Burns & Trauma, 2025, **13**, tkae076
https://doi.org/10.1093/burnst/tkae076
Review

Microneedles in diabetic wound care: multifunctional solutions for enhanced healing

Xichao Jian[1], Yaping Deng[1], Shune Xiao[1,2], Fang Qi[1,2,*], Chengliang Deng[1,2,*]

[1]Department of Burns and Plastic Surgery, Affiliated Hospital of Zunyi Medical University, No. 149 Dalian Road, Huichuan District, Zunyi, Guizhou 563003, P.R. China
[2]Collaborative Innovation Center of Tissue Repair and Regenerative Medicine, No. 6 Xuefu West Road, Xinpu New District, Zunyi, Guizhou 563003, P.R. China

*Corresponding authors. Fang Qi, Email: qifang1993@163.com; Chengliang Deng, Email: cheliadeng@sina.com

Abstract

Diabetic wounds present a significant challenge in clinical treatment and are characterized by chronic inflammation, oxidative stress, impaired angiogenesis, peripheral neuropathy, and a heightened risk of infection during the healing process. By creating small channels in the surface of the skin, microneedle technology offers a minimally invasive and efficient approach for drug delivery and treatment. This article begins by outlining the biological foundation of normal skin wound healing and the unique pathophysiological mechanisms of diabetic wounds. It then delves into the various types, materials, and preparation processes of microneedles. The focus is on the application of multifunctional microneedles in diabetic wound treatment, highlighting their antibacterial, anti-inflammatory, immunomodulatory, antioxidant, angiogenic and neural repair properties. These multifunctional microneedles demonstrate synergistic therapeutic effects by directly influencing the wound microenvironment, ultimately accelerating the healing of diabetic wounds. The advancement of microneedle technology not only holds promise for enhancing the treatment outcomes of diabetic wounds but also offers new strategies for addressing other chronic wounds.

Keywords: Diabetic wounds; Microneedles; Wound healing; Therapeutic potential

Highlights

- Microneedle technology provides a minimally invasive and effective method of administration that can improve the treatment of diabetic wounds.
- Multifunctional microneedles play crucial roles in diabetic wound treatment and have antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant functions and promote angiogenesis, accelerating wound healing.
- The synergy among multifunctional microneedles, along with phototherapy and electrotherapy, significantly enhances treatment outcomes, providing a more effective therapeutic strategy for diabetic wound healing.

Background

The skin, the largest organ of the human body, plays a crucial role in shielding internal tissues from various forms of harm, such as mechanical damage, chemical exposure, microbial infections, ultraviolet radiation, and extreme temperatures [1]. However, as the primary defense mechanism of human tissue, the skin is highly vulnerable to damage, particularly in chronic conditions such as diabetes. With an estimated 463 million individuals worldwide currently living with diabetes, a number projected to rise to 700 million by 2045, diabetic foot ulcers account for approximately 7.2–15% of cases [2, 3]. Approximately 50% to 60% of diabetic foot ulcers develop secondary infections, with approximately 20% classified as moderate to severe and potentially leading to lower limb amputation [4]. The 5-year mortality rate for patients with diabetic foot ulcers is approximately 30%, whereas for those who undergo major amputations, the rate exceeds 70% [4]. Compared with diabetic patients without foot ulcers, those with diabetic foot ulcers have a higher mortality rate (approximately 231 deaths per 1000 person-years) [4]. These rates increase with the increasing number of diabetic patients, placing significant burdens on both patients and health care systems [3, 5].

Wound healing is a complex process involving various biological and molecular events, including cell migration, cell proliferation, neovascularization, extracellular matrix (ECM) deposition, and epithelial regeneration [1]. However, diabetic patients often experience challenges such as chronic inflammation, excessive oxidative stress, angiogenesis disorders, neuropathy, and bacterial infections in wounds due to prolonged hyperglycemia [4, 6–8]. These factors can disrupt the normal wound healing process and lead to delays in healing. Traditional treatments have focused on glycemic control, debridement, grafting, and wound dressings have not consistently provided effective and universally applicable therapies [4]. Thus, there is an urgent need for carefully planned integration of treatments to address these issues.

Microneedle technology, as an emerging treatment method, offers new possibilities for enhancing diabetic wound healing. In the initial stages (hours to days), microneedling has been shown to reduce inflammatory responses, scavenge ROS, and moderately polarize macrophages. As healing progresses

Received: June 20, 2024. **Revised:** September 19, 2024. **Accepted:** November 9, 2024

Table 1. Comparison of traditional treatment and microneedle therapy for diabetes wounds

Therapeutic method	Advantages	Limitations	References
Localized medication (antibiotics, anti-inflammatory drugs)	Drug directly acts on the wound site, effectively combating local infections and inflammation; low cost; easy to obtain; wide indications.	Poor permeability, easy drug resistance, allergic reactions or other side effects.	[17, 18]
Debridement	Remove necrotic tissue and reduce the risk of infection.	Invasive, painful and uncomfortable, requiring anesthesia or analgesic drugs.	[4, 18, 19]
Moist dressings	Keeping the wound moist helps with healing; High comfort level.	Frequent replacement, may lead to wound adhesion.	[4, 18, 20]
Negative pressure wound treatment	Remove wound secretions, promote the formation of new tissue, improve local blood flow, and reduce swelling.	Large device and higher expense.	[18, 20, 21]
Oxygen therapy	Improve oxygen supply, accelerate wound healing, and reduce infection.	Long treatment cycle, expensive special equipment and costs.	[22–24]
Autologous skin transplantation	Effective repair, suitable for large or deep wounds; low exclusion risk.	Surgical risk, long recovery period.	[20, 25]
Microneedle therapy	Accurate targeted delivery, simultaneous delivery of multiple therapeutic substances (multi-faceted therapy), high delivery efficiency, low side effects, simple operation, minimally invasive, high comfort, and high patient compliance.	At present, the technology is still in the development stage, no unified standard and no clinical trials have confirmed its effectiveness.	[20]

into the middle and late stages (days to months), it aids in promoting cell proliferation, angiogenesis, oxidation, and collagen deposition [9]. Importantly, these effects are primarily observed when microneedles are used in conjunction with additional therapeutic substances, such as anti-inflammatory agents or antioxidant materials [9, 10]. A basic microneedle alone may not exhibit these effects to the same extent in the absence of such enhancements.

To address the specific microenvironment of diabetic wounds, microneedles with antibacterial, anti-inflammatory, antioxidant, immunomodulatory, and proangiogenic properties have been developed [11–13]. Microneedle therapy presents significant advantages for diabetic wound care because of its microtargeted delivery approach. By facilitating the precise delivery of drugs [13, 14], genes [12, 15], cells [11], and other functional materials [12, 16] directly to the wound site, microneedles enhance therapeutic efficacy while minimizing systemic side effects. This targeted approach allows for higher local concentrations of therapeutic agents, which can accelerate wound healing and improve overall treatment outcomes. Compared with traditional methods (Localized medication [17, 18], Debridement [4, 18, 19], Moist dressings [4, 18, 20], Negative pressure wound treatment [18, 20, 21], Oxygen therapy [22–24] and Autologous skin transplantation [20, 25]), microneedle therapy is a less invasive and more comfortable alternative, resulting in reduced pain and improved patient compliance (Table 1) [26, 27]. Furthermore, the ability of microneedles to deliver gases [26, 28–30], metal ions [31], and bioactive nanoparticles [32] further highlights their therapeutic potential, making them a versatile and promising solution for the management of diabetic wounds.

While numerous reviews on microneedling exist, there remains a notable deficiency of reviews that specifically address multifunctional microneedles for the treatment of diabetic wounds, particularly concerning the synergistic effects of microneedles in conjunction with phototherapy and electrotherapy. The aim of this review is to provide guidance for the development of microneedle treatments for diabetic wound healing and to serve as a valuable reference for related research and clinical practice. This review offers a comprehensive overview of recent research on the use of microneedles in diabetic wound healing. This article first discusses the delayed healing mechanism of diabetic wounds. It then delves into the detailed preparation of microneedles, including material selection, structural design, and preparation methods. This review further explores the various mechanisms of action of microneedles in diabetic wound healing, such as antibacterial, anti-inflammatory, immunoregulatory, antioxidant, and proangiogenic effects. Additionally, this study highlights the synergistic therapeutic effect of microneedles when combined with drug therapy, phototherapy, and other methods, suggesting the potential for improved therapeutic outcomes.

Review

Diabetic wounds: mechanism of delayed healing

Intact skin serves as the primary barrier against external factors and houses sebaceous glands, sweat glands, and hair follicles [1]. The dermis is abundant in ECM, blood vessels, and mechanoreceptors and offers structural support, nourishment, and immune defense. Subcutaneous adipose tissue lies below the dermis, acting as both an energy reservoir and a source of growth factors for the skin. Additionally, each skin layer hosts resident immune cells that surveil for damage. In the event of injury, these cellular layers must coordinate precisely for effective healing [1, 33]. As a result, skin repair is one of the most intricate biological processes in the human body.

In the context of wound healing, the process is typically categorized into stages, including hemostasis, inflammation, proliferation, and remodeling (Figure 1) [1]. The hemostatic stage involves rapid vessel constriction, platelet aggregation, and thrombus formation to prevent blood loss [34]. The inflammatory phase involves the release of mediators that attract immune cells to clear pathogens and dead cells, initiating repair [35]. The proliferation stage involves cell proliferation and migration to fill the wound, whereas remodeling involves rebuilding the ECM and regenerating blood vessels and nerves to restore tissue structure and function [34]. Effective coordination of these stages enables the skin to heal complex wounds, restoring integrity and functionality [36]. However,

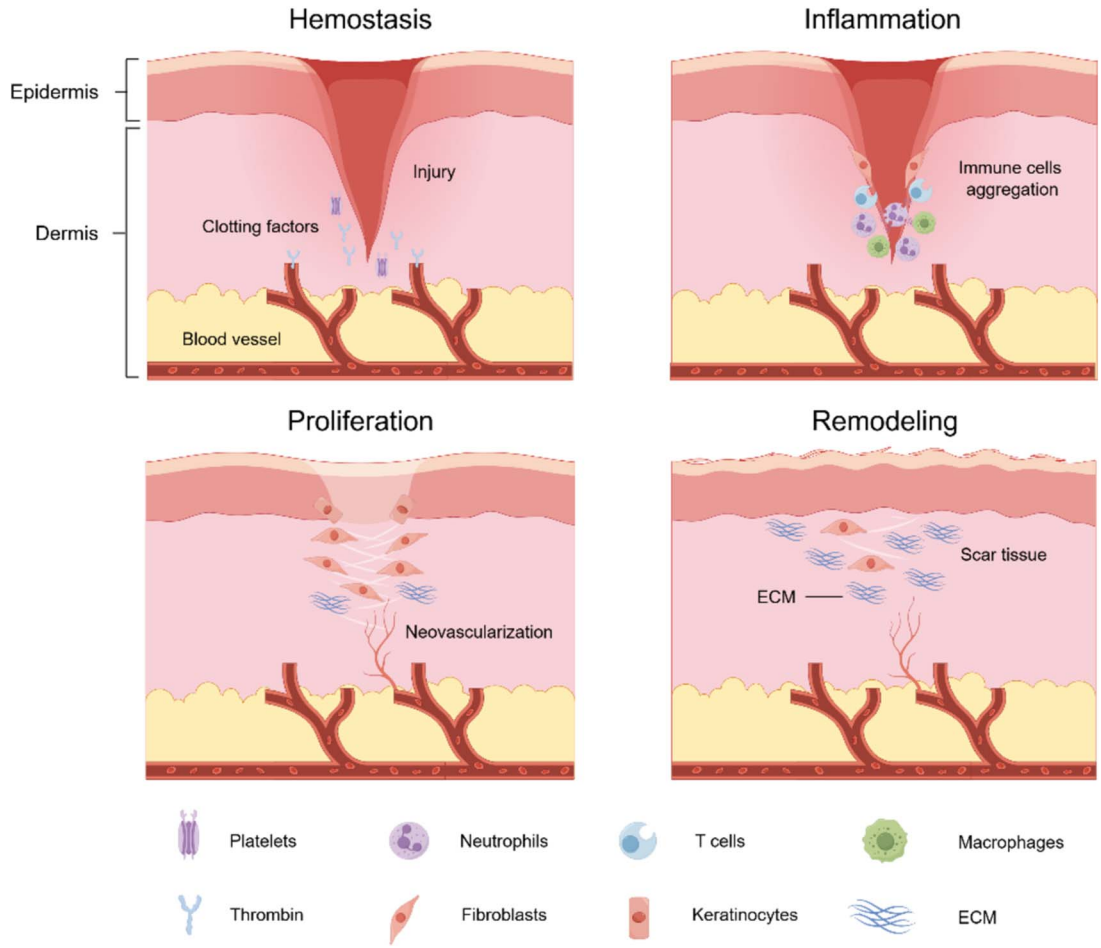

Figure 1. The normal wound healing process: Hemostasis, inflammation, proliferation, and remodeling (by Figdraw). *ECM* extracellular matrix

in diabetic wounds, prolonged hyperglycemia disrupts these stages, leading to delayed healing. Therefore, understanding the physiological and pathological mechanisms of skin wound healing is crucial for managing chronic conditions such as diabetes.

Delayed diabetic wound healing is a multifaceted process influenced by various biological processes. Prolonged hyperglycemia triggers cellular and molecular changes that significantly impact the healing process. The accumulation of advanced glycation end products (AGEs) disrupts cell and matrix function [37], whereas chronic inflammation disturbs the immune environment around the wound, further impeding healing [38]. Impaired angiogenesis and peripheral neuropathy exacerbate this problem by compromising the blood supply and innervation of the affected area, slowing recovery [4, 28]. Additionally, hindered ECM remodeling limits the formation of new tissue [1]. Infection is another significant factor in delayed diabetic wound healing, as elevated blood sugar levels create an optimal environment for bacterial growth and weaken the immune response [39]. These interconnected factors create a complex biological network that challenges wound management in diabetic patients. Understanding these influencing factors and developing targeted treatment approaches are crucial. Investigating the mechanisms behind the delayed healing of diabetic wounds can enhance clinical practice and lead to more effective treatment strategies, ultimately improving patients' quality of life and accelerating recovery. The supplementary file outlines specific details of the delayed wound healing mechanisms in diabetic wounds (supplementary file).

In summary, the delayed healing of diabetic wounds is attributed to the accumulation of AGEs, chronic inflammation, impaired angiogenesis, peripheral neuropathy, and limited ECM remodeling.

Microneedles

Microneedle technology has significantly advanced over the years, leading to breakthroughs in transdermal drug delivery. By using micron-sized needle tips to create tiny channels in the stratum corneum layer of the skin [40], this innovative method offers advantages such as the ability to deliver high-molecular-weight drugs and create customizable treatments, with various clinical applications [41]. The continuous evolution and optimization of microneedle technology has expanded its potential applications. Different types of microneedles provide diverse options for drug delivery, but ongoing research has focused on identifying materials suitable for microneedle preparation and increasing the stability and efficiency of the delivery process [41]. These efforts drive the progress of microneedle technology, fostering innovation and advancements in drug delivery.

Classification of microneedles

Microneedles can be produced in various shapes, such as rectangular, pyramidal, cylindrical, conical, or quadrilateral shapes, with tip sizes typically ranging from 1 to 25 μm [41].

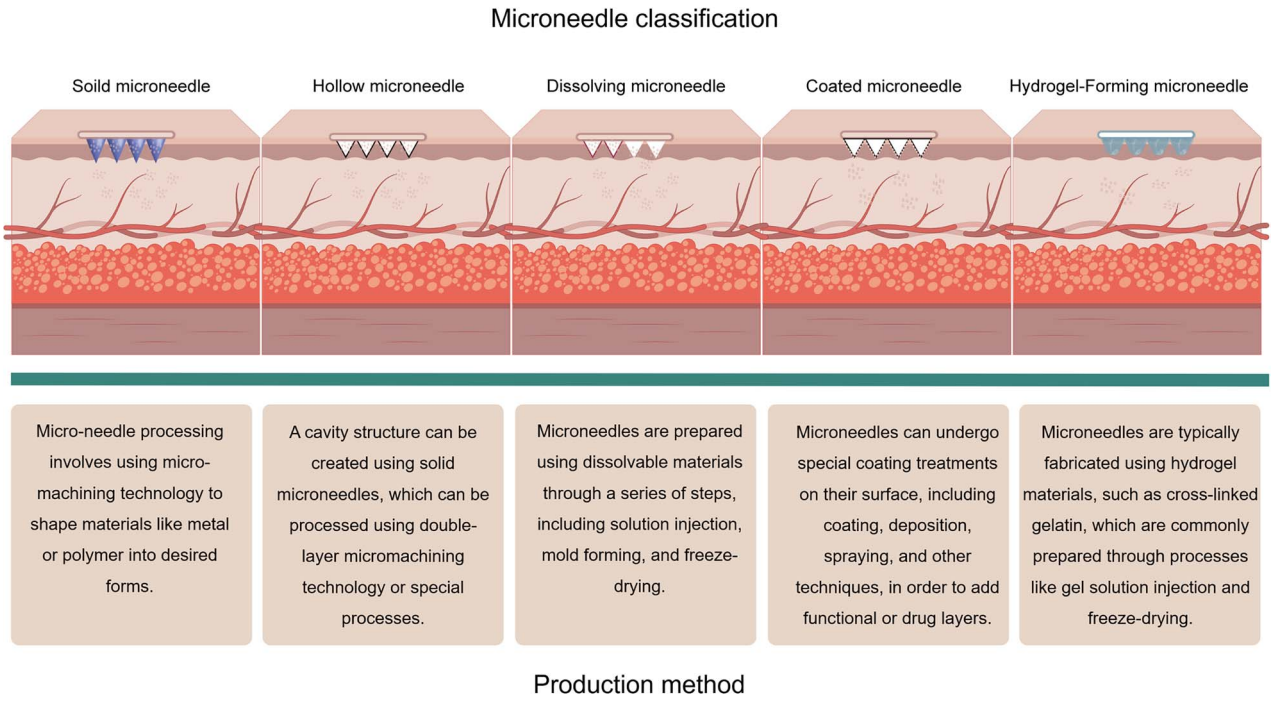

Figure 2. Classification and production method of microneedles (by Figdraw)

They are categorized as solid, coated, hollow, dissolving, or hydrogel-forming microneedles based on their structure (Figure 2) [41, 42]. Each type offers unique advantages for applications in drug delivery and treatment. Solid microneedles are designed for direct drug delivery to target tissues and are made of strong materials to ensure effective penetration [40, 43]. Coated microneedles have a thin drug layer for controlled release near the skin [44]. Hollow microneedles feature channels for liquid drug injection or sample extraction, preventing drug–material interactions [44]. Dissolving microneedles dissolve in the skin, releasing drugs without the need for removal, simplifying their use and reducing waste [42, 45]. Hydrogel-forming microneedles are microneedles made from hydrogel materials. Upon contact with the skin, they rapidly absorb moisture from the skin surface, forming a gel that adheres to the skin and allows noninvasive delivery of medications. This method is particularly suitable for situations where minimizing skin trauma is important [15, 46]. In summary, choosing the appropriate type of microneedle based on specific drug delivery requirements and treatment objectives can lead to more precise and effective drug delivery and treatment outcomes.

Material selection for microneedles

The success of microneedle technology is closely linked to the material selection of microneedles. Therefore, it is essential to choose materials with specific biocompatibility, mechanical properties, and drug release capabilities to ensure the effectiveness and safety of microneedle therapy [41].

Biocompatibility is a key factor in assessing how materials interact with biological systems, encompassing tissue response, cell attachment, and biodegradation. These materials should not induce significant tissue inflammation or rejection but instead should possess suitable bioaffinity to enhance cell attachment and tissue growth. Moreover, they should not elicit a strong immune response or trigger inflammatory processes, and careful consideration of chemical composition and structural design is needed to minimize irritation to the human immune system. Additionally, the biodegradability of microneedle materials is crucial to ensure that they can be safely removed posttreatment and leave minimal residues [47, 48]. Furthermore, comprehensive biocompatibility testing, including cytotoxicity and skin irritation assessments, is essential during material design and selection to support safe application [36]. For example, Yuan et al. [15] utilized LIVE/DEAD cell staining and CCK-8 assays to assess the biocompatibility of GelMA/PEGDA gel, and the results demonstrated high cell viability and low toxicity of the degradation products. Zeng et al. [12] conducted a study where major organs were collected from diabetic rats in both a control group and a microneedle group to assess the safety of microneedle therapy. The findings indicated that the liver and kidney functions of the rats treated with microneedles were within normal ranges and that there were no significant microscopic differences between the two groups. These findings suggest that the microneedle treatment was nontoxic to the diabetic rats. In a separate study by Li et al. [49], an in vitro evaluation of the cellular and hemocompatibility of different concentrations of all-in-one self-powered microneedles (TZ@mMNs) was conducted. The results from LIVE/DEAD staining and the CCK-8 assay demonstrated that TZ@mMNs exhibited minimal cytotoxicity to NHDFs and HUVECs, with cell viability exceeding 98%. Furthermore, blood compatibility testing revealed that the hemolysis rate of the TZ@mMNs was less than 5%, indicating excellent blood compatibility.

The mechanical properties of microneedles are crucial for their ability to penetrate the skin and release drugs effectively. These properties include strength, stiffness, sharpness, and stability in tissues [45]. Microneedles must be strong and rigid enough to avoid breakage or deformation during use but sharp enough to minimize trauma and pain [36]. They create small pores in the skin surface, allowing drugs to enter

the dermal microcirculation. The success of penetration can be assessed via models such as paraffin film or pig skin, with a 100% success rate indicating that all microneedles penetrated the skin [50, 51]. Parameters such as tip diameter, base width, length, and mechanical strength directly impact the size of microchannels. Zhang et al. [52] conducted mechanical testing of microneedles using a universal testing machine and reported that higher concentrations of hyaluronic acid (HA) increased the mechanical strength. The force (30 N) of the microneedles at 450 μm of displacement was sufficient for skin piercing. Furthermore, catechol groups on the surface of microneedles enhance adhesion to wound tissue through hydrogen and covalent bonds. The tip of the microneedle serves as the regeneration center for the microskin island, and its distribution density plays a crucial role in regulating biological cell behavior and wound healing. A higher microneedle density can significantly increase the specific surface area of micronuclei, enhancing resistance to deformation caused by directional cell migration and growth and ultimately benefiting tissue regeneration. However, an excessively high microneedle density may result in increased hydrophobicity, limiting cell migration and proliferation [11]. Huang et al. [11] investigated the impact of different needle spacings (2000 μm, 1500 μm, 1000 μm, and 500 μm) on cell proliferation and migration to study the interaction between microneedle density and tissue. The study revealed that changes in microneedle density did not significantly affect cell proliferation. Nevertheless, greater mobility was observed with the 1500 μm, 1000 μm, and 500 μm spacing than with the 2000 μm spacing, with the 1000 μm spacing resulting in the greatest mobility. This finding indicates that increasing the microneedle density can increase the directional migration rate of cells but that an excessively high density may hinder cell migration.

The drug release performance of microneedles is a crucial aspect of microneedle technology in drug delivery and is essential for achieving effective therapeutic outcomes. When investigating microneedle drug release performance, several factors must be considered. First, the material chosen for microneedles significantly influences drug release. Different materials may interact with drugs in various ways, impacting the rate and manner of drug release. For example, some materials may chemically react with drugs, leading to slow drug release [13, 53], whereas others may exhibit better drug compatibility, facilitating rapid drug release [49]. Second, the characteristics of the drug itself play vital roles in release performance. Factors such as molecular weight, solubility, and formulation affect drug diffusion and release rates in microneedles [54, 55]. Moreover, surface coatings on microneedles can also modulate drug release properties. Certain coatings may delay drug release, creating a sustained-release effect, whereas others may accelerate drug release for quicker therapeutic effects [13, 53, 56]. Therefore, by comprehensively considering factors such as microneedle materials, drug properties, and surface coatings, microneedle systems with superior drug release properties can be developed, offering critical technical support for effective drug delivery and therapeutic outcomes.

Traditional materials for microneedle production include metal, glass, and silicon. While these materials exhibit high hardness, they are also brittle, which can lead to skin rupture or the presence of foreign matter residues, potentially resulting in various side effects [57]. In recent years, polymer materials—such as gelatin, chitosan, silk protein, HA, polylactic acid (PLA), and polyethylene glycol (PEG)—have gained popularity because of their superior biocompatibility, mechanical properties, and degradability [15, 28, 31, 33]. Compared with traditional materials, polymer options offer enhanced biocompatibility and reduced cytotoxicity, as well as the ability to decompose naturally, thereby minimizing complication rates, particularly during prolonged or repeated applications [58–60]. In terms of their mechanical properties, polymer microneedles typically exhibit greater flexibility and adaptability, enabling them to distribute pressure evenly across the skin and decrease the risk of skin breakdown [61]. Furthermore, by optimizing the formulation and preparation processes, the mechanical properties of polymer microneedles can be tailored to meet specific application requirements [57]. For example, PLA and PEG can provide the necessary hardness and elasticity to ensure the stability and comfort of microneedles during skin penetration [62, 63]. Additionally, polymer materials demonstrate effective drug release capabilities, achieving sustained drug release by modulating the degradation rate or employing various drug loading technologies. Natural polymers, such as gelatin and silk proteins, exhibit excellent drug carrier properties and can effectively deliver drugs while maintaining their biological activity [64, 65]. Additionally, HA and chitosan can significantly regulate drug release, facilitating sustained release and enhancing therapeutic efficacy [58, 66]. Compared with that for metal and glass microneedles, the manufacturing process for polymer microneedles is more flexible and cost-effective, making it suitable for large-scale production. Moreover, the size and shape of microneedles can be tailored to meet various application requirements [57].

In summary, polymer materials offer substantial advantages over traditional materials concerning biocompatibility, mechanical properties, degradability, drug release performance, and manufacturing processes, establishing them as the preferred choice in microneedle technology. Particularly in scenarios necessitating long-term or repeated applications, polymer microneedles can deliver a safer and more effective solution. Future research should further investigate the performance of these materials across various clinical applications to facilitate the continued advancement of microneedle technology.

Microneedle preparation technology

The method of microneedle preparation significantly impacts the performance and applications of microneedles. Common preparation techniques currently include cutting, etching, photolithography, micromolding, and 3D printing. Each method has its own advantages and disadvantages (Figure 3) [48, 67].

Cutting technology typically employs lasers and computer-aided design software to precisely engrave solid microneedles onto stainless steel plates, rendering it suitable for mass production. This method offers high manufacturing precision and production efficiency; however, it also involves challenges, such as material waste, difficulties in fabricating complex shapes, and high initial mold costs [45]. Additionally, owing to the advantages of polymer materials, the use of solid metal microneedles is rare, and related research remains limited. Conversely, etching technology uses corrosive liquids to carve the surfaces of microneedles, allowing for precise control over size and shape, making it particularly well suited for

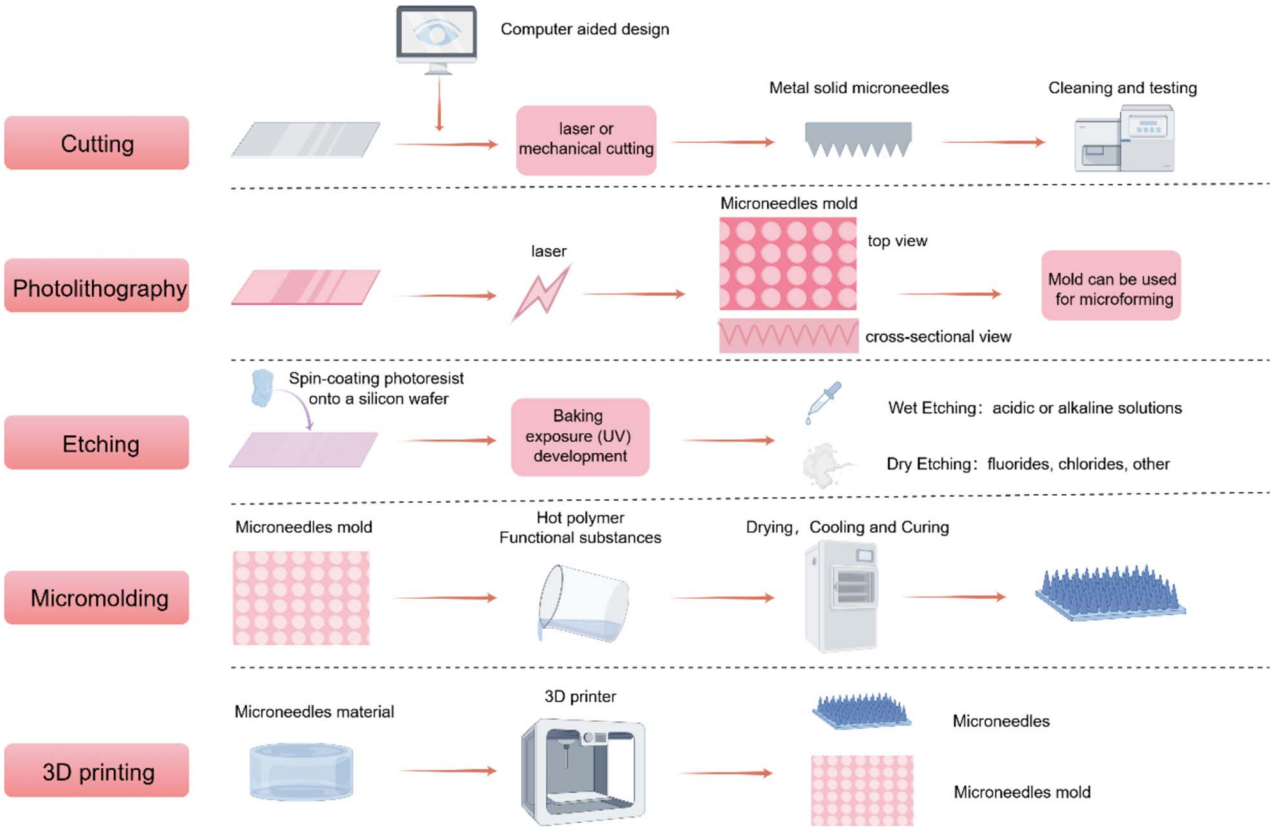

Figure 3. Schematic diagram of the microneedle preparation method (by Figdraw)

producing arrays of specific structures [45]. For example, Li et al. employed double-sided etching to fabricate microneedles on silicon wafers, utilizing an oxide/nitride mask and KOH for deep etching [68]. The advantages of this technology include high resolution and good adaptability; however, it is suitable primarily for brittle materials, and the process is complex and costly. Photolithography employs a light source to create microneedle patterns on a substrate, offering extreme precision and design flexibility. For example, Sun et al. utilized a laser to create tapered microneedle cavities on a female PDMS mold [69]. Similarly, Evens et al. employed a femtosecond laser system to ablate microneedle molds [70]. Although photolithography can produce complex-shaped microneedles, it is hindered by expensive equipment, process complexity, and certain restrictions on material selection. On the other hand, micromolding involves pouring hot polymers into micron- or nanometer-sized molds, followed by centrifugation, drying, and cooling to yield consistent and accurately sized microneedle products, which are suitable for medical devices, biosensors, and other applications [11, 30, 33, 53]. For example, Sun et al. fabricated microneedles using a PVA solution and microneedle molds [69], whereas Guo et al. instilled silk fibroin solution into a mold to prepare microneedles [71]. This technology is advantageous for large-scale production, offering high production efficiency and good dimensional consistency; however, it is primarily suitable for thermoplastic polymers, and mold wear may compromise production quality. 3D printing technology simplifies the microneedle manufacturing process by adding materials layer by layer according to computer-aided design models, making it suitable for personalized customization and small batch production [72]. 3D printing enables the production of high-quality microneedles with adjustable properties from a variety of materials [73–75]. One study employed fused deposition modeling 3D printing technology to create conical and neiloid microneedles, subsequently verifying their potential for transdermal drug delivery via a skin model [76]. Additionally, Fitaihi et al. developed a soluble microneedle patch through stereoscopic lithography and 3D printing [77]. While 3D printing technology offers high design flexibility and a diverse range of material options, it still faces certain limitations regarding accuracy and production speed.

Importantly, the aforementioned techniques can be employed individually or in combination. For example, the claw-inspired microneedle developed by Zhang et al. integrates both etching and photolithography techniques [78]. Additionally, several studies have explored the combination of photolithography with micromolding or 3D printing [74, 79]. Consequently, considerations regarding structural specifications, production costs, and production scale become critical. A rational selection and optimization of preparation techniques will facilitate the fulfillment of diverse microneedle designs and application requirements.

Application of multifunctional microneedles in diabetic wound healing

Wound healing is a complex and dynamic process that involves the interaction of various cells, cytokines, and growth factors. The diabetic wound microenvironment is characterized by chronic inflammation, bacterial infection, excessive oxidative stress, and impaired angiogenesis [6, 9]. To address these challenges, multifunctional microneedles

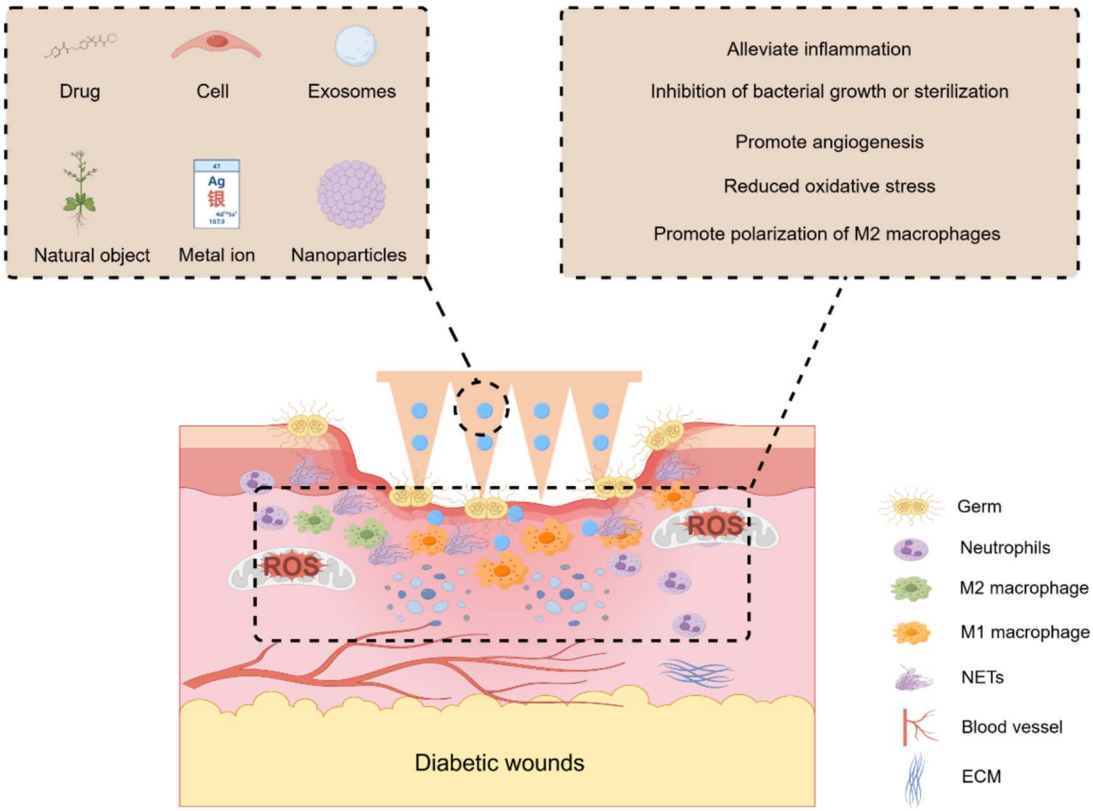

Figure 4. Application of microneedle in wound healing of diabetes (by Figdraw). *ECM* extracellular matrix

have been designed to enhance wound healing. Microneedles can modulate the microenvironment and act as carriers for cells, nanoparticles, drugs, or other therapeutic substances (Figure 4 and Table 2) [15, 31, 49, 54, 55, 80–91].

Anti-inflammatory and immunomodulatory microneedles

In diabetic wounds, inflammatory factors and immune cells play pivotal roles. The inflammatory response is often exacerbated by continuous cytokine stimulation and the recruitment of immune cells. High blood sugar levels can also impact the function and quantity of immune cells, resulting in abnormal or insufficient inflammatory reactions. Dysfunctional immune cells, such as M1 macrophages and neutrophils, release proinflammatory chemokines, contributing to chronic inflammation [6, 92]. To mitigate the inflammatory response and enhance diabetic wound healing, researchers have explored the use of anti-inflammatory microneedles. These microneedles can be loaded with cells [11], extracellular vesicles [12], anti-inflammatory drugs, and natural ingredients [55], among others. Moreover, anti-inflammatory materials can be incorporated into microneedles to regulate macrophage polarization and facilitate wound healing through immunomodulation [32].

Metformin, a drug commonly used to treat type 2 diabetes, not only helps regulate blood sugar levels but also has intrinsic anti-inflammatory effects [93]. Liu et al. [14] developed a composite hydrogel-backed porcupine feather-like microneedle system that improved adhesion to the skin through physical interlocking and chemical bonding of multilayered microneedles. Additionally, the microneedles were loaded with CaO2-HA nanoparticles and metformin within the polycaprolactone tips, resulting in antibacterial, anti-inflammatory, and hypoglycemic effects that may facilitate the healing of diabetic wounds. However, this study is limited by the absence of long-term biocompatibility assessments, in vivo and in vitro toxicity evaluations, and a more comprehensive exploration of the underlying mechanisms. Exosomes, vesicles released by various cells, play a key role in intercellular communication by delivering their contents [94]. Their potential in tissue regeneration is significant because of their biocompatibility, low immunogenicity, and therapeutic targeting ability. Preclinical studies have demonstrated the therapeutic effects of exosomes in multiple systems, including nervous, muscular, skeletal, pulmonary, and cardiovascular systems. These vesicles carry biological molecules such as proteins, DNA, mRNAs, and miRNAs from the parent cell, offering similar biological advantages [94]. For example, M2 macrophages, known for their anti-inflammatory properties, are involved in allergies, parasitic infections, and tissue remodeling. Stimulating M2 macrophages can promote wound healing by inhibiting apoptosis and inflammatory responses [86, 95]. Studies have shown that M2 macrophage-derived exosomes (MEs) exhibit anti-inflammatory effects and resistance to inflammation in inflammatory diseases [96]. MEs can also facilitate the transformation of macrophages from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby accelerating skin wound healing [97]. Owing to the limitations of exosomes, such as their short half-life and instability and the chronic hyperactive inflammation of diabetic wounds, the use of biomaterials loaded with MEs could be an effective strategy to enhance diabetic wound healing. Zeng et al. [12] developed a double-layered microneedle-based wound dressing system

Table 2. Multifunctional microneedle characteristics for promoting wound healing in diabetes.

Synthetics	Load substance	Functions	References
SilMA	CaO_2, AgNPs, catalase	Antibacterial, anti-inflammatory, and pro angiogenic	[53]
GelMA	TA@ZnO	Antibacterial, antioxidant, anti-inflammatory, promoting angiogenesis and increasing collagen deposition	[49]
GelMA-CS	KC and FB	Promote re epithelialization and vascularization	[11]
GelMA	PC	Anti inflammation and immune regulation	[54]
HA, pyrrole, DA	ZIF-8 nanoparticles loaded with GOx and HRP	Hypoglycemic, antibacterial, anti-inflammatory, and bioelectric stimulation	[52]
HAMA and PVA	MEs and PDA NPs	Anti inflammation and promotion of vascular regeneration	[12]
PSBMA	HMPs,ZnONPs and asiaticoside	Antibacterial and anti-inflammatory	[55]
PDMS and PVA	SeC@PA	Antibacterial, antioxidant, anti-inflammatory	[56]
PCL	Sodium hyaluronate modified CaO_2 nanoparticles and metformin	Antibacterial, anti-inflammatory, antioxidant, and pro angiogenic properties	[14]
PLGA	MgH2	Anti inflammation and antioxidant properties	[31]
Gelatin	FeIIITA	Antibacterial, anti-inflammatory, and pro angiogenic	[80]
PVP	NIR-II, GOx and catalase	Antibacterial and hypoglycemic effects	[81]
HA, CS and SF	TCH and DFO	Antibacterial, pro angiogenic, anti-inflammatory, and pro collagen deposition	[28]
GelMA	G-Insulin and AFPBA	Anti inflammation, hypoglycemic and promoting collagen deposition	[46]
HA and HAMA	Fe-MSC-NV and PDA NPs	Antioxidant, anti-inflammatory, and pro angiogenic	[33]
γ-PGA	Asiaticoside	Promoting angiogenesis and epithelial regeneration	[82]
CS	Fe2C NPs and GOx	Antibacterial	[83]
MOF	NO and NIR	Promote cell migration and angiogenesis	[30]
HA and GelMA	TCH and rh-EGF	Antibacterial, anti-inflammatory, promoting angiogenesis and collagen deposition	[65]
HA	ZCO	Antibacterial, anti-inflammatory, and promoting angiogenesis	[32]
PVA	MSC-Exos	Anti inflammation and promotion of angiogenesis	[74]
GelMA and PVA	Cv	Promote cell proliferation, migration, and angiogenesis	[29]
HA	HMPs, ZnO, VEGF and bFGF	Antibacterial, anti-inflammatory, and promoting angiogenesis	[16]
SFM	PBN, VEGF and polymyxin	Promoting angiogenesis, antioxidant and antibacterial properties	[13]
CS and PVP	Mg and PNS	Antibacterial, anti-inflammatory, and promoting angiogenesis	[84]
γ-PGA and GO-Ag	Mg-MOFs and gallic acid	Antibacterial and antioxidant properties	[85]
PDMS and HA	NPF nanoparticles and PA	Hypoglycemic and anti-inflammatory	[86]
HA	PDGF-BB, SOS and quercetin	Anti-inflammatory, pro-angiogenic and long-term moisturizing properties	[87]
PVA and HA	CuS NPs and TM NPs	Photothermal antimicrobial, ROS scavenging, immunomodulatory, and angiogenesis	[88]
γ-PGA	Ag, CeO2 and MSN	Antibacterial, reactive oxygen species-lowering, macrophage ecological niche-regulating, promoting vascular regeneration and collagen deposition	[89]
PVA and PBA	POGa and insulin	Antibacterial and Hypoglycemic	[90]
PVA and HEMA	Catalase and polymyxin B	Immunoregulation and antibacterial	[91]

SilMA Methacrylic anhydride silk fibroin, *GelMA* Gelatin methacryloyl, *GelMA-CS* Gelatin methacryloyl-Chitosan, *HA* hydroxyapatite, *DA* Dopamine, *HAMA* hyaluronic acid methacrylate, *PVA* Polyvinyl alcohol, *PSBMA* Poly (sulfobetaine methacrylate), *PDMS* Polydimethylsiloxane, *PCL* Polycaprolactone, *PLGA* Poly (lactic-co-glycolic acid), *PVP* Polyvinylpyrrolidone, *SF* Silk Fibroin, *γ-PGA* Poly-γ-glutamic acid, *SFM* Silk fibroin methacryloyl, *AlgMA* Alginate Methacrylate, *GO-Ag* graphene oxide-silver nanocomposites, *AgNPs* Silver nanoparticles, *TA@ZnO* Tannin@ZnO microparticles, *KC* Keratinocytes, *FB* Fibroblasts, *PC* Purpurolide C, *GOx* Glucose oxidase, *HRP* horseradish peroxidase, *MEs* M2 macrophage-derived exosomes, *PDA NPs* polydopamine nanoparticles, *HMPs* photothermal hair particles, *ZnO NPs* zinc oxide nanoparticles, *SeC@PA* Dopamine-coated hybrid nanoparticles containing selenium and chlorin e6, *MgH2* magnesium hydride, *FeIIITA* iron/tannic acid, *NIR-II* Near infrared II response, *TCH* tetracycline hydrochloride, *DFO* deferoxamine, *G-insulin* gluconic insulin, *AFPBA* glucose-responsive monomer 4-(2-acrylamidoethylcarbamoyl)-3-fluorophenylboronic acid, *Fe-MSC-NVs* ferrum-mesenchymal stem cell-derived artificial nanovesicles, *PDA NPs* polydopamine nanoparticles, *Fe2C NPs* Fe2C nanoparticles, *SPs* stem cell spheroids, *rh-EGF* recombinant human epidermal growth factor, *ZCO* cerium/zinc-based nanomaterial, *MSC-Exos* mesenchymal stem cell -exosomes, *Cv* C. vulgaris, *ZnO* Zinc oxide, *VEGF* vascular endothelial growth factor, *bFGF* basic fibroblast growth factor, *PBN* Prussian blue nanozymes, *TSA* Trichostatin A, *Mg* magnesium, *PNS* panax notoginseng saponins, *Mg-MOFs* Multifunctional magnesium organic frameworks, *NPF* Acid-responsive Nisin@PA@Fe, *PA* Protocatechualdehyde, *PDGF-BB* Platelet-derived Growth Factor-BB, *SOS* Sucrose Octasulfate, *TM NPs* Tannin-europium metal–organic framework nanoparticles, *CeO2* cerium dioxide, *MSN* mesoporous silica nanoparticles, *PBA* phenylboronic acid, *POGa* gallium porphyrin modified with 3-amino-1,2 propanediol, *HEMA* hydroxyethyl methacrylate

(MEs@PMN) by incorporating MEs in the needle tips and polydopamine (PDA) nanoparticles in the backing layer to simultaneously reduce inflammation and enhance angiogenesis at the wound site. In vitro studies revealed that the released MEs promoted macrophage polarization toward the M2 phenotype. The application of MEs@PMN in a diabetic rat wound model resulted in a significant decrease in the number of M1 macrophages and an increase in the number of M2 macrophages, which was consistent with the in vitro findings. Similarly, Ma et al. [33] proposed a novel

core-shell HA microneedle encapsulated with iron-mesenchymal stem cell-derived artificial nanovesicles (Fe-MSC-NVs) and polydopamine nanoparticles (PDA NPs). The release of PDA NPs from the MN patch at the lesion site effectively inhibited the inflammatory response induced by ROS. The combination of PDA NPs and Fe-MSC-NVs facilitated M2 macrophage polarization, resulting in decreased wound inflammation and expedited healing of diabetic wounds. However, despite the promising therapeutic potential of extracellular vesicle-based microneedles, the large-scale production of extracellular vesicles poses a significant challenge, thereby limiting their clinical application.

In recent decades, researchers have been actively developing and studying new drugs and materials that modulate macrophage function. Natural products, particularly fungal metabolites, have long been crucial in drug discovery. PC, a rare bergamot sesquiterpene derived from the fungus Penicillium purpurogenum IMM003, possesses a unique 6/4/5/5 tetracyclic ring system [98]. Research indicates that PC exhibits significant anti-inflammatory properties and can effectively inhibit the activation of M1 macrophages without causing cytotoxicity [54]. These findings suggest the potential of PC in regulating local macrophage function and facilitating diabetic wound healing. Liu et al. [54] innovatively developed a PC-based microneedle patch to address challenges related to the poor water solubility and limited skin permeability of PC. By inhibiting TLR4-MD2 dimerization and MYD88 phosphorylation, the microneedle patch successfully delivers PC to local tissues, thereby suppressing M1 macrophage activation and promoting diabetic wound healing. However, the study did not explore the dose–effect relationship or optimal administration regimen of PC in sufficient depth. Additionally, gallic acid, a natural organic compound with phenolic properties, has anti-inflammatory effects. Yin et al. [85] incorporated gallic acid into a microneedle patch containing a magnesium organic framework to enhance its anti-inflammatory properties. Additionally, some metal ions, such as Mg2+, also have anti-inflammatory effects. Wang et al. [31] developed a poly(lactic-glycolic acid) (PLGA)-based microneedle patch loaded with magnesium hydride (MgH2) (MN-MgH2) for treating diabetic wounds. These microneedle patches enable transdermal delivery and sustained release of MgH2, leading to the generation of hydrogen gas (H2) and magnesium ions (Mg2+) upon interaction with body fluids. The released Mg2+ aids in promoting the polarization of M2 macrophages. Nanomaterials, such as ZnO NPs and ZCO, possess anti-inflammatory properties. In a study by Li et al. [49], ZnO NPs were loaded onto GelMA hydrogel microneedles, resulting in reduced inflammation by lowering TNF-α and IL-6 expression. In another study by Yang et al. [32], ZCO was combined with HA to create ZCO-HA microneedles, which demonstrated effective anti-inflammatory activity via the NF-κB pathway. This pathway helps decrease macrophage inflammation and enhances cell proliferation, migration, and angiogenesis. Metal ions have the potential to modulate inflammation and immunity; however, challenges such as unclear mechanisms, dose optimization, potential toxicity, safety concerns, and the need for clinical validation remain unresolved.

While anti-inflammatory drugs or ingredients can effectively modulate immune cell activity, their efficacy is contingent upon their concentration. Diabetic wound healing is a protracted process, and slow drug release may mitigate drug toxicity and enhance efficacy by delaying absorption. Nevertheless, the long-term safety of these delivery systems requires thorough evaluation, particularly regarding sustained release, biocompatibility, and the cumulative effects of the drug over time.

Antibacterial microneedles

When the skin is damaged, its protective mechanisms are lost, complicating the wound healing process in diabetic patients. Infections are a major factor in delayed wound healing among individuals with diabetes, with persistent high blood sugar levels creating an environment conducive to bacterial growth and invasion [53]. Common bacteria found in diabetic wounds include *Streptococcus pyogenes*, *Staphylococcus aureus (S. aureus)*, *Escherichia coli (E. coli)*, and *Pseudomonas aeruginosa* [49, 53]. These bacteria can form biofilms that shield them from antibiotics and the body's immune cells, leading to excessive inflammation and hindering the resolution of the inflammatory response [6].

Various microneedles with antimicrobial properties have been developed and utilized for diabetic wound healing. These include antibacterial microneedles containing antibacterial ingredients and intrinsic antibacterial microneedles. While antibiotics have been a staple in the antibacterial field since the discovery of penicillin, they also present challenges in terms of solubility, overdosing, and cytotoxicity. To address the issue of drug-resistant pathogens, microneedles incorporating metal ions, metal oxides, and biological extracts have been explored for antibacterial treatment [31, 55]. Microneedles offer advantages such as minimal invasiveness, localized drug release, and sustained treatment, and antibacterial microneedles enhance their antibacterial efficacy. Additionally, microneedles incorporating antimicrobial polymers, peptides, or zwitterions possess inherent antimicrobial properties [49, 55, 80]. Furthermore, therapies such as photothermal therapy (PTT) [30, 55], photodynamic therapy [56, 80], and electrical stimulation (ES) [49] have been integrated with microneedles to aid in the healing of infected wounds.

Significant challenges are being encountered in the development and utilization of antibiotics, which are the most commonly used and effective antibacterial drugs, because of the increase in drug resistance. One approach to address this issue involves reducing the dosage of traditional antibiotics by continuously releasing them at the infection site through microneedle delivery systems. Tetracycline, trichostatin A, and polymyxin have been incorporated into microneedles to address bacterial infections in diabetic wounds [13, 28, 65, 99]. In studies conducted by Liu et al. and Gao et al., tetracycline was loaded onto the tips of microneedles to facilitate rapid release and enhance bactericidal activity, thereby improving their antibacterial efficacy in diabetic wounds [28, 65]. Biological extracts and natural ingredients, such as PC and madecassoside, have been the focus of extensive research [54, 55]. One study reported the incorporation of polyphenols into multifunctional microneedles, with antibacterial tests demonstrating that these microneedles exhibited favorable antibacterial properties [88]. Tannin (TA), a plant-derived polyphenol approved by the FDA for medical use, displays both antioxidant and antibacterial properties. Qi et al. reported that TA loaded onto microneedles effectively inhibited invasive pathogens, increased microbial diversity at the wound site, and facilitated the healing of infected wounds by reducing ROS levels [100]. Another investigation revealed

that TA was integrated into microneedles through hydrogen bonding with gelatin, resulting in significant antimicrobial activity, with nearly a 100% antibacterial rate against *S. aureus* and *E. coli*. This approach effectively eradicated *S. aureus* in rat wounds, suppressed inflammation, promoted vascular proliferation, and accelerated the healing of infected wounds [101].

Various metal ions, metal oxides, and inorganic particles have been developed to address source and stability limitations. These include Ca^{2+} [53], Se^{2+} [56], Ag^{+} [85], Cu^{2+} [14, 30], Zn^{2+} [32], $Ce^{3+/4+}$ [32], Fe^{2+} [33, 83], Mg^{2+} [31], Au^{+} [81], ZnO [49, 55], CaO_2 [14, 53], and silver nanoparticles (AgNPs) [53], which have been reported as antibacterial agents in microneedle combinations. Yu et al. incorporated Ag and Ce into soluble microneedles to facilitate deep tissue release, thereby accelerating the healing of infectious diabetic wounds through their antibacterial activity, reducing levels of reactive oxygen species, and modulating the macrophage environment [89]. Sun et al. further enhanced the antibacterial properties of microneedles by coating their bases with AgNPs [53]. Another study demonstrated that under near-infrared (NIR) irradiation, Fe2+/Fe3+ generates a substantial amount of ROS, attacks bacterial membranes, and induces ferroptosis, effectively resulting in antibacterial activity. This mechanism not only eliminates bacteria via ferroptosis, Fe2+ overload, and lipid peroxidation but also promotes the ferroptosis of intracellular bacteria. Additionally, Fe2+/Fe3+ activates the AMP-AMPK pathway, assisting macrophages in evading ferroptosis and thereby enhancing biocompatibility, in turn significantly accelerating the healing of diabetic infected wounds [102]. Although current research indicates the effectiveness of these ions in promoting the healing of infectious diabetic wounds, further studies are warranted. However, there is ongoing debate regarding their potential antibacterial mechanisms. One prevailing perspective suggests that the antibacterial activity can be attributed to the damage caused to bacterial cell membranes by metal ions and NPs [53]. Iron/-tannic acid (FeIIITA) composite nanoparticles and ZnO NPs have both gained attention in the biomedical field. FeIIITA nanoparticles enhance the antibacterial efficacy of hydrogel microneedles by combining their photothermal effect with the natural antibacterial properties of polylysine. Moreover, ZnO NPs are known for their broad-spectrum antibacterial activity, biocompatibility, and biosafety. In addition to eliminating bacteria, ZnO NPs release Zn2+ under physiological conditions, promoting cell proliferation, growth, and angiogenesis during wound healing [49]. Recent studies have indicated that TZ@mMN, engineered by Li et al. [49], demonstrates highly effective antibacterial properties (antibacterial rate > 99%) against both *S. aureus* and *E. coli* through the delivery of TA and Zn2+. Furthermore, various particles or structures with photothermal properties have been incorporated into microneedles to enhance their photothermal characteristics. The antibacterial efficacy of these materials is attributed to their photothermal properties, including the use of polydopamine (PDA) nanoparticles [12, 33], photothermal particles (HMPs) [55], and NIR [16, 30, 81], as documented in previous studies. For example, one study developed a degradable microneedle patch that incorporates near-infrared light-responsive photothermal agents. This patch not only continuously kills bacteria and prevents biofilm formation but also significantly promotes wound healing by remodeling the microenvironment of bacterium-infected wounds through its antibacterial effects [59]. Additionally, microneedles capable of releasing high concentrations of NO and H2 have also been employed to facilitate diabetic wound healing, potentially by eradicating or disrupting bacterial biofilms [30, 80, 103].

Intrinsically antimicrobial polymers, such as CS and its derivatives, PEI, PILs, EPL, PANI, PVA, and antimicrobial peptides, are commonly utilized in various applications [29, 65, 74, 84, 90, 104–106]. These polymers typically possess positive charges that can interact with negative charges on bacterial cell membranes, leading to cell membrane disruption and bacterial death [105]. These antimicrobial polymers have been employed in the development of antimicrobial microneedles to enhance wound healing. For instance, Zhao et al. [29] created detachable microneedles loaded with *Chlorella vulgaris* (Cv) via a polyvinyl acetate (PVA) matrix and a gelatin methacryloyl (GelMA) tip containing Cv. Zhang et al. [74] utilized a novel manufacturing approach that combines template replication and 3D transfer printing to fabricate a biomimetic, adaptive, indwelling microneedle. This microneedle featured a PVA hydrogel tip with mesenchymal stem cell (MSC) exosomes, supported by a removable 3 M medical tape base plate assembly. The mechanical properties of the PVA hydrogel tip were modulated by ion-responsive Hofmeister effects, ensuring appropriate skin penetration and tissue adaptation upon tip detachment. In addition to intrinsic antibacterial polymers, microneedles also demonstrate exceptional antibacterial effects under physiological conditions due to their positive charge. To further enhance the antibacterial efficacy of microneedles, a combination of multiple antibacterial methods has been employed to demonstrate a synergistic effect. The incorporation of tetracycline hydrochloride (TCH) and recombinant human epidermal growth factor (rh-EGF) into carboxymethyl chitosan (CMC) and CS microneedles aimed to increase antibacterial activity and achieve rapid sterilization [28, 65]. However, intrinsic antimicrobial polymers still face shortcomings in terms of long-term stability (degradation or failure), biocompatibility (allergic reactions or toxic responses), production cost, and sustained antimicrobial efficacy.

Multifunctional microneedles have demonstrated excellent therapeutic effects in preclinical studies of diabetic wounds. Sun et al. [53] introduced an innovative antimicrobial oxygenic silk fibroin methacryloyl hydrogel MN patch with calcium peroxide and catalase (CAT)-encapsulated tips, along with a coating of antimicrobial AgNPs. The AgNPs at the base effectively combat microbial infections and promote wound healing. Diabetic wounds often develop bacterial biofilms, hindering the healing process. Yang et al. [56] proposed a novel treatment approach involving an SeC@PA MN bandage with dopamine-coated hybrid nanoparticles (SeC@PA) containing selenium and chlorin e6 that is adaptable to the wound microenvironment. This bandage regulates the production of ROS and RNS bidirectionally, disrupting the wound barrier and efficiently delivering SeC@PA to deplete endogenous glutathione (GSH) and enhance the antibiofilm effects of ROS and RNS. SeC@PA also breaks down GSH in biofilms through a cascade reaction, generating more potent ROS and RNS to eradicate biofilms. Cai et al. [55] utilized the zwitterionic polymer polysulfobetaine methacrylate (PSBMA) and HMPs to develop a microneedle dressing base material capable of absorbing wound exudate, disrupting the bacterial environment within the wound, and demonstrating a remarkable photothermal bactericidal effect that aids in enhancing wound

healing. By incorporating ZnO NPs and asiaticoside at the needle tip, the drug diffuses into the wound area as the needle degrades, resulting in efficient antibacterial and anti-inflammatory effects that facilitate deep wound healing and tissue regeneration. The application of these MNs to wounds infected with *S. aureus* in diabetic rats led to accelerated tissue regeneration, increased collagen deposition, and significantly improved wound healing. Drawing inspiration from glucose metabolism, Shan et al. [81] introduced an encapsulated, near-infrared-II-responsive Au-Cu2MoS4 nanocatalytic microneedle patch (Au-CMS NS) with dual nanozyme activity for the treatment of diabetic wound infections. Gao et al. [28] prepared microneedles with varying concentrations of TCH (1, 2, and 3 mg/mL) in HA solution at the tip and a mixture of CS and SF as the matrix. In vitro antimicrobial testing on *E. coli* and *S. aureus* agar plates demonstrated that the microneedles had antibacterial effects against both bacterial strains, with a stronger effect against *S. aureus*. This disparity may be attributed to the outer membrane of gram-negative bacteria providing resistance to bactericides and bacteriostats.

Antibacterial microneedles offer significant advantages in the treatment of diabetic wounds, including precise local drug delivery, multiple antimicrobial mechanisms, and improved wound healing. They effectively combat infections by delivering drugs directly to the wound site, thereby reducing systemic side effects. Moreover, microneedles equipped with photothermal properties can enhance antimicrobial effects through light activation. However, these microneedles also face limitations, such as challenges related to long-term stability, high production costs, and concerns regarding biocompatibility. Additionally, their effectiveness may be restricted to certain pathogens, and their application necessitates advanced technical expertise. Addressing and optimizing these factors is essential for their practical use.

Antioxidant microneedles

In the context of normal physiological activities, ROS play crucial roles in regulating cell signaling, proliferation, apoptosis, and other vital cellular functions. However, in diabetic wounds, excessive production of ROS can lead to oxidative stress, causing damage to cells and tissues and ultimately hindering the wound healing process. ROS can induce lipid peroxidation, protein denaturation, and DNA damage and inhibit the functionality of endogenous stem cells and macrophages, further impeding wound healing [6]. As a result, various antioxidant materials have been developed to modulate the overexpression of ROS and restore cellular health. Antioxidant microneedles are designed to target intracellular oxidative stress and metabolic dysregulation with the aim of improving overall cellular health.

The body's antioxidant system consists of various enzymes, vitamins, and compounds, such as superoxide dismutase, peroxidase (POD), CAT, and glutathione peroxidase (GPx), to combat free radicals and oxidative stress [52, 107]. Enzymatic antioxidants and nonenzymatic antioxidants, such as vitamin E, vitamin C, polyphenols, and melanin, play crucial roles in neutralizing free radicals and protecting cells and tissues [6]. The antioxidant system functions by capturing free radicals, repairing damaged molecules and cells, and regenerating antioxidant molecules. However, enzymatic antioxidants face limitations in terms of stability, availability, and half-life. Ren et al. [107] developed a biohybrid dressing with microneedles containing CAT in the inner layer to address oxidative stress, promote fibroblast proliferation, inhibit proinflammatory macrophage polarization, and enhance epithelialization in diabetic wounds. Some nonantioxidant enzymatic substances are also used in anti-inflammatory microneedles and indirectly exert anti-inflammatory effects through catalysis or interactions with other molecules. For example, Zhang et al. [52] designed and fabricated a self-powered, enzyme-coated microneedle patch consisting of anode and cathode MN arrays respectively containing glucose oxidase (GOx) and horseradish peroxidase (HRP) encapsulated in ZIF-8 nanoparticles that can generate stable and sustained currents by consuming blood glucose to reduce the blood glucose concentration around the wound. This patch also has excellent antimicrobial properties and efficiently suppresses inflammation. To increase the stability, availability, and half-life of enzymatic antioxidants, artificial enzymes have been developed. These artificial enzymes include metal-based nanomaterials, such as graphene oxide–silver nanocomposites [85], PBN [13], ZCO [32], Au–Cu2MoS4 nanosheets [81], and SeC@PA [56]. Nanoparticles such as ZnO particles [55], AgNPs [53], Fe2C nanoparticles [83], graphene oxide (GO) particles [30], and PDA particles [108] are also utilized. Natural antioxidants such as total saponins from Panax notoginseng [84], Cv [29], TA [49], and gallic acid [85] are widely distributed and have shown potential in promoting wound healing. Furthermore, amino acids and their derivatives, such as NAC and arginine derivatives, have been found to combat excessive ROS generation and stimulate angiogenesis [6].

Natural and artificial antioxidants are crucial for enhancing diabetic wound healing, leading to a surge in interest in antioxidant-based wound dressings. Among these, microneedles are particularly noteworthy for their potent antioxidant properties. Antioxidant microneedles include those containing antioxidants as well as those generated from antioxidant polymers or similar materials. In a prior study, Yin et al. successfully loaded gallic acid onto microneedle patches using magnesium organic frameworks for diabetic wounds. This approach enabled the slow release of gallic acid into the deep dermis, effectively clearing excessive ROS, promoting antioxidant activity, and accelerating wound healing [85]. Subsequent research has increasingly focused on developing various antioxidant microneedles for diabetic wounds to address ROS accumulation and modulate the wound microenvironment. Ma et al. [33] encapsulated PDA NPs in the outer methacrylated HAMA shell of the MN tip. As the HAMA patch tip gradually degrades in the skin, PDA NPs are continuously released in the diabetic wound to inhibit ROS-induced inflammation. The hair-derived HMP designed by Zhang et al. [16] showed the ability to scavenge ROS, thereby preventing ROS-induced damage to blood vessels. Yang et al. [32] embedded HA microneedles into cerium/ZCO to produce ZCO-H, which can disrupt the oxidative balance of bacteria and kill bacteria by regulating the release of Zn^{2+} and $Ce^{3+/4+}$. This helps scavenge ROS and relieve oxidative stress. GPx is an important endogenous POD, and Se is a component of the GPx enzyme system. Yang et al. [56] designed an SeC@PA MN bandage; after being delivered to highly inflamed wound tissue, SeC@PA exhibited notable antioxidant effects by rapidly clearing RS and enhancing GPx activity. POD plays an important antioxidant role in cells. Sun et al. [53] encapsulated calcium peroxide and POD at the MN tip, allowing it to release oxygen continuously and inhibit the

production of reactive oxygen species. These existing studies have shown that antioxidant microneedles have efficient and stable antioxidant capabilities, scavenge ROS, and accelerate diabetic wound healing.

Angiogenesis-promoting microneedles

During the wound healing process, the formation of new blood vessels is essential, as it provides the necessary nutrients and oxygen for healing, eliminates metabolic waste, and facilitates the transportation of cells, growth factors, and signaling molecules crucial for repair [109]. In patients with diabetes, angiogenesis is often compromised due to vascular dysfunction caused by chronic hyperglycemia [82]. Therefore, promoting revascularization in the wound area is crucial for diabetic wound healing. Key regulatory factors include hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF). HIF-1α controls gene expression under hypoxic conditions, facilitating angiogenesis and cell metabolism adaptation, whereas VEGF is a vital regulator of angiogenesis and enhances blood circulation [16, 87, 107]. Currently, growth factors such as VEGF, bFGF, and EGF are extensively utilized in tissue engineering to promote angiogenesis [6].

HIF-1α serves as a crucial regulator of angiogenesis, but prolonged hyperglycemia can disrupt its function along with that of its target genes, such as VEGF, thereby hindering neovascularization. Ren et al. [107] introduced a bilayered, biohybrid MN-based dressing that leverages the unique properties of pineapple leaves, such as photosynthesis and self-drainage, in combination with the therapeutic effects of artificial materials capable of glucose degradation and ROS scavenging. The chloroplasts within this dressing generate ample oxygen to increase the amount of GOx-catalyzed glucose degradation, leading to a reduction in local glucose levels and the stabilization of HIF-1α, consequently promoting angiogenesis. Additionally, DFO can stabilize HIF-1α, increase VEGF secretion, and thereby facilitate vascular regeneration [110]. Gao et al. [28] utilized a blend of chitosan and silk fibroin embedded with the angiogenic drug DFO as a substrate for MNs, resulting in remarkable proangiogenic properties. Growth factors play crucial roles in promoting cell proliferation, differentiation, and tissue repair, which are essential for maintaining tissue health and supporting wound healing [111]. However, the direct application of growth factors to diabetic wounds faces challenges such as rapid degradation, limited penetration into target tissue, and potential side effects from high dosages [16]. Microneedle technology offers a promising solution by enhancing the stability and local concentration of growth factors in diabetic wound treatment, thus reducing side effects. For instance, Zhang et al. [16] successfully incorporated VEGF and bFGF into microneedles, improving drug permeability. The application of these microneedles in a diabetic wound rat model significantly enhanced angiogenesis in the wound and accelerated healing. Similarly, Guan et al. [13] utilized silk fibroin methacryloyl to encapsulate VEGF in microneedles, resulting in controlled release, reduced toxicity, and enhanced efficacy. An evaluation of the sustained drug release capability of microneedle patches using FITC-BSA as a marker revealed approximately 40% release within 12 hours and 93% release within 6 days, indicating sustained drug release. In vitro experiments revealed that microneedles attenuated the adverse effects of high glucose on HUVEC migration and tube formation by releasing VEGF, a result corroborated by in vivo animal studies showing improved blood vessel density and faster wound healing in the VEGF group.

Tazarotene, a retinoic acid drug, has been shown to effectively promote angiogenesis, hair follicle formation, and collagen regeneration in wound repair [15, 112]. However, its limited application is hindered by poor water solubility and low transdermal efficiency. Exosomes, nanoscale vesicles secreted by cells, have the potential to carry a variety of biomolecules and regulate angiogenesis [113]. However, the direct use of exosomes in the treatment of diabetic wounds faces challenges such as dose control, targeting, and stability [114]. Microneedles offer a solution by enabling the controlled release of tazarotene and exosomes directly at the wound site, improving stability and biological activity. Yuan et al. [15] encapsulated exosomes and tazarotene in microneedles made from GelMA and PEGDA to increase their effectiveness. Their study demonstrated that the microneedles facilitated targeted drug and exosome release in diabetic mouse models, accelerating cell proliferation, migration, and angiogenesis both in vitro and in vivo. While progress has been made in microneedle research for promoting angiogenesis, further investigation is needed to develop biomimetic microneedles that fully leverage the biological environment of diabetic wounds to enhance tissue repair.

Neural repair and regeneration-promoting microneedles

Diabetic peripheral neuropathy is a multifactorial condition characterized by sensory, motor, and autonomic neuropathy resulting from diabetes. These neuropathies lead not only to a loss of protective sensation and foot deformities but also to the formation of calluses, which increase the susceptibility of the foot to minor trauma and inflammation during weight-bearing activities. This progression may ultimately result in the development of full-thickness ulcers [4]. Consequently, addressing the nerve damage and promoting nerve repair or regeneration are urgent challenges that must be addressed in the treatment of diabetic foot ulcers.

In recent years, microneedling has demonstrated potential in the field of nerve repair. Although related research is still in its early stages, findings indicate that microneedles can positively influence nerve regeneration and repair by stimulating local tissue and facilitating localized drug delivery. For example, the surface microneedle electrode designed by Soltanzadeh et al. for peripheral nerve ES employs the biocompatible metal molybdenum as the conductive layer. This design effectively reduces contact resistance and increases the low-frequency bandwidth and current density, thereby providing an improved solution for transcutaneous nerve stimulation [115]. Notably, the bionic microneedle nerve guidance catheter developed by Hu et al. integrates microneedle and microchannel technology to replicate the structure and piezoelectric function of sea cucumbers. By incorporating specific nanoparticles into polycaprolactone scaffolds, the electrical conductivity and piezoelectric properties are enhanced, thereby facilitating remyelination and axonal growth during nerve repair [116]. Additionally, the self-powered, enzyme-linked microneedle nerve conduit encapsulating GOx and HRP designed by Zhang et al. generates a microcurrent through an enzymatic cascade reaction, significantly accelerating the repair of sciatic nerve damage [117]. Recently, research by Cai et al. has further advanced the application of microneedle therapy in

diabetic wound healing. They utilized CAT as a biological template to synthesize microneedles with enhanced enzymatic activity and antibacterial properties. This microneedle not only promotes angiogenesis and nerve regeneration by increasing M2 macrophage levels and reducing levels of the proinflammatory cytokine TNF-α but also effectively facilitates the healing of diabetic wounds [91].

While current research has demonstrated the potential of microneedling for nerve repair and regeneration, studies focusing on its application for diabetic wound treatment remain relatively rare. In the future, with ongoing technological advancements and more comprehensive research, it is anticipated that microneedle therapy will play a more significant role in nerve repair and regeneration, thereby offering more effective treatment options for diabetic patients.

Synergistic microneedle therapy

Diabetic wounds are characterized by persistent inflammation, excessive oxidative stress, impaired angiogenesis, and bacterial infections [6]. Traditional microneedle patches face challenges in targeting multiple aspects simultaneously for diabetic wound treatment. To address this issue, researchers have developed multifunctional microneedles that accelerate the healing of diabetic wounds. These microneedles play crucial roles in promoting wound recovery through various mechanisms, such as anti-inflammatory effects, immunoregulation, antioxidant properties, proangiogenic effects, and antibacterial defense. Combining these strategies has been shown to have a synergistic effect, offering a more effective therapeutic approach for diabetic wound healing. Building on previous studies [57], this paper presents a concise overview of the latest research on synergistic microneedle treatments for diabetic wounds.

Synergy between microneedle functions. The complex microenvironment of diabetic wounds necessitates multifaceted treatment strategies that integrate antibacterial, anti-inflammatory, immunomodulatory, antioxidant, and proangiogenic approaches to expedite healing. Bacterial infections pose considerable therapeutic obstacles, particularly when the protective barrier of the skin is compromised, rendering wounds susceptible to microbial invasion. Antimicrobial microneedling has emerged as a pivotal tool for addressing diabetic wound infections. Nonetheless, given the chronic nature of diabetic wounds, solely focusing on antibacterial treatment is insufficient for comprehensive healing. To address this, the research team combined antibacterial agents with other therapies to target the distinctive microenvironment of diabetic wounds, such as excessive ROS and inflammatory mediators, prolonged inflammation, inadequate angiogenesis, and M1 macrophage activity [83]. For example, the MN patch developed by Sun et al. [53] incorporates calcium peroxide and CAT to continuously release oxygen, diminish ROS levels, increase cell proliferation and migration, facilitate M2 macrophage polarization, and stimulate blood vessel formation, thereby expediting wound healing. Moreover, the AgNPs in the patch effectively combat microbial infections and support wound healing. Yang et al.'s [56] SeC@PA MN bandage not only eradicates bacterial biofilms but also induces M2 macrophage polarization, demonstrating anti-inflammatory properties. The ZCO-HA reported by Yang et al. [32] effectively eradicates bacteria, reduces ROS levels, diminishes inflammation via the NF-κB pathway, and promotes cell proliferation and blood vessel formation by modulating the release of zinc ions and cerium ions. These studies illustrate that the synergistic effects of microneedles, when combined with diverse functional strategies, can significantly enhance diabetic wound healing.

Synergy between multifunctional microneedles and electrotherapy. Exogenous ES at the wound site has been shown to expedite the wound healing process by facilitating cell proliferation and migration, as well as by promoting angiogenesis and collagen deposition [118–120]. Triboelectric nanogenerators (TENGs) are commonly used as effective ES devices because of their flexibility, wear resistance, light weight, low cost, comfort, and biocompatibility [49, 121]. However, ES alone may not be adequate to effectively enhance diabetic wound healing. In response, Li et al. [49] introduced a novel integrated self-powered microneedle device named TZ@mMN-TENG, which incorporates tannins, ZnO particles, and TENG technology. In vitro experiments demonstrated that TZ@mMN has remarkable conductivity, antioxidant properties, and antibacterial capabilities. In a diabetic rat model with full-thickness skin wounds infected with *S. aureus*, TZ@mMN-TENG was able to eradicate bacteria, expedite epidermal growth, increase collagen deposition, reduce inflammation, and promote angiogenesis (as evidenced by increased CD31 and VEGF expression), ultimately accelerating healing of the infected wounds.

Synergy between multifunctional microneedles and phototherapy. Infrared light-induced PTT effectively utilizes specific wavelengths of light to kill bacteria and accelerate wound healing [122, 123]. HMPs extracted from hair are used as photothermal agents because of their cost-effectiveness, low immunogenicity, high conversion rate, and good biocompatibility [55]. This makes them ideal for use in developing photothermal wound dressings. The microneedle dressing developed by Cai et al. [55] combines PSBMA and HMPs to create an antimicrobial barrier that uses light and heat to promote wound healing. Additionally, the dressing contains ZnO NPs and asiaticoside, which are released as the microneedle degrades, exerting antibacterial and anti-inflammatory effects to aid in tissue regeneration. In a rat model of diabetic wounds infected with *S. aureus*, this dressing combined drug delivery and photothermal therapy to accelerate tissue regeneration, collagen deposition, and overall wound healing. Yao et al. [30] reported that MOF MNs exhibit an photothermal response to infrared exposure that enables the controlled release of NO molecules. Owing to their porous structure, larger specific surface area, and sufficient mechanical strength, MNs facilitate the more accurate and deeper delivery of NO molecules to wounds. Similarly, Zhang et al.'s [16] near-infrared-responsive MN patch offers painless, accurate, and controllable drug delivery to limbs under near-infrared radiation. Research indicates that mild heat can increase the proliferation of human ECs, leading to increased new blood vessel density. Zeng et al. [12] developed a photosensitive MN incorporating exosomes and PDA that synergistically generates a mild photothermal effect under 808 nm laser irradiation. This approach inhibits inflammation and promotes angiogenesis and granulation tissue formation.

Synergy between multifunctional microneedles and photobiomodulation. Recently developed wound dressings containing GOx have shown promising results in reducing hyperglycemia and controlling bacteria by releasing hydrogen

Table 3. Challenges, solutions, and prospects of microneedle therapy

Type	Challenges	Solution	Prospect
Multi-functional microneedle	Complexity, long-term efficacy, compatibility, and safety.	Adopting modular design or smart materials technology, high biocompatibility materials, and rigorous laboratory testing and clinical trials.	Broad development prospects: significant therapeutic effects, personalized medicine, integration of smart technology, standardization of clinical applications, and reasonable pricing.
Multi-functional microneedles and electrotherapy	Stability, safety, intensity, frequency, and compatibility of the electric current.	Integrated power technology, intelligent control, and interdisciplinary collaboration.	
Multi-functional microneedles and phototherapy	Integration of light sources, light efficacy, and deep tissue penetration.	Efficient light sources, optical design, and personalized adjustments.	
Multi-functional microneedles and photobiomodulation	Stability of photobiomodulation, high complexity, and lack of standardized protocols for plant-based applications.	Unified standards, improved stability, and simplified design.	

peroxide (H_2O_2) [7]. However, the potential for H_2O_2 to cause oxidative damage and inflammation poses a challenge. To address this issue, researchers have proposed a novel approach that involves the use of oxygen produced through plant photosynthesis to neutralize H_2O_2. By creating microneedles that combine these elements, the concentration of H_2O_2 in the wound area can be effectively controlled, leading to improved wound healing outcomes without excessive oxidative damage or inflammation. For example, Ren et al. [107] leveraged the photosynthetic and self-draining properties of pineapple leaves, along with the glucose degradation and ROS scavenging capabilities of artificial materials. Chloroplast-rich pineapple leaves generate ample amounts of oxygen, enhancing the breakdown of glucose catalyzed by GOx. This process reduces local glucose levels, stabilizes HIF-1α, promotes angiogenesis, and eliminates wound bacteria through hydrogen peroxide production. Moreover, the conductive tissue of the leaves aids in draining excess wound exudate, creating an optimal microenvironment for wound healing. Similarly, Zhao et al. [29] incorporated Cv into MNs to continuously produce and release oxygen in a controlled, eco-friendly manner. This innovative approach harnesses the unique biological properties of plants to offer a promising strategy for wound healing.

The complex characteristics of diabetic wounds can be effectively addressed by the use of multifunctional microneedles in combination with electrotherapy, phototherapy, photosynthesis, and other treatment methods. These strategies combine antibacterial, anti-inflammatory, immunomodulatory, antioxidant, and proangiogenic functions to target the unique microenvironment of diabetic wounds. By eliminating bacterial infection, reducing the inflammatory response, and promoting angiogenesis and cell proliferation, the wound healing process is accelerated. This comprehensive strategy not only overcomes the limitations of individual treatments but also provides an effective solution for addressing complex diabetic wound infections and promoting healing. Despite the significant potential demonstrated by these combined therapies, several research limitations remain. The primary issues include the following: the stability and consistency of the therapeutic effects have not been fully verified; the combined use of different treatment modalities may introduce unknown safety and biocompatibility concerns; the costs associated with complex equipment and the operational challenges in practical applications need to be addressed; and existing studies generally focus on short-term effects, whereas long-term effects and sustained stability require further investigation.

Current advantages and limitations of microneedles

Multifunctional microneedle technology has demonstrated significant advantages in the treatment of diabetic wounds (Table 1). First, these microneedles can address multiple aspects of wound care, including through anti-inflammatory, antibacterial, and antioxidant properties, as well as by promoting angiogenesis and nerve regeneration. This holistic treatment approach simultaneously addresses various challenges in the wound healing process, leading to improved overall outcomes. Second, microneedle technology is minimally invasive, which reduces patient discomfort and the risk of infection, making it safer and more convenient than traditional treatment methods. Furthermore, the combination of microneedling with other therapies, such as electrotherapy or light therapy, can create a synergistic effect that further accelerates the wound healing process.

While multifunctional microneedles offer numerous advantages in the treatment of diabetic wounds, their design and application face several challenges (Table 3). First, the design and manufacturing processes for these microneedles are complex, necessitating the integration of multiple therapeutic agents and technologies, which can result in high production costs and technical difficulties. Second, the stability and compatibility of various therapeutic agents require careful consideration to ensure their effectiveness and safety throughout the treatment duration. Furthermore, there is currently a lack of sufficient clinical evidence supporting the use of these microneedles, as extensive clinical trial data to confirm their long-term efficacy and safety are limited, potentially hindering their broader clinical application.

To fully realize the potential of multifunctional microneedles, future research should focus on several key aspects. First, optimizing the design and materials of microneedles is essential to increase their stability, efficacy, and biocompatibility while also reducing production costs. Second, additional clinical trials are necessary to gather sufficient safety and efficacy data to facilitate the clinical application of these microneedles. Furthermore, the integration of advanced technologies, such as nanotechnology and smart drug delivery systems, could significantly increase the functionality and

precision of microneedles. Concurrently, the development of personalized microneedle systems that provide customized treatments tailored to the specific needs of various patients and wounds will contribute to improved treatment outcomes. Finally, it is critical to establish clear regulatory guidelines and safety frameworks for the development and application of multifunctional microneedles to ensure their safety and effectiveness in clinical practice.

Conclusions

The treatment of diabetic wounds presents several challenges, including chronic inflammation, excessive oxidative stress, impaired angiogenesis, peripheral nerve damage, and frequent bacterial infections, all of which contribute to poor outcomes with traditional treatment methods. The emergence of MN technology in recent years has offered new approaches to address these challenges. By combining multiple therapeutic mechanisms, such as those based on antimicrobial, anti-inflammatory, immunomodulatory, antioxidant, and proangiogenic properties, multifunctional microneedles demonstrate high capability for effectively treating diabetic wounds. Their unique design significantly enhances treatment outcomes. The use of multifunctional microneedles provides advantages such as painlessness, a minimally invasive nature, ease of self-management, and simple operation, improving patient acceptance and compliance, while reducing the burden on the health care system. Additionally, microneedle technology allows for precise drug delivery, facilitating deeper penetration into skin layers than can be achieved by traditional bandages and hydrogels, thereby increasing drug delivery efficiency and bioavailability. Importantly, peripheral neuropathy plays a crucial role in hindering the healing of diabetic wounds; however, research on microneedle therapy targeting nerve damage is limited. Future studies could focus on developing new microneedles specifically tailored for treating neuropathy, thus making diabetic wound treatment more comprehensive and effective. Furthermore, continuous development and innovation in new materials and technologies are anticipated to lead to the creation of more efficient and safer microneedle systems, enabling the development of personalized and precise treatment plans for diabetic wounds. Interdisciplinary collaboration among the fields of materials science, nanotechnology, biomedical engineering, and clinical medicine will play a crucial role in advancing microneedle technology. Particularly in the complex treatment landscape of diabetic wounds, comprehensive approaches based on multifunctional microneedles surpass traditional methods, demonstrating unique therapeutic potential and promising broad application prospects.

Acknowledgements

We would like to thank Figraw (www.figdraw.com) for providing the platform for figure production.

Author contributions

Xichao Jian (Methodology [equal], Writing—original draft [lead], Writing—review & editing [lead]), Yaping Deng (Writing—review & editing [supporting]), Shune Xiao (Writing—review & editing [supporting]), Fang Qi (Conceptualization [equal], Data Curation [equal], Formal Analysis [equal], Project Administration [equal], Resources [equal]), Chengliang Deng (Conceptualization [equal], Data Curation [equal], Formal Analysis [equal], Funding Acquisition [equal], Project Administration [equal], Resources [equal]).

Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

Funding

This study was supported by the National Natural Science Foundation of China (82203902), and the Projects of Science and Technology Program of Guizhou Province (ZK2021–011).

Conflict of interest

The authors declare no competing or financial interests.

References

1. Peña OA, Martin P. Cellular and molecular mechanisms of skin wound healing. *Nat Rev Mol Cell Biol* 2024;**25**:599–616. https://doi.org/10.1038/s41580-024-00715-1.
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition. *Diabetes Res Clin Pract* 2019;**157**:107843. https://doi.org/10.1016/j.diabres.2019.107843.
3. Ong KL, Stafford LK, McLaughlin SA, Boyko EJ, Vollset SE, Smith AE, *et al.* Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet* 2023;**402**:203–34. https://doi.org/10.1016/S0140-6736(23)01301-6.
4. Armstrong DG, Tan T-W, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. *JAMA* 2023;**330**:62–75. https://doi.org/10.1001/jama.2023.10578.
5. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, *et al.* Global and regional estimates and projections of diabetes-related health expenditure: results from the international diabetes federation diabetes atlas, 9th edition. *Diabetes Res Clin Pract* 2020;**162**:108072. https://doi.org/10.1016/j.diabres.2020.108072.
6. Xiang T, Guo Q, Jia L, Yin T, Huang W, Zhang X, *et al.* Multifunctional hydrogels for the healing of diabetic wounds. *Adv Healthcare Materials*. 2024;**13**:2301885. https://doi.org/10.1002/adhm.202301885.
7. Wang L, Chen G, Fan L, Chen H, Zhao Y, Lu L, *et al.* Biomimetic enzyme Cascade structural color hydrogel microparticles for diabetic wound healing management. *Advanced Science* 2023;**10**:e2206900. https://doi.org/10.1002/advs.202206900.
8. Liu L, Liu D. Bioengineered mesenchymal stem cell-derived exosomes: emerging strategies for diabetic wound healing. *Burns & Trauma* 2024;**12**:tkae030. https://doi.org/10.1093/burnst/tkae030.
9. Uberoi A, McCready-Vangi A, Grice EA. The wound microbiota: microbial mechanisms of impaired wound healing and infection. *Nat Rev Microbiol* 2024;**22**:507–21. https://doi.org/10.1038/s41579-024-01035-z.
10. Hu Z, Shan J, Cui Y, Cheng L, Chen X, Wang X. Nanozyme-incorporated microneedles for the treatment of chronic wounds. *Adv Healthcare Materials*. 2024;**13**:e2400101. https://doi.org/10.1002/adhm.202400101.

11. Huang X, Niu X, Ma Y, Wang X, Su T, He Y, *et al.* Hierarchical double-layer microneedles accomplish multicenter skin regeneration in diabetic full-thickness wounds. *J Adv Res* 2024;S2090-1232(24)00002-X. https://doi.org/10.1016/j.jare.2024.01.002.
12. Zeng J, Sun Z, Zeng F, Gu C, Chen X. M2 macrophage-derived exosome-encapsulated microneedles with mild photothermal therapy for accelerated diabetic wound healing. *Mater Today Bio* 2023;**20**:100649. https://doi.org/10.1016/j.mtbio.2023.100649.
13. Guan G, Zhang Q, Jiang Z, Liu J, Wan J, Jin P, *et al.* Multifunctional silk fibroin Methacryloyl microneedle for diabetic wound healing. *Small* 2022;**18**:e2203064. https://doi.org/10.1002/smll.202203064.
14. Liu T, Sun Y, Jiang G, Zhang W, Wang R, Nie L, *et al.* Porcupine-inspired microneedles coupled with an adhesive back patching as dressing for accelerating diabetic wound healing. *Acta Biomater* 2023;**160**:32–44. https://doi.org/10.1016/j.actbio.2023.01.059.
15. Yuan M, Liu K, Jiang T, Li S, Chen J, Wu Z, *et al.* GelMA/PEGDA microneedles patch loaded with HUVECs-derived exosomes and Tazarotene promote diabetic wound healing. *J Nanobiotechnol* 2022;**20**:147. https://doi.org/10.1186/s12951-022-01354-4.
16. Zhang J, Liu H, Yu Q, Zhan Z, Li T, Shu L, *et al.* Hair derived microneedle patches for both diabetic foot ulcer prevention and healing. *ACS Biomater Sci Eng* 2023;**9**:363–74. https://doi.org/10.1021/acsbiomaterials.2c01333.
17. Ali MS, Buddhiraju HS, Gubige M, Basa A, Gupta K G, Veeresh B, *et al.* Multifunctional Nanosystem for dual anti-inflammatory and antibacterial photodynamic therapy in infectious diabetic wounds. *ACS Infect Dis* 2024;**10**:2978–90. https://doi.org/10.1021/acsinfecdis.4c00306.
18. Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, *et al.* Practical guidelines on the prevention and management of diabetes-related foot disease (IWGDF 2023 update). *Diabetes Metabolism Res* 2024;**40**:e3657. https://doi.org/10.1002/dmrr.3657.
19. Moghaddam Ahmadi M, Ashoobi MT, Darabi Z, Ramezannezhad H, Moghaddam AM. Characteristics and outcomes of diabetic foot ulcers treated with surgical debridement and standardized wound care. *Int Wound J* 2024;**21**:e14859. https://doi.org/10.1111/iwj.14859.
20. Zhao C, Wu Z, Pan B, Zhang R, Golestani A, Feng Z, *et al.* Functional biomacromolecules-based microneedle patch for the treatment of diabetic wound. *Int J Biol Macromol* 2024;**267**:131650. https://doi.org/10.1016/j.ijbiomac.2024.131650.
21. Älgå A, Löfgren J, Haweizy R, Bashaireh K, Wong S, Forsberg BC, *et al.* Cost analysis of negative-pressure wound therapy versus standard treatment of acute conflict-related extremity wounds within a randomized controlled trial. *World J Emerg Surg* 2022;**17**:9. https://doi.org/10.1186/s13017-022-00415-1.
22. Capó X, Monserrat-Mesquida M, Quetglas-Llabrés M, Batle JM, Tur JA, Pons A, *et al.* Hyperbaric oxygen therapy reduces oxidative stress and inflammation, and increases growth factors favouring the healing process of diabetic wounds. *IJMS* 2023;**24**:7040. https://doi.org/10.3390/ijms24087040.
23. Parnis J, Magrin AMF, Hassan H. The role, safety, and efficacy of hyperbaric oxygen therapy in aesthetic practice—An evidence-based review. *J of Cosmetic Dermatology* 2024;**23**:1940–55. https://doi.org/10.1111/jocd.16228.
24. Sen S, Sen S. Therapeutic effects of hyperbaric oxygen: integrated review. *Medical Gas Research* 2021;**11**:30–3. https://doi.org/10.4103/2045-9912.310057.
25. Ou C-Y, Wu M-S, Lin M-C, Chang C-M. Short-term and long-term outcomes of free flap reconstruction versus amputation for diabetic foot reconstruction in patients with end-stage renal disease. *J Plast Reconstr Aesthet Surg* 2022;**75**:2511–9. https://doi.org/10.1016/j.bjps.2022.04.024.
26. Ji W, Li B, Li N, Xing C. Design strategy of microneedle Systems for Skin Wound Healing: based on the structure of tips and therapeutic methodologies. *ACS Appl Bio Mater* 2024;**7**:4254–69. https://doi.org/10.1021/acsabm.4c00532.
27. Yang SY, O'Cearbhaill ED, Sisk GC, Park KM, Cho WK, Villiger M, *et al.* A bio-inspired swellable microneedle adhesive for mechanical interlocking with tissue. *Nat Commun* 2013;**4**:1702. https://doi.org/10.1038/ncomms2715.
28. Gao S, Zhang W, Zhai X, Zhao X, Wang J, Weng J, *et al.* An antibacterial and proangiogenic double-layer drug-loaded microneedle patch for accelerating diabetic wound healing. *Biomater Sci* 2023;**11**:533–41. https://doi.org/10.1039/D2BM01588A.
29. Zhao E, Xiao T, Tan Y, Zhou X, Li Y, Wang X, *et al.* Separable microneedles with photosynthesis-driven oxygen manufactory for diabetic wound healing. *ACS Appl Mater Interfaces* 2023;**15**:7725–34. https://doi.org/10.1021/acsami.2c18809.
30. Yao S, Wang Y, Chi J, Yu Y, Zhao Y, Luo Y, *et al.* Porous MOF microneedle Array patch with Photothermal responsive nitric oxide delivery for wound healing. *Advanced Science* 2022;**9**:e2103449. https://doi.org/10.1002/advs.202103449.
31. Wang P, Wu J, Yang H, Liu H, Yao T, Liu C, *et al.* Intelligent microneedle patch with prolonged local release of hydrogen and magnesium ions for diabetic wound healing. *Bioactive Materials*. 2023;**24**:463–76. https://doi.org/10.1016/j.bioactmat.2023.01.001.
32. Yang J, Chu Z, Jiang Y, Zheng W, Sun J, Xu L, *et al.* Multifunctional hyaluronic acid microneedle patch embedded by cerium/zinc-based composites for accelerating diabetes wound healing. *Adv Healthcare Materials* 2023;**12**:e2300725. https://doi.org/10.1002/adhm.202300725.
33. Ma W, Zhang X, Liu Y, Fan L, Gan J, Liu W, *et al.* Polydopamine decorated microneedles with Fe-MSC-derived Nanovesicles encapsulation for wound healing. *Advanced Science*. 2022;**9**:e2103317. https://doi.org/10.1002/advs.202103317.
34. Vulliamy P, Armstrong PC. Platelets in Hemostasis, thrombosis, and inflammation after major trauma. *ATVB* 2024;**44**:545–57. https://doi.org/10.1161/ATVBAHA.123.318801.
35. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev* 2019;**99**:665–706. https://doi.org/10.1152/physrev.00067.2017.
36. Barnum L, Samandari M, Schmidt TA, Tamayol A. Microneedle arrays for the treatment of chronic wounds. *Expert Opin Drug Deliv* 2020;**17**:1767–80. https://doi.org/10.1080/17425247.2020.1819787.
37. Jin Y, Huang Y, Zeng G, Hu J, Li M, Tian M, *et al.* Advanced glycation end products regulate macrophage apoptosis and influence the healing of diabetic foot wound through miR-361-3p/CSF1R and PI3K/AKT pathway. *Heliyon* 2024;**10**:e24598. https://doi.org/10.1016/j.heliyon.2024.e24598.
38. Wan L, Bai X, Zhou Q, Chen C, Wang H, Liu T, *et al.* The advanced glycation end-products (AGEs)/ROS/NLRP3 inflammasome axis contributes to delayed diabetic corneal wound healing and nerve regeneration. *Int J Biol Sci* 2022;**18**:809–25. https://doi.org/10.7150/ijbs.63219.
39. Chang M, Nguyen TT. Strategy for treatment of infected diabetic foot ulcers. *Acc Chem Res* 2021;**54**:1080–93. https://doi.org/10.1021/acs.accounts.0c00864.
40. Tuan-Mahmood T-M, McCrudden MTC, Torrisi BM, McAlister E, Garland MJ, Singh TRR, *et al.* Microneedles for intradermal and transdermal drug delivery. *Eur J Pharm Sci* 2013;**50**:623–37. https://doi.org/10.1016/j.ejps.2013.05.005.
41. Ahmed Saeed AL-Japairai K, Mahmood S, Hamed Almurisi S, Reddy Venugopal J, Rebhi Hilles A, Azmana M, *et al.* Current trends in polymer microneedle for transdermal drug delivery. *Int J Pharm* 2020;**587**:119673. https://doi.org/10.1016/j.ijpharm.2020.119673.
42. Rajput A, Kulkarni M, Deshmukh P, Pingale P, Garkal A, Gandhi S, *et al.* A key role by polymers in microneedle technology: a new era. *Drug Dev Ind Pharm* 2021;**47**:1713–32. https://doi.org/10.1080/03639045.2022.2058531.
43. Omolu A, Bailly M, Day RM. Assessment of solid microneedle rollers to enhance transmembrane delivery of doxycycline and

inhibition of MMP activity. *Drug Delivery* 2017;**24**:942–51. https://doi.org/10.1080/10717544.2017.1337826.
44. Pamornpathomkul B, Wongkajornsilp A, Laiwattanapaisal W, Rojanarata T, Opanasopit P, Ngawhirunpat T. A combined approach of hollow microneedles and nanocarriers for skin immunization with plasmid DNA encoding ovalbumin. *IJN* 2017;**Volume 12**:885–98. https://doi.org/10.2147/IJN.S125945.
45. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, *et al.* Microneedles: a smart approach and increasing potential for transdermal drug delivery system. *Biomed Pharmacother* 2019;**109**:1249–58. https://doi.org/10.1016/j.biopha.2018.10.078.
46. Guo Z, Liu H, Shi Z, Lin L, Li Y, Wang M, *et al.* Responsive hydrogel-based microneedle dressing for diabetic wound healing. *J Mater Chem B* 2022;**10**:3501–11. https://doi.org/10.1039/D2TB00126H.
47. Gao Z, Sheng T, Zhang W, Feng H, Yu J, Gu Z, *et al.* Microneedle-mediated cell therapy. *Advanced Science*. 2024;**11**:2304124. https://doi.org/10.1002/advs.202304124.
48. Desai VM, Priya S, Gorantla S, Singhvi G. Revolutionizing therapeutic delivery with microneedle Technology for Tumor Treatment. *Pharmaceutics* 2022;**15**:14. https://doi.org/10.3390/pharmaceutics15010014.
49. Li W, Liu Z, Tan X, Yang N, Liang Y, Feng D, *et al.* All-in-one self-powered microneedle device for accelerating infected diabetic wound repair. *Adv Healthcare Materials*. 2024;**13**:2304365. https://doi.org/10.1002/adhm.202304365.
50. Chen BZ, Ashfaq M, Zhang XP, Zhang JN, Guo XD. In vitro and in vivo assessment of polymer microneedles for controlled transdermal drug delivery. *J Drug Target* 2018;**26**:720–9. https://doi.org/10.1080/1061186X.2018.1424859.
51. Lee I-C, He J-S, Tsai M-T, Lin K-C. Fabrication of a novel partially dissolving polymer microneedle patch for transdermal drug delivery. *J Mater Chem B* 2015;**3**:276–85. https://doi.org/10.1039/C4TB01555J.
52. Zhang X, Wang Z, Jiang H, Zeng H, An N, Liu B, *et al.* Self-powered enzyme-linked microneedle patch for scar-prevention healing of diabetic wounds. *Sci Adv* 2023;**9**:eadh1415. https://doi.org/10.1126/sciadv.adh1415.
53. Sun M, Zhong X, Dai M, Feng X, Tang C, Cao L, *et al.* Antibacterial microneedle patch releases oxygen to enhance diabetic wound healing. *Materials Today Bio* 2024;**24**:100945. https://doi.org/10.1016/j.mtbio.2024.100945.
54. Liu Y, Xia G, Chen Y, Xia H, Xu J, Guo L, *et al.* Purpurolide C-based microneedle promotes macrophage-mediated diabetic wound healing via inhibiting TLR4-MD2 dimerization and MYD88 phosphorylation. *Acta Pharm Sin B* 2023;**13**:5060–73. https://doi.org/10.1016/j.apsb.2023.05.032.
55. Cai Y, Xu X, Wu M, Liu J, Feng J, Zhang J. Multifunctional zwitterionic microneedle dressings for accelerated healing of chronic infected wounds in diabetic rat models. *Biomater Sci*. 2023;**11**:2750–8. https://doi.org/10.1039/D2BM02101C.
56. Yang L, Zhang D, Li W, Lin H, Ding C, Liu Q, *et al.* Biofilm microenvironment triggered self-enhancing photodynamic immunomodulatory microneedle for diabetic wound therapy. *Nat Commun* 2023;**14**:7658. https://doi.org/10.1038/s41467-023-43067-8.
57. Ghiyasi Y, Prewett PD, Davies GJ, Faraji RZ. The role of microneedles in the healing of chronic wounds. *Int J Pharm* 2023;**641**:123087. https://doi.org/10.1016/j.ijpharm.2023.123087.
58. Chi J, Zhang X, Chen C, Shao C, Zhao Y, Wang Y. Antibacterial and angiogenic chitosan microneedle array patch for promoting wound healing. *Bioactive Materials* 2020;**5**:253–9. https://doi.org/10.1016/j.bioactmat.2020.02.004.
59. Yin X, Wei J, Hou J, Xu S, Wang L. Degradable microneedle patch with Photothermal-promoted bacteria-infected wound healing and microenvironment Remodeling. *ACS Appl Mater Interfaces* 2024;**16**:32017–26. https://doi.org/10.1021/acsami.4c04414.
60. Liu X, Wang M, Cao L, Zhuang J, Wang D, Wu M, *et al.* Living artificial skin: photosensitizer and cell sandwiched bacterial cellulose for chronic wound healing. *Adv Mater* 2024;**36**:2403355. https://doi.org/10.1002/adma.202403355.
61. Hu F, Gao Q, Liu J, Chen W, Zheng C, Bai Q, *et al.* Smart microneedle patches for wound healing and management. *J Mater Chem B* 2023;**11**:2830–51. https://doi.org/10.1039/D2TB02596E.
62. Kang S, Song JE, Jun S-H, Park S-G, Kang N-G. Sugar-triggered burst drug releasing poly-lactic acid (PLA) microneedles and its fabrication based on solvent-casting approach. *Pharmaceutics*. 2022;**14**:1758. https://doi.org/10.3390/pharmaceutics14091758.
63. Ma Z, Chen Y, Tang K, Yang H, Tian M, Xi X, *et al.* Highly efficient prevention of radiation dermatitis using a PEGylated superoxide dismutase dissolving microneedle patch. *Eur J Pharm Biopharm* 2024;**201**:114347. https://doi.org/10.1016/j.ejpb.2024.114347.
64. Qi Z, Yan Z, Tan G, Jia T, Geng Y, Shao H, *et al.* Silk fibroin microneedles for transdermal drug delivery: where do we stand and how far can we proceed? *Pharmaceutics* 2023;**15**:355. https://doi.org/10.3390/pharmaceutics15020355.
65. Liu W, Zhai X, Zhao X, Cai Y, Zhang X, Xu K, *et al.* Multifunctional double-layer and dual drug-loaded microneedle patch promotes diabetic wound healing. *Adv Healthcare Materials*. 2023;**12**:e2300297. https://doi.org/10.1002/adhm.202300297.
66. Li S, Wang X, Yan Z, Wang T, Chen Z, Song H, *et al.* Microneedle patches with antimicrobial and Immunomodulating properties for infected wound healing. *Advanced Science* 2023;**10**:e2300576. https://doi.org/10.1002/advs.202300576.
67. Ganeson K, Alias AH, Murugaiyah V, Amirul A-AA, Ramakrishna S, Vigneswari S. Microneedles for efficient and precise drug delivery in cancer therapy. *Pharmaceutics* 2023;**15**:744. https://doi.org/10.3390/pharmaceutics15030744.
68. Li Y, Zhang H, Yang R, Tazrin F, Zhu C, Kaddoura M, *et al.* In-plane silicon microneedles with open capillary microfluidic networks by deep reactive ion etching and sacrificial layer based sharpening. *Sensors Actuators A Phys* 2019;**292**:149–57. https://doi.org/10.1016/j.sna.2019.04.008.
69. Sun Y, Liu J, Wang H, Li S, Pan X, Xu B, *et al.* NIR laser-triggered microneedle-based liquid band-aid for wound care. *Adv Funct Materials* 2021;**31**:2100218. https://doi.org/10.1002/adfm.202100218.
70. Evens T, Malek O, Castagne S, Seveno D, Van Bael A. Controlling the geometry of laser ablated microneedle cavities in different mould materials and assessing the replication fidelity within polymer injection moulding. *J Manuf Process* 2021;**62**:535–45. https://doi.org/10.1016/j.jmapro.2020.12.035.
71. Guo M, Wang Y, Gao B, He B. Shark tooth-inspired microneedle dressing for intelligent wound management. *ACS Nano* 2021;**15**:15316–27. https://doi.org/10.1021/acsnano.1c06279.
72. Huang J, Yang R, Jiao J, Li Z, Wang P, Liu Y, *et al.* A click chemistry-mediated all-peptide cell printing hydrogel platform for diabetic wound healing. *Nat Commun* 2023;**14**:7856. https://doi.org/10.1038/s41467-023-43364-2.
73. Biswas AA, Dhondale MR, Agrawal AK, Serrano DR, Mishra B, Kumar D. Advancements in microneedle fabrication techniques: artificial intelligence assisted 3D-printing technology. *Drug Deliv and Transl Res* 2024;**14**:1458–79. https://doi.org/10.1007/s13346-023-01510-9.
74. Zhang X, Gan J, Fan L, Luo Z, Zhao Y. Bioinspired adaptable indwelling microneedles for treatment of diabetic ulcers. *Adv Mater* 2023;**35**:e2210903. https://doi.org/10.1002/adma.202210903.
75. Liu H, Zhou X, Nail A, Yu H, Yu Z, Sun Y, *et al.* Multi-material 3D printed eutectogel microneedle patches integrated with fast customization and tunable drug delivery. *J Control Release* 2024;**368**:115–30. https://doi.org/10.1016/j.jconrel.2024.02.023.

76. Song K-Y, Zhang W-J, Behzadfar M. 3D printing redefines microneedle fabrication for transdermal drug delivery. *Biomed Eng Lett* 2024;**14**:737–46. https://doi.org/10.1007/s13534-024-00368-1.
77. Fitaihi R, Abukhamees S, Chung SH, Craig DQM. Optimization of stereolithography 3D printing of microneedle micro-molds for ocular drug delivery. *Int J Pharm* 2024;**658**:124195. https://doi.org/10.1016/j.ijpharm.2024.124195.
78. Zhang X, Chen G, Sun L, Ye F, Shen X, Zhao Y. Claw-inspired microneedle patches with liquid metal encapsulation for accelerating incisional wound healing. *Chem Eng J* 2021;**406**:126741. https://doi.org/10.1016/j.cej.2020.126741.
79. Ghelich P, Samandari M, Hassani Najafabadi A, Tanguay A, Quint J, Menon N, *et al.* Dissolvable immunomodulatory microneedles for treatment of skin wounds. *Adv Healthcare Materials* 2024;**13**:e2302836. https://doi.org/10.1002/adhm.202302836.
80. Wang P, Pu Y, Ren Y, Kong W, Xu L, Zhang W, *et al.* Enzyme-regulated NO programmed to release from hydrogel-forming microneedles with endogenous/photodynamic synergistic antibacterial for diabetic wound healing. *Int J Biol Macromol* 2023;**226**:813–22. https://doi.org/10.1016/j.ijbiomac.2022.12.063.
81. Shan J, Zhang X, Cheng Y, Song C, Chen G, Gu Z, *et al.* Glucose metabolism-inspired catalytic patches for NIR-II phototherapy of diabetic wound infection. *Acta Biomater* 2023;**157**:200–9. https://doi.org/10.1016/j.actbio.2022.12.001.
82. Wang P, Wang Y, Yi Y, Gong Y, Ji H, Gan Y, *et al.* MXenes-integrated microneedle combined with asiaticoside to penetrate the cuticle for treatment of diabetic foot ulcer. *J Nanobiotechnol* 2022;**20**:259. https://doi.org/10.1186/s12951-022-01468-9.
83. Sun C, Zhou X, Liu C, Deng S, Song Y, Yang J, *et al.* An integrated therapeutic and preventive Nanozyme-based microneedle for biofilm-infected diabetic wound healing. *Adv Healthc Mater* 2023;**12**:e2301474. https://doi.org/10.1002/adhm.202301474.
84. Ning T, Yang F, Chen D, Jia Z, Yuan R, Du Z, *et al.* Synergistically detachable microneedle dressing for programmed treatment of chronic wounds. *Adv Healthcare Materials*. 2022;**11**:e2102180. https://doi.org/10.1002/adhm.202102180.
85. Yin M, Wu J, Deng M, Wang P, Ji G, Wang M, *et al.* Multifunctional magnesium organic framework-based microneedle patch for accelerating diabetic wound healing. *ACS Nano* 2021;**15**:17842–53. https://doi.org/10.1021/acsnano.1c06036.
86. Yang Y, Fan L, Jiang J, Sun J, Xue L, Ma X, *et al.* M2 macrophage-polarized anti-inflammatory microneedle patch for accelerating biofilm-infected diabetic wound healing via modulating the insulin pathway. *J Nanobiotechnol* 2024;**22**:489. https://doi.org/10.1186/s12951-024-02731-x.
87. Wang A, Ruan X, Wang X, Ren Y, Shen C, Zhang K, *et al.* A one-stop integrated natural antimicrobial microneedles with anti-inflammatory, pro-angiogenic and long-term moisturizing properties to accelerate diabetic wound healing. *Eur J Pharm Biopharm* 2024;**203**:114448. https://doi.org/10.1016/j.ejpb.2024.114448.
88. Guo Y, Zhang C, Xie B, Xu W, Rao Z, Zhou P, *et al.* Multifunctional microneedle patch based on metal-phenolic network with Photothermal antimicrobial, ROS scavenging, immunomodulatory, and angiogenesis for programmed treatment of diabetic wound healing. *ACS Appl Mater Interfaces* 2024;**16**:33205–22. https://doi.org/10.1021/acsami.4c07091.
89. Yu D, Chen L, Yan T, Zhang Y, Sun X, Lv G, *et al.* Enhancing infected diabetic wound healing through multifunctional nanocomposite-loaded microneedle patch: inducing multiple regenerative sites. *Adv Healthcare Materials* 2024;**13**:2301985. https://doi.org/10.1002/adhm.202301985.
90. Liu M, You J, Zhang Y, Zhang L, Quni S, Wang H, *et al.* Glucose-responsive self-healing bilayer drug microneedles promote diabetic wound healing via a Trojan-horse strategy. *ACS Appl Mater Interfaces* 2024;**16**:24351–71. https://doi.org/10.1021/acsami.4c03050.
91. Cai G, Li R, Chai X, Cai X, Zheng K, Wang Y, *et al.* Catalase-templated nanozyme-loaded microneedles integrated with polymyxin B for immunoregulation and antibacterial activity in diabetic wounds. *J Colloid Interface Sci* 2024;**667**:529–42. https://doi.org/10.1016/j.jcis.2024.04.121.
92. Ding X, Yang C, Li Y, He T, Xu Y, Cheng X, *et al.* Reshaped commensal wound microbiome via topical application of *Calvatia gigantea* extract contributes to faster diabetic wound healing. *Burns & Trauma* 2024;**12**:tkae037. https://doi.org/10.1093/burnst/tkae037.
93. Bharath LP, Agrawal M, McCambridge G, Nicholas DA, Hasturk H, Liu J, *et al.* Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. *Cell Metab* 2020;**32**:44–55.e6. https://doi.org/10.1016/j.cmet.2020.04.015.
94. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science* 2020;**367**:eaau6977. https://doi.org/10.1126/science.aau6977.
95. Gensel JC, Zhang B. Macrophage activation and its role in repair and pathology after spinal cord injury. *Brain Res* 2015;**1619**:1–11. https://doi.org/10.1016/j.brainres.2014.12.045.
96. Wu G, Zhang J, Zhao Q, Zhuang W, Ding J, Zhang C, *et al.* Molecularly engineered macrophage-derived exosomes with inflammation tropism and intrinsic Heme biosynthesis for atherosclerosis treatment. *Angew Chem Int Ed Engl* 2020;**59**:4068–74. https://doi.org/10.1002/anie.201913700.
97. Kim H, Wang SY, Kwak G, Yang Y, Kwon IC, Kim SH. Exosome-guided phenotypic switch of M1 to M2 macrophages for cutaneous wound healing. *Adv Sci (Weinh)* 2019;**6**:1900513. https://doi.org/10.1002/advs.201900513.
98. Xia G-Y, Wang L-Y, Zhang J-F, Wu Y-Z, Ge G-B, Wang Y-N, *et al.* Three new polyoxygenated bergamotanes from the endophytic fungus Penicillium purpurogenum IMM 003 and their inhibitory activity against pancreatic lipase. *Chin J Nat Med* 2020;**18**:75–80. https://doi.org/10.1016/S1875-5364(20)30007-8.
99. Xue Y, Chen C, Tan R, Zhang J, Fang Q, Jin R, *et al.* Artificial intelligence-assisted bioinformatics, microneedle, and diabetic wound healing: a "new deal" of an old drug. *ACS Appl Mater Interfaces* 2022;**14**:37396–409. https://doi.org/10.1021/acsami.2c08994.
100. Qi F, Xu Y, Zheng B, Li Y, Zhang J, Liu Z, *et al.* The Core-Shell microneedle with probiotic extracellular vesicles for infected wound healing and microbial homeostasis restoration. *Small* 2024;e2401551. https://doi.org/10.1002/smll.202401551.
101. Li W, Yang N, Tan X, Liu Z, Huang Y, Yuan R, *et al.* Layer-by-layer microneedle patch with antibacterial and antioxidant dual activities for accelerating bacterial-infected wound healing. *Colloids Surf B: Biointerfaces* 2023;**231**:113569. https://doi.org/10.1016/j.colsurfb.2023.113569.
102. Dai W, Shu R, Yang F, Li B, Johnson HM, Yu S, *et al.* Engineered bio-heterojunction confers extra- and intracellular bacterial Ferroptosis and hunger-triggered cell protection for diabetic wound repair. *Adv Mater* 2024;**36**:e2305277. https://doi.org/10.1002/adma.202305277.
103. Xu Q, Chen S, Jiang L, Xia C, Zeng L, Cai X, *et al.* Sonocatalytic hydrogen/hole-combined therapy for anti-biofilm and infected diabetic wound healing. National science. *Review* 2023;**10**:nwad063. https://doi.org/10.1093/nsr/nwad063.
104. Inphonlek S, Pimpha N, Sunintaboon P. Synthesis of poly(methyl methacrylate) core/chitosan-mixed-polyethyleneimine shell nanoparticles and their antibacterial property. *Colloids Surf B: Biointerfaces* 2010;**77**:219–26. https://doi.org/10.1016/j.colsurfb.2010.01.029.
105. You K, Gao B, Wang M, Wang X, Okoro KC, Rakhimbekzoda A, *et al.* Versatile polymer-based strategies for antibacterial drug delivery systems and antibacterial coatings. *J Mater Chem B* 2022;**10**:1005–18. https://doi.org/10.1039/D1TB02417E.

106. Cui Z, Luo Q, Bannon MS, Gray VP, Bloom TG, Clore MF, *et al*. Molecular engineering of antimicrobial peptide (AMP)–polymer conjugates. *Biomater Sci* 2021;**9**:5069–91. https://doi.org/10.1039/D1BM00423A.
107. Ren X, Hou Z, Pang B, Gao C, Tang R. Photosynthetic and self-draining biohybrid dressing for accelerating healing of diabetic wound. *Adv Healthcare Materials*. 2024;**13**:e2302287. https://doi.org/10.1002/adhm.202302287.
108. Zeng Z, Jiang G, Sun Y, Aharodnikau UE, Yunusov KE, Gao X, *et al*. Rational design of flexible microneedles coupled with CaO_2 @PDA-loaded nanofiber films for skin wound healing on diabetic rats. *Biomater Sci* 2022;**10**:5326–39. https://doi.org/10.1039/D2BM00861K.
109. Yang S, Sun Y, Yan C. Recent advances in the use of extracellular vesicles from adipose-derived stem cells for regenerative medical therapeutics. *J Nanobiotechnology* 2024;**22**:316. https://doi.org/10.1186/s12951-024-02603-4.
110. Zhu Y, Chang B, Pang Y, Wang H, Zhou Y. Advances in hypoxia-inducible factor-1α stabilizer Deferoxamine in tissue engineering. *Tissue Eng Part B Rev* 2023;**29**:347–57. https://doi.org/10.1089/ten.teb.2022.0168.
111. Behm B, Babilas P, Landthaler M, Schreml S. Cytokines, chemokines and growth factors in wound healing. *Acad Dermatol Venereol* 2012;**26**:812–20. https://doi.org/10.1111/j.1468-3083.2011.04415.x.
112. Zhu Z, Liu Y, Xue Y, Cheng X, Zhao W, Wang J, *et al*. Tazarotene released from aligned electrospun membrane facilitates cutaneous wound healing by promoting angiogenesis. *ACS Appl Mater Interfaces* 2019;**11**:36141–53. https://doi.org/10.1021/acsami.9b13271.
113. Pegtel DM, Gould SJ. Exosomes. *Annu Rev Biochem* 2019;**88**:487–514. https://doi.org/10.1146/annurev-biochem-013118-111902.
114. Hao Z, Ren L, Zhang Z, Yang Z, Wu S, Liu G, *et al*. A multifunctional neuromodulation platform utilizing Schwann cell-derived exosomes orchestrates bone microenvironment via immunomodulation, angiogenesis and osteogenesis. *Bioactive Materials* 2023;**23**:206–22. https://doi.org/10.1016/j.bioactmat.2022.10.018.
115. Soltanzadeh R, Afsharipour E, Shafai C, Anssari N, Mansouri B, Moussavi Z. Molybdenum coated SU-8 microneedle electrodes for transcutaneous electrical nerve stimulation. *Biomed Microdevices* 2018;**20**:1. https://doi.org/10.1007/s10544-017-0241-9.
116. Hu C, Liu B, Huang X, Wang Z, Qin K, Sun L, *et al*. Sea cucumber-inspired microneedle nerve guidance conduit for synergistically inhibiting muscle atrophy and promoting nerve regeneration. *ACS Nano* 2024;**18**:14427–40. https://doi.org/10.1021/acsnano.4c00794.
117. Zhang X, Ma Y, Chen Z, Jiang H, Fan Z. Implantable nerve conduit made of a self-powered microneedle patch for sciatic nerve repair. *Adv Healthcare Materials*. 2023;**12**:e2301729. https://doi.org/10.1002/adhm.202301729.
118. Verdes M, Mace K, Margetts L, Cartmell S. Status and challenges of electrical stimulation use in chronic wound healing. *Curr Opin Biotechnol* 2022;**75**:102710. https://doi.org/10.1016/j.copbio.2022.102710.
119. Greig T, Torah R, Yang K. Electrical stimulation for wound healing: opportunities for E-textiles. *IEEE Rev Biomed Eng* 2024;**17**:264–79. https://doi.org/10.1109/RBME.2022.3210598.
120. Luo R, Dai J, Zhang J, Li Z. Accelerated skin wound healing by electrical stimulation. *Adv Healthc Mater* 2021;**10**:e2100557. https://doi.org/10.1002/adhm.202100557.
121. Pace G, Del Rio Castillo AE, Lamperti A, Lauciello S, Bonaccorso F. 2D materials-based electrochemical triboelectric Nanogenerators. *Adv Mater* 2023;**35**:2211037. https://doi.org/10.1002/adma.202211037.
122. Zhu S, Zhao B, Li M, Wang H, Zhu J, Li Q, *et al*. Microenvironment responsive nanocomposite hydrogel with NIR photothermal therapy, vascularization and anti-inflammation for diabetic infected wound healing. *Bioactive Materials* 2023;**26**:306–20. https://doi.org/10.1016/j.bioactmat.2023.03.005.
123. Jin X, Ou Z, Zhang G, Shi R, Yang J, Liu W, *et al*. A CO-mediated photothermal therapy to kill drug-resistant bacteria and minimize thermal injury for infected diabetic wound healing. *Biomater Sci*. 2023;**11**:6236–51. https://doi.org/10.1039/D3BM00774J.

Burns & Trauma, 2025, 13, tkae076
https://doi.org/10.1093/burnst/tkae076
Review