]. As a promising metal-based material, metal-organic frameworks (MOF) have recently attracted a lot

of interest as a bactericide and drug delivery platform due to their high specific surface area and porosity structure[83, 84]. For example, Yin et al. produced a Mg-MOF material comprised of magnesium ions and gallic acid by hydrothermal method and then loaded it into γ-PGA hydrogel fabricated MA **(Figure 7b)**[85]. Magnesium ions (Mg^{2+}) can promote endothelial cell proliferation as well as low cytotoxicity. Gallic acid can also minimize wound inflammation by scavenging reactive oxygen species. In vivo experiment proved that such composite MA can significantly promote diabetic wound healing. Antimicrobial peptides (AMPs) are natural antibiotics that protect the body against pathogens. Su et al. created a Janus-type dressing composed of soluble MA and electrospun nanofibers that could transport the AMPs both inside and outside the biofilm **(Figure 7c)**[86]. Their findings showed that Janus-Type dressing was more effective at delivering AMPs into biofilms than free drugs, and that the biofilm formed by multidrug-resistant bacteria could also be totally removed. Chinese medicine is a mixture of herbs produced by prescribed prescriptions and preparation technologies, with wound healing benefits. Aloe vera, berberine, angelica sinensis, and sophora flavescens has all been used in Chinese medicine for thousands of years as antimicrobial drugs[87-89]. Chi et al. mixed premna microphylla with centella asiatica as medicinal ingredients, constructing a Chinese herb MA by brine-induced solidification **(Figure 7d)**[90]. Experiments *in vivo* revealed that the herb MA was beneficial for antibacterial and tissue regeneration, and it is predicted to be used in the future.

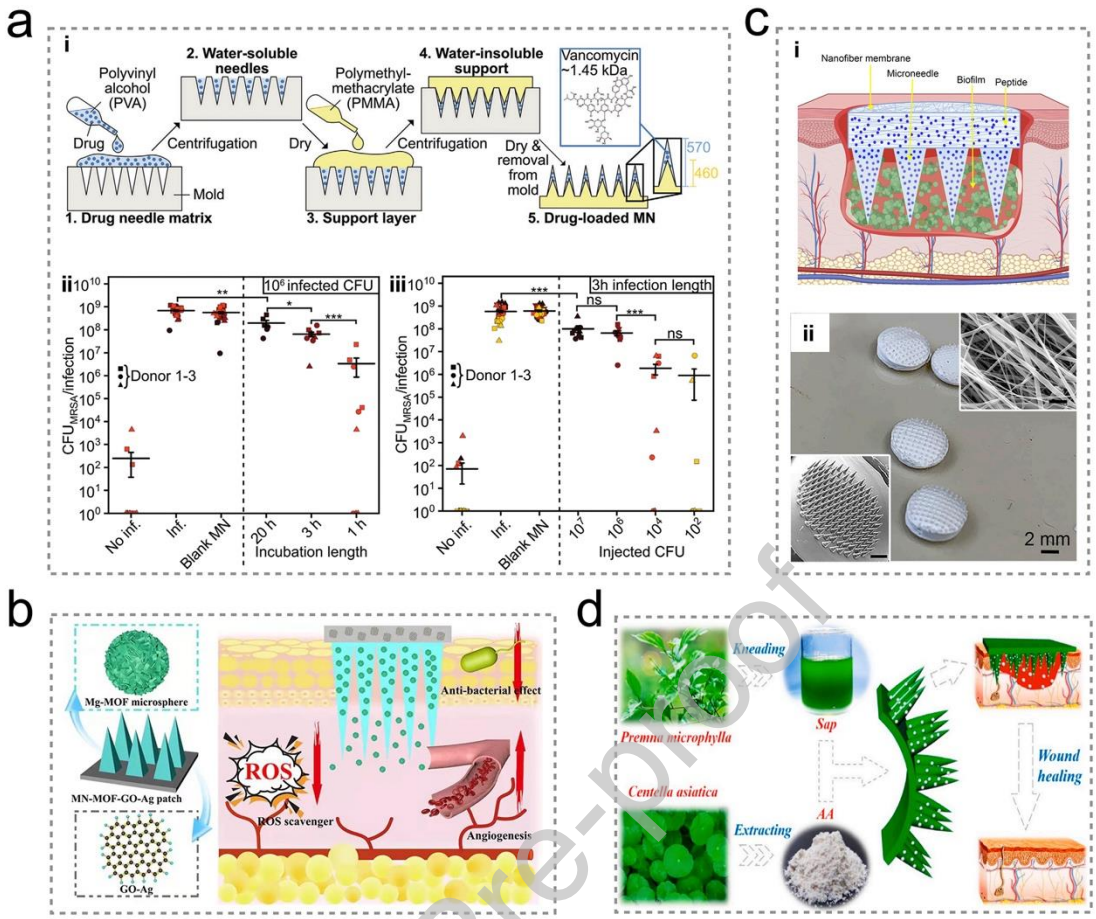

Figure 7. (a) The preparation process of vancomycin-loaded MA (i) and the antibacterial effect against MRSA (ii-iii). (reprinted with permission from [76]) (b) Mg-MOF loaded MA to promote diabetic wound healing. (reprinted with permission from [85]) (c) Schematic drawings of Janus-type antimicrobial MA for biofilm treatment (i) with its optical and scanning electron microscope (SEM) images (ii). (reprinted with permission from [86]) (d) Schematic diagram of Chinese herbs extract MA for wound healing. (reprinted with permission from [90])

3.2. Living components-loaded MAs for tissue restoration

As a bioactive component, proteins can be used as therapeutic agents for wound healing. However, proteins administration *in vivo* is still a concern because they may denature fast if kept incorrectly or in unfavorable conditions. To solve the problem, MAs have been employed as a unique protein delivery platform to avoid exposure to the gastrointestinal or blood environments. For example, Yao et al. created a polyvinyl alcohol (PVA)-based transdermal drug delivery MA loaded with

parathyroid hormone (PTH) for speeding wound healing **(Figure 8a)**[91]. They showed that the PTH could be released in a stable manner, accelerating wound collagen deposition via the Smad3/mTOR pathway. In another example, the recombinant humanized collagen type III (rhCol III) and Naproxen were combined within MA and then applied to chronic wounds[92]. Results showed that rhCol III may enhance the proliferation and migration of fibroblasts by using MA transdermal method, which is favorable for wound healing. Apart from proteins, cells encapsulated MAs are another promising wound healing technique[93-96]. Lee et al. were the first to propose using MA loaded with mesenchymal stem cells (MSC) to promote targeted MSC delivery **(Figure 8b)**[97]. To maintain the vitality of MSC inside the MA, poly(lactic-co-glycolic) acid (PLGA) was used as a shell in the outer layer of the needle tips to protect the GelMA-MSC mixture inside the needle tips. Results showed that the MSC may keep their vitality and function for up to 24 hr after manufacture, which was beneficial for wound healing. Because the MA environment cannot sustain cell viability for a long time, and most transplanted MSC undergo apoptosis, they are unable to engage in tissue regeneration directly. As a result, using MSC-exosomes to treat wounds is becoming a new trend. Ma et al. designed a ferrum-mesenchymal stem cell-derived artificial nanovesicles (Fe-MSC-NVs) and encapsulated them in MA **(Figure 8c)**[98]. Fe-MSC-NVs contained a range of growth factors, including VEGF, HIF-1, HGF, and FGF2, which contributed to endothelial cell proliferation and migration, as well as significantly promote wound healing. Limited by the easy inactivation of biologically active substances, researches on MAs as carriers are still in their infancy. In the future, engineered MAs are expected to load more abundant components such as cells, proteins, nucleic acids, and vesicles to exert better therapeutic effect[99-104].

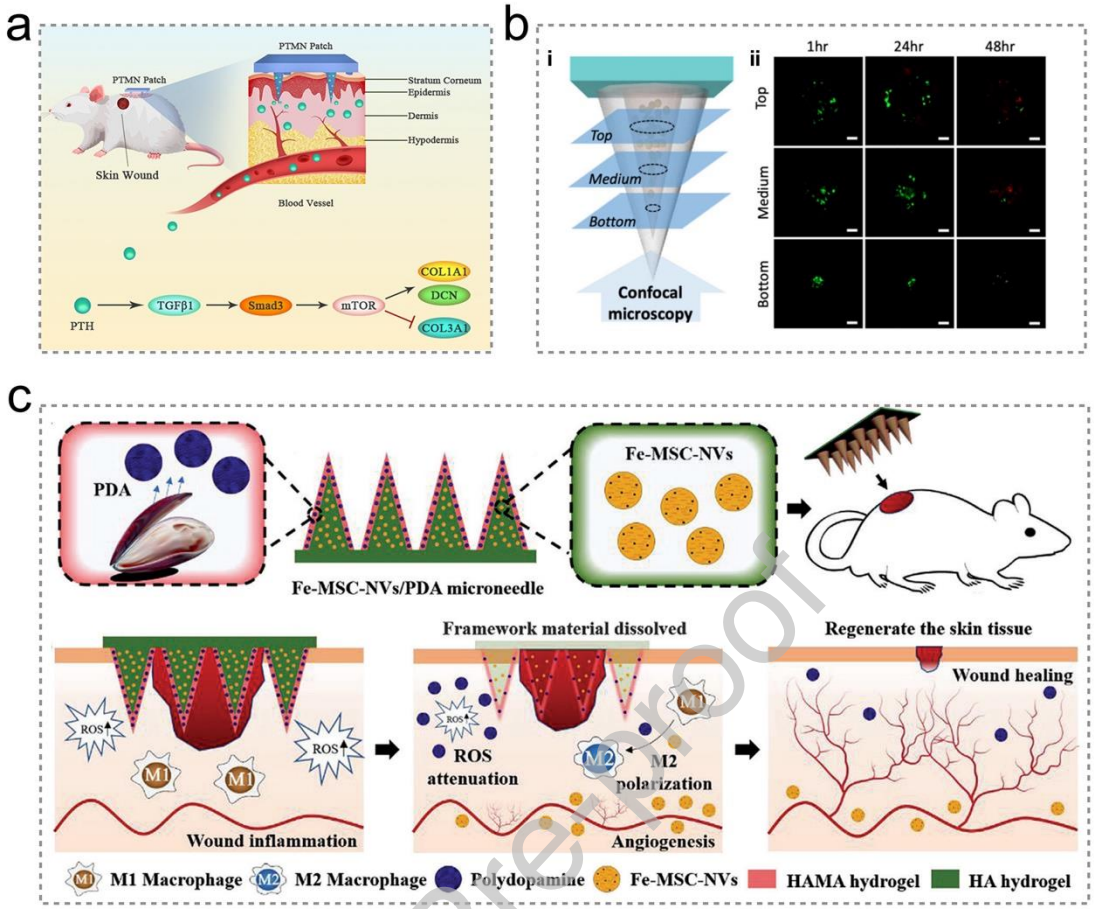

Figure 8. Schematic diagram of PTH loaded MA for wound healing. (reprinted with permission from [91]) (b) Structure diagram of MSC-loaded MA (i) and the MSC vitality at distinct time points (ii). (reprinted with permission from [97]) (c) Schematic diagram of Fe-MSC-NVs encapsulated MA for wound healing. (reprinted with permission from [98])

4. Conclusion

Wound healing refers to a series of pathophysiological processes of local tissue repair caused by complex factors. Local variables such as poor vascular function, severe inflammatory response and high pressure effects are the key causes contributing to poor healing. In addition, systemic issues such as advanced age, poor immune function and malnutrition can also induce chronic wounds. In recent years, due to the excellent performance of artificial biomaterials and biodevices for regulating cellular behavior and repairing tissue defects, it has become the key technology of wound regeneration. Herein, we focused on the recent advances of

MAs as a new transdermal delivery method for wound healing. It begins with a classification of engineered MAs design strategies including bionic design, intelligent-responsive design, actively-triggered design, matrix materials innovation, and composite smart design. In the next sections, different substance-loaded MAs such as drug-loaded MAs and living component-loaded MAs have been presented. With that, we plan to outline the latest progress of engineering MAs for tissue repair and regeneration in order to speed up the development and application in this field.

Despite significant advancements in MAs design and encapsulated contents, there are still constraints in medication delivery efficiency, therapeutic impact, and wound remodeling. As a result, these regions need to be given more attention and promotion[105-108]. First, despite their ultra-high specific surface area, the anti-inflammatory and wound-healing capacity of MAs are limited by the micro-sized needle tips. Few studies have looked at the influence of needle tip size and density on wound healing when compared to standard dressings. Apart from structural flaws, certain antigens incorporated or encapsulated in new biomaterials may induce unknown local or systemic immune responses, lowering wound healing effectiveness significantly. Finally, the single-encapsulated pharmaceuticals and extremely low drug loading have trouble adjusting to the complex and changing wound environment, necessitating more scientific and reasonable design methods to overcome the conflict.

In the future, MAs will be required to provide efficient transdermal medication at a lower cost. In addition, multifunctional MAs with wound environment monitoring and treatment are more conducive to wound management. They are expert in measuring physiological conditions like pH and temperature using flexible sensors and transferring feedback information to actuators for controlled medication release. Finally, core physiological factors such as exosomes, miRNA, siRNA, and growth factors can help with regeneration. More convenient, versatile, and intelligent MAs are projected to provide unique wound healing options.

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.

Acknowledgements

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