



Cite this: *J. Mater. Chem. B*, 2023, **11**, 2830

## Smart microneedle patches for wound healing and management

Fangfang Hu, Qian Gao, Jinxi Liu, Wenting Chen, Caiyun Zheng, Que Bai, Na Sun, Wenhui Zhang, Yanni Zhang\* and Tingli Lu \*

The number of patients with non-healing wounds is generally increasing globally, placing a huge social and economic burden on every country. The complexity of the wound-healing process remains a major health challenge despite the numerous studies that have been reported on conventional wound dressings. Therefore, a therapeutic system that combines diagnostic and therapeutic modalities is essential to monitor wound-related biomarkers and facilitate wound healing in real time. Microneedles, as a multifunctional platform, are promising for transdermal diagnostics and drug delivery. Their advantages are mainly reflected in painless transdermal drug delivery, good biocompatibility, and ease of self-administration. In this work, we review recent advances in the use of microneedle patches for wound healing and monitoring. The paper first provides a brief overview of the skin structure and the wound healing process, and then discusses the current state of research and prospects for the development of wound-related biomarkers and their real-time monitoring based on microneedle sensors. It summarizes the current state of research based on the unique design of microneedle patches, including biomimetic, conductive, and environmentally responsive, to achieve wound healing. It further summarizes the prospects for the application of different microneedle-based drug delivery modalities and drug delivery substances for wound healing, due to their superior transdermal drug delivery advantages. It concludes with challenges and expectations for the use of smart microneedle patches for wound healing and management.

Received 29th November 2022,  
Accepted 24th January 2023

DOI: 10.1039/d2tb02596e

rsc.li/materials-b

School of Life Sciences, Northwestern Polytechnical University 127 West Youyi Road, Beilin District, Xi'an Shaanxi, 710072, P. R. China.  
E-mail: lutinglixinxin@nwpu.edu.cn; Tel: +86 136 5918 8506

### 1. Introduction

Skin wounds have a substantial negative impact on healthcare systems and economies worldwide. On the one hand, wound management is a core issue in clinical care due to the constant occurrence of traumatic injuries and the growing prevalence of chronic wounds such as diabetic ulcers and pressure sores.<sup>1</sup>



Fangfang Hu

Fangfang Hu holds a BS degree in pharmaceutical engineering from Northwestern Normal University in 2021. She is a graduate student in biomedical engineering at the School of Life at Northwestern Polytechnical University. Her current interests include microneedling patches and wound repair materials.



Qian Gao

Qian Gao was born in Shaanxi Province, China. She holds a master's degree in pharmacology from Southwest Medical University. During her master's degree, she studied at the Cardiovascular Research Center on diabetes-related glucose regulation. She is currently a PhD candidate in biomedical engineering at Northwestern Polytechnical University. Her main research interests are metal-organic frameworks, hydrogels, molecular biology and biochemistry.

The increased prevalence also brings huge economic costs. First, diabetic foot ulcers are one of the most chronic wounds, with a lifetime risk of developing foot ulcers of up to 25%.<sup>2,3</sup> The healthcare costs for diabetic ulcers and amputations in the UK in 2014–2015 were estimated to be between £837 million and £962 million.<sup>4</sup> On the other hand, low healing rates exacerbate the problem.<sup>5</sup> In the real world, cure rates for complex patients are reported to be no higher than 40%, which contradicts the reported rates almost close to 100%.<sup>6</sup>

While treatments including oxygen, growth factors, small drug molecules, autologous and stem cells, gene therapy and tissue engineering have been used to promote wound healing, to modulate various physiological processes, recent reports have pointed to an important factor-point delivery.<sup>7,8</sup> In general, chronic wounds are covered with a layer of hard skin and necrotic tissue, and the various enzymes contained in the wound exudate locally flush out the therapeutic drugs, which greatly reduces their bioavailability.<sup>7,9</sup> Microneedle patches with micro-nanostructures enable targeted therapeutic drug delivery to living tissues for optimal therapeutic results.<sup>10</sup> The wound healing phase requires care to ensure a better healing state, mainly because the healing process is influenced by a

variety of factors including environment, age, nutrition, and medications.<sup>11</sup> Wounds are in an environment where both internal and external environments work together, and these factors affect the healing process.<sup>12</sup> Limited by the subjective experience of traditional visual assessment of wounds, the specific conditions of wounds cannot be accurately reflected.<sup>13</sup> For early diagnosis, it is necessary to determine wound characteristics including, most importantly, biomarkers, and to examine the wound environment to monitor the healing process.

In recent years, many wearable devices have been applied for wound monitoring to help understand the wound environment in real time by taking wound environment markers as input.<sup>11</sup> Therefore, the new type of wound dressing should simultaneously satisfy real-time monitoring, and early diagnosis, and help achieve accurate treatment. In addition to being developed as a drug delivery system, a significant advantage of microneedle devices is their ability to accommodate multiple independent sensors on a single small array to provide timely multiplexed molecular information.<sup>14</sup> Thus, the concept of microneedle patches combining diagnostic and therapeutic modalities in a therapeutic system to achieve real-time monitoring of wound-related biomarkers and promote wound



Jinxi Liu

*Jinxi Liu is a graduate student in the School of Life Sciences, Northwestern Polytechnical University. He graduated from Huaqiao University with his BS degree in 2019. His current research interests include the development of novel aggregation-induced luminescent molecules for use in disease marker diagnosis and phototherapy.*



Wenting Chen

*Wenting Chen is a graduate student in the School of Life Sciences, Northwestern Polytechnical University. She graduated from Xi'an University with her BS degree in 2020. Her current research interests include the design and synthesis of multifunctional nanostructures for cancer therapy, focusing on photodynamic therapy and chemodynamic therapy.*



Caiyun Zheng

*Caiyun Zheng holds a master's degree in biology from Jiangsu University of Science and Technology. During her master's degree, she studied algae genetic engineering at the Institute of Oceanology, Chinese Academy of Sciences. Currently, she is a PhD student in Biomedical Engineering at Northwestern Polytechnic University. Her research interests are porous nanomaterials, hemostatic materials, and photocatalytic traumatic antibacterial gel materials.*



Tingli Lu

*Tingli Lu is a professor at Northwestern Polytechnical University (China). She received her PhD (2007) in Materialogy from Northwestern Polytechnical University, China. Since 2013, she has been working at the School of Life sciences, Northwestern Polytechnic University. Her research focuses on biological 3D printing, self-healing hydrogels, and medicinal carrier materials.*



**Fig. 1** Schematic diagram of wound intelligent management microneedle patches. Smart microneedle patches combine treatment and monitoring for real-time diagnosis. To summarize, they have five therapeutic modalities: antibacterial, anti-inflammatory, hemostatic, tissue adhesion, and controlled-release drug release. From the monitoring perspective, microneedle patches enable the monitoring of relevant markers such as temperature, humidity, pH, inflammatory factors, and enzymes produced by bacteria.

healing was further elaborated (Fig. 1). Thus, the concept of microneedle patches combining diagnostic and therapeutic modalities in a therapeutic system to achieve real-time monitoring of wound-related biomarkers and promote wound healing is further elaborated. In this review, we describe the skin structure and wound healing process. Then the current research status and development prospects of microneedle sensor-based wound-related biomarkers and their real-time monitoring are discussed. The status of research on microneedle patches based on unique designs, including bionic, conductive, and environmentally responsive, for wound healing is summarized. The prospects of different microneedle-based drug delivery methods and drug delivery substances for wound healing are further summarized. It concludes with challenges and expectations for the use of smart microneedle patches for wound healing and management.

## 2. Skin structure and the wound healing process

### 2.1 Skin structure

The human skin is a multilayered structure that primarily consists of the epidermis, dermis, and subcutaneous tissue.<sup>15</sup> The epidermis, mainly composed of cuticles, is the outermost layer of skin. It could resist environmental disturbances such as ultraviolet radiation, pathogenic bacteria, and uncontrollable mechanical damage.<sup>16</sup> It can also prevent dehydration by regulating moisture.<sup>15</sup> The dermis, a thick, collagen-rich connective tissue, is the close-by layer. The extracellular matrix (ECM), living cells, nerve endings, and blood vessels that are abundant in the dermis support the skin's structural integrity, elasticity, and nutrition.<sup>16,17</sup> The communication between the epidermis and dermis could establish, maintain, and restore

tissue homeostasis.<sup>18</sup> The deepest layer is subcutaneous tissue. It is mainly composed of vascularized loose peri areolar connective tissue and adipose tissue,<sup>19</sup> which provides thermal isolation and mechanical protection to the body.<sup>16</sup> A schematic diagram of the skin structure is shown in Fig. 2A.

### 2.2 Wound healing process

The normal wound healing process has three stages and is a complex and dynamic process. The first stage is hemostasis and inflammation, which occurs immediately after tissue damage (Fig. 2B). Hemostasis begins with platelet degranulation and the coagulation cascade, culminating in the formation of a hemostatic fibrin clot.<sup>20</sup> Fibrin clots then become a scaffold for the infiltration of inflammatory cells such as neutrophils and macrophages, which then migrate to the wound site to remove pathogens (such as bacteria) and cell/tissue debris.<sup>21</sup> In order to stimulate fibroblasts and epithelial cells to migrate towards the wound site, macrophages also release cytokines such as TGF- $\alpha$ .<sup>22</sup>

The proliferative phase starts after the inflammatory phase and occurs after about 4–21 days (Fig. 2C).<sup>23,24</sup> During this phase, dermal and epidermal cells migrate to and hyperproliferate at the wound site, with the typical events of regenerative epithelialization, collagen deposition, angiogenesis, and formation of granulation tissue.<sup>23</sup> Regenerative epithelialization is the process of establishing an intact epidermis to repair skin damage. This involves the migration and proliferation of keratin-forming cells within the trabecular bed, the differentiation of new epithelial cells into a stratified epidermis, and the restoration of the intact basement membrane zone between the epidermis and dermis.<sup>25</sup> Angiogenesis is a process of budding the preexisting blood vessels near the wound, involving endothelial cells migration, proliferation, and branching for the formation of



**Fig. 2** Wound healing stage. (A) Skin structure is mainly divided into three layers: epidermis, dermis, and subcutaneous tissue. (B) Hemostatic/inflammatory stage. (C) Proliferation stage. (D) Remodeling stage.

new blood vessels.<sup>25</sup> Based on newly formed blood vessels, proliferating fibroblasts invade the clot to form constricted granulation tissue.<sup>26</sup>

The longest reconstruction phase usually lasts from a few weeks to a few months and is the ultimate stage of wound healing (Fig. 2D).<sup>21</sup> At this stage, cell proliferation and protein synthesis slow down, and collagen is remodeled into organized fibrils.<sup>6,21</sup> Type III collagen is gradually being replaced with type I collagen.<sup>6</sup>

Wounds can be divided into acute wounds and chronic wounds according to their stage of healing. Acute wounds undergo the normal wound healing process. In contrast, chronic wounds undergo a disturbed wound repair phase that manifests as a persistent inflammatory phase.<sup>27</sup> They may last for weeks, months, or even years and the wounds are highly susceptible to bacterial infections such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and methicillin-resistant *Staphylococcus aureus* (MRSA) that can form biofilms at the wound site.<sup>28</sup> Pathological features of chronic wounds include prolonged exposure to pro-inflammatory cytokines, imbalance in the expression of proteases and their inhibitors, altered availability and activity of growth factors, tissue hypoxia and high levels of oxidative stress.<sup>29</sup> It is worth noting that chronic wounds are often associated with diseases such as diabetes, obesity, etc. Among the major problems of chronic wounds, diabetes is the most threatening.<sup>30</sup> Angiogenesis plays a crucial role in wound healing by providing nutrients and oxygen and by removing metabolic waste products.<sup>31</sup> In the high glucose environment caused by diabetes, vascular endothelial cells are damaged by oxidative stress, resulting in low cellular activity and reduced proliferation capacity, which delays diabetic wound healing.<sup>32</sup> Achieving rapid healing of diabetic wounds is a pressing issue.

### 3. Microneedle patch for wound monitoring

#### 3.1 Physiological data for monitoring the wound status

It is significant to monitor wound status, which is beneficial to predict the wound trends for real-time treatment.<sup>33,34</sup> The physiological processes involved in wound healing are intricate. It is also susceptible to environmental factors that can impede or prolong healing, which may contribute to high treatment costs.<sup>13</sup> Wound dressings that are tailored according to a specific healing situation based on the stage of healing, inflammatory state, moisture levels, and exudation rates are currently used to treat chronic wounds.<sup>35,36</sup> However, the majority of the time, wound status is assessed through visual inspection, which carries the risk of secondary injury due to frequent replacement and visual errors.<sup>13,37</sup> Next-generation wound dressings that are capable of real-time monitoring, early diagnosis, and on-demand therapy have received a lot of attention to overcome the wound-healing process's "black box" status.<sup>38–40</sup> Injured tissue generates exudate, a fluid rich in proteins such as electrolytes, creatinine, fibrinogen, matrix metalloproteinases (MMPs) and c-reactive protein (CRP), and tumor necrosis factor-alpha (TNF- $\alpha$ ).<sup>41,42</sup> Additionally, certain physical wound environment factors, such as temperature, pH, humidity, and exercise, influence wound healing.<sup>43–48</sup> To achieve early diagnosis of wounds, physiological data related to the wound environment become the main target of monitoring.

During the process of wound healing, pH is an important parameter. Intact skin has a pH of 4.8–6.0.<sup>49,50</sup> Once stratum corneum is damaged, the underlying tissue is exposed, displaying a normally regulated pH of 7.4. On around day 2, a normally healing wound goes through a brief acidic period with a pH between 4 and 6.5, which helps prevent bacterial growth and



promotes angiogenesis and epithelialization.<sup>49–51</sup> After a transient decrease in pH, it returns to a neutral pH along with the wound closure.<sup>51</sup> In the meantime, the newly formed skin recovers an acidic milieu. However, the pH tends to remain in a weakly alkaline range at the chronic wound as well as the wound with long-term bacterial colonization.<sup>51,52</sup> Another crucial parameter in the wound-healing process is temperature. Inflammation or infection may be the cause of a sudden rise in temperature at the site of the wound.<sup>49</sup> A decrease in temperature at the wound may be caused by ischemia, which tends to hamper wound healing.<sup>50</sup> It has been demonstrated that a temperature change of approximately 2 °C is the threshold for wound deterioration.<sup>50</sup> Accordingly, temperature monitoring is generally employed as a potential method of estimating wound status. An inflammatory marker linked to the onset of inflammatory conditions and infection is C-reactive protein (CRP).<sup>53</sup> CRP concentrations in the blood suddenly rise from approximately 0.8 mg L<sup>-1</sup> to 600–1000 mg L<sup>-1</sup> during the acute phase response to inflammation, peaking after approximately 48 h.<sup>42,54</sup> A biomarker known as urea (UA) has a strong connection to wound healing.<sup>55</sup> Associated with oxidative stress and bacterial infection in the wound area, uric acid levels rise in unhealed chronic wounds and fall as the wound heals.<sup>42,56,57</sup> Wound moisture is a key parameter in ensuring optimal healing conditions in wound care.<sup>47,58</sup> However, moisture-induced infection might increase the exuding of tissue fluid, rendering wounds to be too wet and thus aggravating wound infection.<sup>47,58</sup> Consequently, moisture monitoring is also important for wounds treated with moist dressings.<sup>47,58</sup> In addition, studies have reported that glucose,<sup>59–61</sup> inflammatory factors,<sup>62</sup> exercise,<sup>63</sup> *etc.* can be used as indicators to monitor wound healing.

### 3.2 Microneedle-based sensors

As the microneedle patches only penetrate the viable stratum corneum and viable epidermis and do not reach the nerve endings or blood vessels, they are minimally invasive procedures and therefore patients do not feel any pain.<sup>64,65</sup> The microneedle technology is a transdermal drug delivery strategy that overcomes the disadvantages of hypodermic needles, reduces the risk of infection transmission, reduces anxiety, and allows patient compliance.<sup>66</sup> Microneedle patches have shown high therapeutic advantages in aspects such as immunotherapy,<sup>65</sup> cancer,<sup>67</sup> Alzheimer's disease,<sup>68–71</sup> drug delivery,<sup>72</sup> and disease diagnosis.<sup>73,74</sup> By combining electrodes with micronized array substrates, a variety of microneedle-based devices were proposed as sensors and diagnostic systems,<sup>75</sup> including electrochemical, optical, magnetic, and paper-based biosensors.<sup>76</sup> Microneedle sensors can be hollow microneedles with sensors on top, electrochemically bonded hollow microneedles, surface-functionalized solid microneedles, or metallized solid microneedles.<sup>77</sup> Colorimetry, immunoassays, nucleic acid recognition, or electrochemistry can all be used to detect analytes with these microneedle-based biosensors.<sup>77</sup> Among the existing research reports, electrochemical sensors account for the vast majority. The advantages are small size, speed, low cost, low power consumption, and no sample composition interference.<sup>14</sup> Thanks to the superior biocompatibility and customizable microstructure of microneedle

patches, innovative microneedle-based dressings are likely to be widely used in the future.<sup>78</sup> Rongyan He and his team placed sensing reagents at the tips of microneedle patches to fabricate a colorimetric skin tattoo biosensor fabricated from a four-region segmented microneedle patch, realizing the detection of four typical biomarkers (pH, glucose, temperature, and uric acid) at the same time. Biosensors change color as markers change, allowing further semi-quantitative analysis by naked eye reading or smart camera capture.<sup>79</sup> Researchers have recently developed smart colorimetric microneedle patches containing Fe ion-gallate coordination polymer nanodots (FNDs) for on-demand treatment of infected wounds and real-time reporting of these wounds (Fig. 3A).<sup>80</sup> FNDs have pH-dependent catalase-mimicking activity, and can not only kill bacteria by catalyzing the generation of hydroxyl radicals (OH) from hydrogen peroxide, but also change color depending on pH and hydrogen peroxide. By observing the change in color of the microneedle patch, it is possible to distinguish between normal wounds and bacterially infected wounds.<sup>80</sup> A colorimetric dermal tattoo biosensor fabricated from microneedle patches was developed for monitoring pH, glucose, uric acid, and temperature. The microneedle biosensor exhibits color changes in response to changes in the concentration of the marker allowing for visual semi-quantitative analysis.<sup>79</sup>

Microneedle patch sensors offer significant advantages in drug delivery and sensing physiological signals. For example, microneedle patches can increase permeability and can facilitate the delivery of various drugs. It has also been demonstrated that the same microneedle-based sensor prevents sweat contamination and signal noise during sensing while also minimizing damage to dermal nerves and blood vessels.<sup>81</sup> For wound healing and sensing, an origami smart silk fibroin-based microneedle dressing (i-SMD) with an inverse opal photonic crystal (IO PC) structure, microfluidic channels, and microcircuits was proposed (Fig. 4A).<sup>82</sup> By using capillary force, the microfluidic channels can direct the liquid flow to the area of detection, making it possible to detect biomarkers in liquid without the need for an external power supply.<sup>82</sup> Microelectronic circuits can monitor activity in the trauma area and reduce secondary injuries caused by exercise.



Fig. 3 (A) Schematic diagram of how the ligand polymer nanoparticle enzyme integrated colorimetric microneedle patches are made and how they are used to detect and treat wound infections.<sup>80</sup> Copyright 2022 Elsevier.

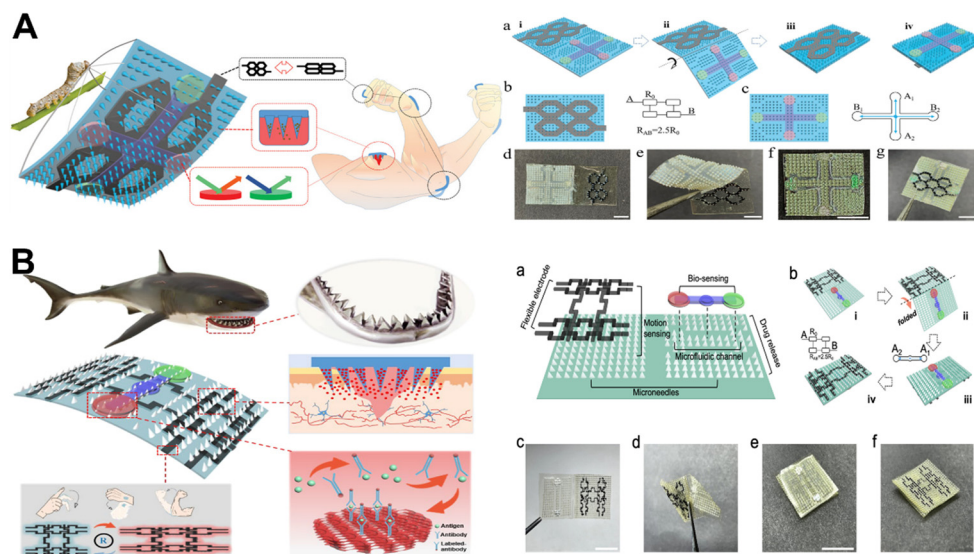


Fig. 4 (A) Diagram of the highly integrated, intelligent, biocompatible, stretchable i-SMD for biochemical sensing, motion monitoring, and wound healing.<sup>82</sup> Copyright 2020 Wiley-VCH. (B) Diagrammatic representation of a microneedle patches based on shark teeth for intelligent wound management.<sup>83</sup> Copyright 2021 American Chemical Society.

Among them, the temperature-responsive *N*-isopropyl acrylamide hydrogel realizes intelligent drug release. On the microneedle patch, a cross-shaped microfluidic channel is made, and the four regions of the channel have IO PC structures.<sup>82</sup> Capillary force allows the liquid to spontaneously diffuse along the microfluidic channel after the smart patch is applied to the wound, bringing it into complete contact with the IO PC structure in the detection area. The relative levels of biomarkers in wound secretions can be read simply by detecting the fluorescent signal in the detection area. The intelligent microneedle patch integrating motion sensing, intelligent drug release, and wound biochemical analysis can realize intelligent management of wounds and provide a reference for management of other diseases. The article proposes that the microneedle patch can be used to analyze a variety of biochemical indicators at the wound healing stage, but the way to achieve this is to directly use a solution containing a high concentration of target molecules, which still has a certain gap with the actual demand.

The team proposed a microneedle patch for smart wound management inspired by the flat and angled structure of a shark's tooth to further enhance the feasibility of smart wound management (Fig. 4B).<sup>83</sup> It was worth noting that the bionic shark teeth enabled the microneedle patches to penetrate the skin with improved grasping force. The microneedle patch was used for the analysis of the effect of IL-6 on inflammatory reaction at the wound site. Interestingly, IL-6 levels increased significantly from day 0 to day 3 and continued to decline from day 3 to day 9 due to treatment, consistent with normal wound healing changes.<sup>83</sup>

## 4. Microneedle design for wound healing

### 4.1 Biomimetic design

Many aspects of wound healing have been studied with microneedle patches. However, as some microneedle patches have

poor adhesion to the skin, they require auxiliary equipment such as medical tape to achieve optimal penetration and fixation.<sup>84,85</sup> The straight and symmetrical structure of the microneedle patches may be the main reason. Inspired by bionics, the researchers have further improved the structure of microneedle patches in order to improve their adhesion and avoid secondary cracking. For example, a microneedle patch with a claw-like tip, inspired by an eagle's claw, enables stable skin adhesion, and promotes wound healing (Fig. 5A).<sup>86</sup> In addition, shark teeth-style patches are inspired by a shark's ability to bite and hold on to their prey, with their microneedle patches being designed to resemble the flat, angled structure of shark teeth.<sup>87</sup> North American porcupines are known for their hair or feathers with tiny, backward-stretching barbs for self-defense, and inspire the new structural design of microneedle patches.<sup>88</sup> Lamprey teeth-inspired microneedle patches are used for directional traction to shrink the wound area.<sup>89</sup> Currently, it is still challenging to fabricate microneedle patches with complex microscopic features using traditional fabrication methods. Daehoon Han *et al.* proposed a 4D-printed microneedle patch with biomimetic reverse-curved barbs to enhance tissue adhesion. The results showed that the tissue adhesion of the prepared microneedle patch was 18 times higher than that of the non-barbed microneedle patch.<sup>90</sup> Microneedle patches based on the bionic concept can be stabilized by 4D printing technology.

A biphasic microneedle patch with shape-variably expanded microneedle tips was developed to mechanically interlock with tissue. The endoparasite *Pomphorhynchus laevis*, which swells its proboscis to attach to the intestinal wall of its host, served as inspiration for the insertion and fixation of microneedle patches.<sup>91</sup> The conical microneedle sheet consists of a poly-(styrene) block poly(acrylic) expandable tip and a non-expandable polystyrene core.<sup>91</sup> Eun *et al.*, inspired by the endoparasite



Fig. 5 (A) Schematic illustration of the claw-inspired microneedle patch with liquid metal encapsulation and its wound healing application.<sup>86</sup> Copyright 2021 Elsevier. (B) Schematic diagram of the working principle of the microneedle patch and the equipment process.<sup>91</sup> Copyright 2017 American Chemical Society. (C) Schematic diagram of the preparation of a hemostatic and bionic pagoda microneedle patch.<sup>99</sup> Copyright 2021 Elsevier.

*Pomphorhynchus laevis*, created a structured microneedle patch with a cross-linked biphasic structure.<sup>92</sup> The microneedle patch comprises an absorbable adhesive external part based on mussel adhesion protein and a rigid internal part based on filament for effective tissue fixation without delamination. The designed novel adhesive microneedle patch achieves mechanical interlocking with tissue and exhibits excellent adhesion on wet and dynamic biological surfaces.<sup>92</sup> Considering the effect of humid environments on microneedle patches, Chen designed an octopus nanosuction microneedle patch to exhibit strong adhesion in both dry and humid environments (Fig. 5B).<sup>93</sup> The biomimetic microneedle patch can provide universal soft tissue adhesion with minimal damage and provide a platform for bioactive therapeutics, reducing the risk of infection and reducing traumatic removal.

The first stage of wound healing is hemostasis. Wound healing depends on hemostatic agents controlling bleeding quickly and effectively. Although currently available hemostatic materials such as cyanoacrylate,<sup>94</sup> glutaraldehyde cross-linked albumin,<sup>95</sup> or fibrin-based bandages<sup>96</sup> can exert high hemostatic efficiency, they have limitations in the treatment of deep bleeding.<sup>96</sup> In addition, hemostatic materials are often difficult to remove, which also brings a lot of trouble to patients.<sup>97,98</sup> Therefore, hemostatic materials with high hemostatic efficiency and easy removal have become the focus of researchers to design new hemostatic materials. The layered microstructure of the feet or stings of insects like ladybugs, gadflies, and wasps served as inspiration for Zhang's team. To achieve rapid hemostasis, a novel dodecyl modified chitosan (DCS) coated pagoda shaped microneedle patch was proposed (Fig. 5C).<sup>99</sup> The multilayered structure allows the

microneedle patch to be firmly anchored to different tissues by physical interlocking, independent of massive blood loss. On the other hand, the DCS coating acts as an anchor on the cell membrane and causes blood cells to coagulate, thus actively promoting hemostasis.<sup>99</sup>

## 4.2 Environment-responsive design

It has been demonstrated that drug delivery that is intelligently controlled can prevent drug resistance around the wound caused by uncontrolled drug release. Precise regulation of the time, area, and flow rate of drug release can effectively improve the wound environment.<sup>100</sup> Signals that can be responsive include physical and chemical signals, such as light,<sup>101–104</sup> electricity,<sup>105</sup> magnetism,<sup>106</sup> temperature,<sup>87,107,108</sup> pH,<sup>109</sup> glucose,<sup>110</sup> and ROS.<sup>111</sup>

Near infrared (NIR) light has received attention due to its ease of manipulation, ability to locally focus on a specific site, and its safety, allowing non-invasive propagation in deeper tissues.<sup>101,112</sup> Light-activated microneedles perform their functions by converting light into heat and raising the ambient temperature.<sup>113</sup> The creation of porous MOF microneedle patches to provide photo-thermally responsive nitric oxide is an example of this (Fig. 6A).<sup>114</sup> The use of reactive graphene oxide (GO) encapsulated with an empty copper 1,3,5-tricarboxylate (HKUST-1) MOF enables the controlled release of NO. The photothermal effect of GO leads to a significant increase in the release of NO molecules at high temperatures.<sup>114</sup> In the process of wound healing, nitric oxide is primarily responsible for cell proliferation, collagen formation, and wound shrinkage.<sup>115</sup> The designed microneedle patch shortens the short half-life of NO. When the microneedle patch is applied to diabetic wounds, the wound





**Fig. 6** (A) Schematic diagram of the preparation and application of the porous MOF microneedle patches.<sup>114</sup> Copyright 2021 Wiley-VCH. (B) Schematic diagram of using NIR response to rapidly release BP quantum dots and oxygen-carrying hemoglobin to promote wound healing.<sup>119</sup> Copyright 2020 American Chemical Society.

closure rate can reach 99% within 13 days.<sup>114</sup> In addition, a near-infrared responsive nitric oxide-releasing microneedle was prepared, using nitrosogluthathione (GSNO) as a nitric oxide donor, adding graphene oxide to enhance the photothermal conversion efficiency, and using near-infrared to achieve a controllable release of nitric oxide.<sup>116</sup> Adequate oxygenation is important for cell proliferation, bacterial defense, angiogenesis, collagen synthesis, and epithelialization.<sup>117,118</sup> Therefore, people also put forward higher requirements for oxygen carriers. Under the condition of meeting biocompatibility, finding a carrier with high oxygen-carrying capacity and controlled release that can act deep in the skin is a hot topic of interest. Zhang and his team have recently reported a microneedle patch that uses near-infrared light to achieve controlled oxygen delivery (Fig. 6B).<sup>119</sup> Hemoglobin (Hb) utilizes the excellent photothermal efficiency of black-scale quantum dots (BP QDs) for its reversible oxygen binding capability.<sup>120</sup> The two were encapsulated at the tip of a separable microneedle, and the responsive release of oxygen was achieved by using local heat generated from near-infrared light. The microneedle patch showed ideal wound healing ability in the treatment of diabetic mouse wounds.<sup>119</sup> By activating the G protein-coupled adenosine receptor, adenosine, a systemic range of active ingredients, can alter cell behavior.<sup>121</sup> Recently, several studies have shown that adenosine can promote angiogenesis and endothelial cell proliferation,<sup>122,123</sup> exploit the ability of borates to dynamically covalently bind adenosine, combined with the powerful photothermal conversion of two-dimensional layered MXenes.<sup>124,125</sup> The controlled release of adenosine is achieved, which promotes wound healing.<sup>126</sup>

The human body's normal physiological temperature is 37 °C. The epidermal temperature in the wound area will rise to 37 °C or higher when there is an infection.<sup>108</sup> The microneedle patch achieves the release of the vascular endothelial growth factor (VEGF) encapsulated by NIPAM hydrogel.<sup>127</sup> *N*-iso-propyl acrylamide (NIPIM) hydrogel is a temperature-sensitive hydrogel. The NIPAM hydrogel has a volume phase transition temperature of 37 °C. At this point, the NIPAM hydrogel shrinks and then releases the encapsulated

contents.<sup>108,128</sup> Controllable and intelligent drug release is achieved through the temperature increase caused by the inflammatory response at the wound site. The microneedle patch achieves ideal wound healing by promoting inflammation inhibition, collagen deposition, angiogenesis, and tissue regeneration.<sup>127</sup> In addition, Wang and his team have achieved controlled drug release from microneedle patches combined with temperature-responsive *n*-isopropylacrylamide (NIPAM) hydrogels.<sup>129</sup> Inverse opal (IO) photonic crystals (PC) have an ordered three-dimensional porous microstructure. Thanks to the porous structure of IOPCs, the drug-carrying capacity of microneedle patches is greatly enhanced. Furthermore, thanks to the temperature-responsive NIPAM hydrogel, the microneedle patch can control drug release.<sup>129</sup>

The pH of the wound may change in accordance with the type of wound, the stage of the healing process, and other characteristics like infection.<sup>130</sup> On a microneedle patch, Asad Ullah and colleagues created a porous polymer coating that automatically 'releases' therapeutic drugs according to the pH of the wound (Fig. 7A).<sup>131</sup> The pH-sensitive polymer Eudragit S100 is soluble in tissue fluid with an alkaline pH (pH greater than or equal to 7) but insoluble in an acidic microenvironment.<sup>132</sup> The test medium contained trace amounts of the microneedle patch released at a pH of 4.5. On the other hand, when the microneedle patch was exposed to wound pH (pH 7.5) conditions, the rate of drug release increased significantly. This study demonstrates the ability of the created microneedle patch to treat contaminated injuries.<sup>131</sup>

The dermal microcirculation is affected when the microneedle patches are inserted into the skin.<sup>113</sup> For diabetic wounds, glucose-responsive microneedle patches enable the controlled release of drugs based on glucose concentration. For diabetic wound repair, a hydrogel microneedle patch that responds to glucose and releases insulin was developed (Fig. 7B).<sup>133</sup> The glucose-responsive insulin release was achieved using hydrogels with phenylboronic acid (PBA) groups. By promoting angiogenesis, epithelial regeneration, and deposition of the extracellular matrix, insulin can act as a growth-like factor to promote wound



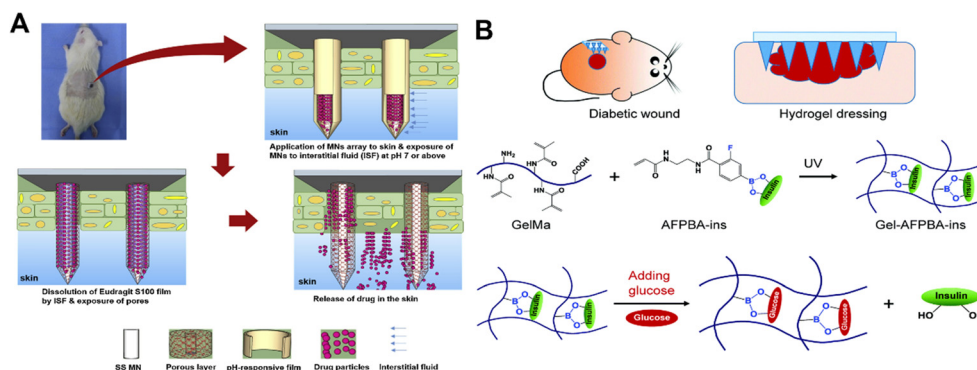


Fig. 7 (A) Wound pH-dependent release system schematic illustration.<sup>131</sup> Copyright 2021 Elsevier. (B) Diagram of glucose responsive microneedle dressing for wound healing in diabetes.<sup>133</sup> Copyright 2022 Royal Society of Chemistry.

healing.<sup>134–136</sup> In conclusion, diabetic wounds may heal more quickly with this hydrogel-based microneedle patches.<sup>133</sup>

### 4.3 Electroconductive design

Electrical signals are the primary guiding cues for directed cell migration in wound healing.<sup>137</sup> Exogenous electrical stimulation is applied to chronic wounds to stimulate electrotaxis (also known as electrotaxis).<sup>138</sup> A spontaneous potential of 10–60 mV exists between the epidermis and sub-epidermal layer of undamaged skin.<sup>139</sup> Ion channels and frequent depolarization and repolarization of the cells are the main causes of this phenomenon.<sup>140</sup> When damaged, a short circuit occurs due to the low resistance of the injured part.<sup>141</sup> The net movement of ions in the layers between the epidermis and dermis creates endogenous electric fields (EFs). EFs participate in the cell healing process by affecting cell migration. This phenomenon of cell migration under the action of an endogenous electric field is called electrotaxis.<sup>140</sup>

To facilitate wound healing, direct cell migration, and encourage cell metabolism, proliferation and differentiation, appropriate electrical stimulation can mimic endogenous wound healing mechanisms.<sup>142,143</sup> Using the conductive properties of liquid metal, it is combined with microneedle patches to guide cell migration and accelerate wound healing under an electric field of  $2 \text{ V cm}^{-1}$  generated by a lithium-ion battery that can be recharged.<sup>86</sup> Recently, a microneedle-based self-powered transcutaneous electrical stimulation system for improving epidermal growth factor pharmacodynamics to promote wound healing has been developed. The system consists of a sliding freestanding frictional electrical nanogenerator and a microneedle patch that enables continuous release of the epidermal growth factor for 24 hours. It is interesting to note that this method converts biomechanical energy generated by finger sliding into biosafe microcurrents.

## 5. Microneedle-based drug delivery in wound healing

### 5.1 Delivering antibacterial agents for combating infection

Bacterial infection of wounds is a common and unavoidable challenge in the wound healing process. At the point when a bacterial contamination happens at the injury site, there might

be a persevering provocative reaction at the injury site because of the microscopic organisms, drawing out the injury recuperating time. At present, the treatment of bacterial infection mainly relies on various antibiotics, but the problem of bacterial resistance emerges one after another.<sup>19</sup> Therefore, how to achieve an efficient sterilization strategy is the focus at present.

It has been found that approximately 75% of chronic wounds suffer from a bacterial infection caused by biofilms produced by bacterial colonization at the wound site.<sup>144</sup> Bacterial biofilms are characterized as different bacterial networks joined in total and encompassed by polysaccharides, discipule fimbriae, extracellular DNA, lipids, and proteins; self-blending grids called hydrated extracellular polymers (EPS).<sup>145,146</sup> Planktonic bacteria are less resistant to antimicrobial compounds than bacterial biofilms.<sup>147</sup> Existing strategies to combat microbial biofilms are limited by the difficulty faced by antimicrobial agents in penetrating their physical barriers.<sup>148</sup> EPS' net negative charge could trap positively charged antimicrobials or repel them. Additionally, some bacteria produce enzymes like beta-lactamases, which accumulate within biofilms and aid in bacterial survival by deactivating specific antibiotic molecules.<sup>149</sup> Microneedle patches appear to be a viable strategy to penetrate these barriers and deliver the loaded cargo to a predetermined depth of the dermis without causing painful, skin damage.<sup>148</sup> We summarize the current status of research on microneedle patch-based delivery of antimicrobial drugs, including delivery drugs, functions, and materials for microneedle preparation as shown in Table 1.

**5.1.1 Antibacterial drugs.** Antibiotics are still the main strategy for treating clinical wound infection. The researchers encapsulated macrolide (erythromycin and azithromycin) antimicrobial agents in polymeric microneedle patches made of hyaluronic acid (HA) and polyvinylpyrrolidone (PVP). Five days after the treatment, the damage is fully recovered and the hair follicles, dermis, and other skin forms are restored.<sup>156</sup> Researchers have reported the fabrication of water-soluble polymer microneedle patches by encapsulating the antibiotic chloramphenicol in gelatin nanoparticles and a polymer matrix (Fig. 8A).<sup>149</sup> When applied to an infected site, the microneedle patches enter the EPS and genuinely upset the biofilm structure. Following rapid dissolution of the polymeric microneedle patches, the gelatin nanoparticles are

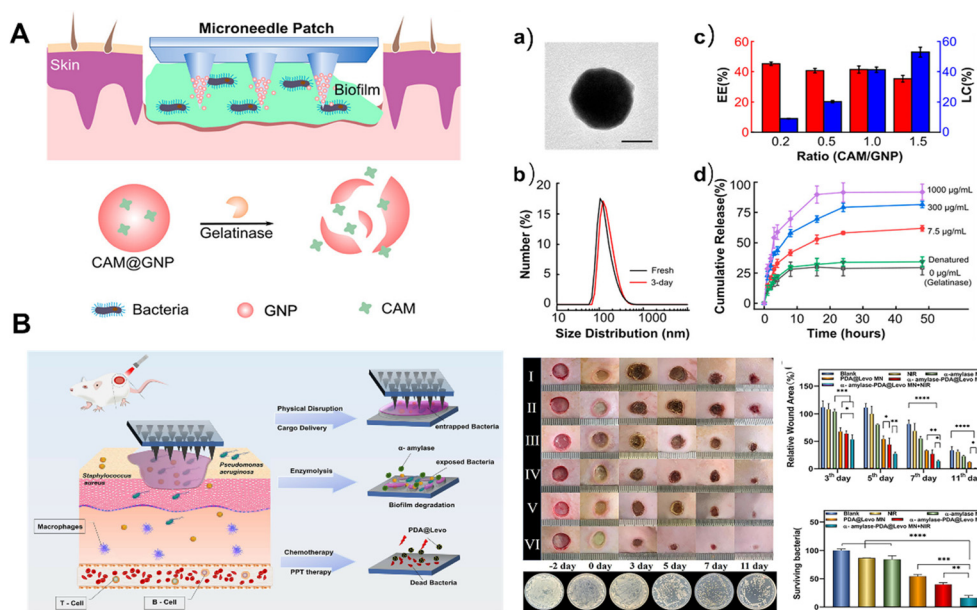
**Table 1** Summary of microneedle-based delivery of antibacterial agents to promote wound healing

Delivery substance	Function	Preparation method	Ref.
Vancomycin	Figureht skin infections caused by MRSA (methicillin-resistant <i>Staphylococcus aureus</i> )	Polyvinyl alcohol	150
Tetracycline	Provide an appealing approach to preventing infections in the local area and prevent pathogen growth.	polymethylmethacrylate Silk fibroin	151
Bacteriophages	An effective method of treating biofilm infections of the skin.	Polyvinyl alcohols	152
Calcium peroxide	Overcome the bacterial biofilm present in chronic nonhealing wounds and co-deliver oxygen and bactericidal agents	Polyvinylpyrrolidone	153
Carvacrol	At infection sites, achieve a lasting antimicrobial effect.	Poly( $\epsilon$ -caprolactone)	154
Antimicrobial Peptide	Treatment of biofilms formed by multidrug-resistant bacteria	Poly( $\epsilon$ -caprolactone) polyvinylpyrrolidone	144
Lysozyme	Lyse bacterial infections for dermal applications	Polyvinylpyrrolidone Hyaluronic acid	155
Erythromycin	Enhanced wound healing and anti-bacterial effect	Poly lactic-co-glycolic acid	156
Azithromycin		Polyvinylpyrrolidone	156
Chloramphenicol	Improve the delivery of a wide range of antimicrobial agents to biofilm contaminated sites.	Hyaluronic acid	149
Gelatin nanoparticles	Combating wound infections-associated bacterial biofilms.	Polyvinylpyrrolidone	157
Levofloxacin poly-dopamine nanoparticles		Polyvinyl alcohol	157
Silver nanoparticles	Fast dissolution rates and potent antibacterial activity	Carboxymethylcellulose	158
Silver nanoparticles	Overcome the problem of skin infection associated with bacterial biofilms	Polyvinyl alcohol	159
Zn-MOF	Dramatically accelerate epithelial regeneration and neovascularization	Polyvinylpyrrolidone	160
Zn <sup>2+</sup>	Eradication of bacterial biofilms	Methacrylated hyaluronic acid	161
Mg and panax notoginseng saponins	Achieves antibacterial, neovascularization, and activating a benign immune response	Chitosan	162
		Chitosan polyvinylpyrrolidone	162

dissociated by gelatinase, allowing the release of the encapsulated chloramphenicol into the biofilm matrix. This approach speeds up wound healing and improves targeting compared to direct chloramphenicol usage.<sup>149</sup>

Extracellular polysaccharides are one of the important components of EPS. They enhance bacterial adhesion and aggregation, mechanical stability, nutrient and ion adsorption, and nutrient storage and act as a protective barrier for antimicrobial

drugs.<sup>163</sup> Enzymatic degradation has been reported to disrupt EPS structural integrity.<sup>164</sup> Dissolvable microneedle patches combined with enzymatic and anti-infective agents and photo-thermal therapy eliminate biofilms from bacterial disease in wounds (Fig. 8B).<sup>157</sup> The microneedle patches have rapid dissolution properties of PVA. The fine tip of the microneedle patch penetrates the biofilm matrix and delivers  $\alpha$ -amylase and levofloxacin adsorbed polydopamine nanoparticles into the



**Fig. 8** (A) Schematic illustration of the microneedle-mediated biofilm treatment.<sup>149</sup> Copyright 2019 American Chemical Society. (B) Schematic illustration of the mechanism for the treatment using biofilms with dissolvable microneedle patches in infected wounds and biofilm elimination.<sup>157</sup> Copyright 2022 Elsevier.

biofilm. In addition, photothermal response to near infrared light can accelerate the release of therapeutic agents, speeding up the healing process. However, photothermal therapy will inevitably cause damage to surrounding normal cells and tissues, and how to reasonably control the treatment time still needs further research.

Antimicrobial peptides are host defense molecules in multicellular organisms due to their special antibacterial mechanism compared with antibiotics.<sup>165</sup> The antimicrobial peptides have broad-spectrum antibacterial properties and low biotoxicity, which can help solve the problem of drug resistance of traditional antibiotics.<sup>166</sup> Su *et al.* combined electrostatic spinning, microneedle patches and antimicrobial peptides to remove biofilms produced by bacterial infections in wounds, based on a database of antimicrobial peptides.<sup>167</sup>

**5.1.2 Antibacterial nanoparticles.** For potential antimicrobial applications, inorganic metal nanoparticles, such as silver,<sup>168</sup> zinc oxide,<sup>169</sup> copper,<sup>170</sup> and other metal-containing nanoparticles,<sup>171</sup> have been extensively investigated. The mechanism of action of nanoparticles on bacteria is mainly manifested in their ability to adsorb on bacterial membranes through electrostatic interactions, destroying the integrity of bacterial membranes.<sup>172</sup> Despite

the safety concerns of nanoparticles, it still does not prevent them from becoming one of the most used antibacterial agents besides antibiotics.

Silver nanoparticles can not only kill bacteria but also inhibit their exopolysaccharide synthesis.<sup>173,174</sup> For example, silver nanoparticles and carboxymethylcellulose are used to create dissolvable microneedle patches with powerful antibacterial properties.<sup>158</sup> Although silver nanoparticles are reported to be effective, they may be harmful to human cells.<sup>175</sup> As a result, a method for selective drug delivery that prevents silver nanoparticles from being delivered to undesirable locations is required. For instance, Andi utilized silver nanoparticles synthesized with green tea extract due to their potential as antibacterial agents against biofilms of *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA) (Fig. 9A).<sup>159</sup> Due to the toxicity of silver nanoparticles, they were incorporated into bacterial reaction particles (MPs) made of chitosan-modified poly-(caprolactone). In the presence of SA and PA, the MPs showed a 9-fold increase in the *in vitro* release of silver NPs, indicating some selectivity.<sup>159</sup>

Metal organic backbones (MOFs) are non-porous materials consisting of metal ions and organic ligands linked to ether by covalent bonds.<sup>176</sup> Metal-organic frameworks (MOFs) are considered



Fig. 9 (A) Schematic illustration of bacteria-responsive microparticles for selective delivery of silver nanoparticles with microneedle patches.<sup>159</sup> Copyright 2020 Elsevier. (B) Schematic diagram of Zn-MOF microneedle patches.<sup>177</sup> Copyright 2021 Wiley-VCH. (C) Schematic diagram of microneedle patches and brief introduction to the process of promoting wound healing.<sup>162</sup> Copyright 2022 Wiley-VCH.



third-generation antimicrobials. They have advantages over conventional bactericidal materials due to their adjustable pore structure, controllable ion release rate, and high specific surface area.<sup>176</sup> The metal ions are gradually released using the metal disassembly of the MOFs to provide long-lasting antimicrobial activity and to achieve the antimicrobial durability of expensive MOFs.<sup>176</sup> For example, Yao *et al.* proposed a novel Zn-MOF-encapsulated microneedle patch with antibacterial activity and degradable properties to promote wound healing, and the  $\text{Zn}^{2+}$  released from the Zn-MOF can destroy the integrity of the bacterial envelope, catalyzing the production of oxygen free radicals, resulting in bacterial death. Additionally, the rough surface of ZIF-8 nanoparticles has the potential to expand the area of contact between MOFs and bacteria, enhancing antibacterial activity (Fig. 9B).<sup>177</sup>

Chitosan (CS) is one of the most encouraging regular polymers known to have antibacterial properties.<sup>178</sup> CS is a natural cationic polysaccharide consisting of (1  $\rightarrow$  4)-2-amino-2-deoxy- $\beta$ -D-glucan, a partially to fully deacetylated form of chitin.<sup>179,180</sup> CS is biodegradable, non-toxic, biocompatible, antibacterial and hemostatic, and is of great value in biomedical applications.<sup>127</sup> The electrostatic interaction between the positively charged CS molecules and the negatively charged cell membrane alters the permeability of the cell membrane, leading to lysis, one of the known mechanisms by which CS acts on microorganisms.<sup>127,181</sup> However, in practical applications, CS and other antibacterial substances are usually used to have a synergistic effect to achieve the antibacterial treatment of wounds. For example, taking advantage of the antibacterial properties of CS and zinc ions ( $\text{Zn}^{2+}$ ), composite microneedle patches of CS and zinc nitrate were prepared to eliminate bacterial biofilms.<sup>161</sup> Due to the needle-like structure, microneedle patches can pierce EPS and can deliver CS and  $\text{Zn}^{2+}$  directly into bacterial biofilms. Compared with the patch without needle structure, the needle design increased the area of contact between the drug transporter and the bacterial biofilm by nearly 14–23%, facilitating drug dispersion. More importantly, the synergistic effect of CS and  $\text{Zn}^{2+}$  enabled the composite microneedle patches to show excellent anti-biofilm properties.<sup>161</sup> Furthermore, Ning *et al.* proposed a synergistic detachable microneedle patch with a bilayer structure (Fig. 9C).<sup>162</sup> The bilayer microneedle structure consists of a CS needle tip, CS hydrogel dressing, and a magnesium (Mg)-doped polyvinylpyrrolidone (PVP) backing. It provides a simple method for the programmed treatment of chronic wound management.

## 5.2 Delivering drugs for regulating inflammation

An excessive or prolonged inflammatory response can cause an undesired polarization of immune cells and lead to wound deterioration.<sup>182</sup> Therefore, the development of dressings with inflammation modulating ability is of great importance to promote wound healing. Macrophages are key players in the wound healing process and serve as important targets for wound healing.<sup>183</sup> Studies have shown that chronic wounds are closely associated with an impaired phenotypic shift of pro-inflammatory macrophages to an anti-inflammatory phenotype in wounds.<sup>184</sup> Focusing on restoring the normal transformation

of the macrophage phenotype facilitates normal wound healing. Numerous immune cells and non-lymphocytes use reactive oxygen species (ROS) as second messengers, regulate angiogenesis, and are necessary for the normal wound healing response.<sup>185</sup> However, it should be noted that while high ROS production can result in oxidative stress and hinder wound healing, low ROS levels may actually help wound healing.<sup>186</sup> In addition to causing severe inflammation, excessive reactive oxygen species (ROS) in wounds also inhibit the function of endogenous stem cells and macrophages, preventing cell proliferation and wound tissue regeneration.<sup>187,188</sup> Therefore, to form a normal wound environment with an appropriate amount of reactive oxygen species, it is necessary to remove excess reactive oxygen species around the wound.

The new microneedle patch designed by Ma and his colleagues encapsulates polydopamine nanoparticles (PDA NPs) in a shell of hyaluronic acid methacrylate (HAMA).<sup>189</sup> The structure of polydopamine is rich in reducing functional groups, such as catechol and imines, which allow the polydopamine molecule to exhibit good antioxidant properties.<sup>19,190</sup> Polydopamine nanoparticles were continuously released to scavenge ROS as HAMA slowly degraded (Fig. 10A).<sup>189</sup> Microneedle patches show antioxidant, anti-inflammatory, and pro-angiogenic properties, and are of some value.

Gallic acid (GA) is a specific plant compound in the phenol group that is also used to promote wound healing.<sup>191</sup> GA has many biological activities, including anti-inflammatory, anti-tumor, immunomodulatory, hypoglycemic, and hyperlipidemic.<sup>192</sup> GA has strong antioxidant activity due to its three hydroxyl groups.<sup>193</sup> A schematic diagram of the multifunctional MOF magnesium microneedle patch prepared with gallic acid and  $\text{Mg}^{2+}$  is shown in Fig. 10B.<sup>194</sup> The Mg-MOFs in an acidic microenvironment slowly release  $\text{Mg}^{2+}$  and gallic acid. The gallic acid released acts as an antioxidant, scavenging excessive production of intracellular reactive oxygen species (ROS), thereby reducing ROS-induced inflammation.<sup>194</sup> *In vivo*, therapeutic effects on diabetic wound healing were significantly improved.

Melanin exists widely in nature and has functions such as antioxidation, temperature regulation, and photoprotection.<sup>196</sup> Cuttlefish ink contains many melanin nanoparticles, which can be extracted as well-dispersed spherical melanin nanoparticles.<sup>197,198</sup> Qi Lei and colleagues presented a hyaluronic acid (HA) microneedle patch functionalized with biomineralized melanin nanoparticles. The microneedle patch enables simultaneous tumor photothermal therapy (PTT) and promotes skin tissue regeneration. Microneedle patches have great potential as adjuvant therapy after skin tumor resection (Fig. 10C).<sup>195</sup> In addition, the researchers designed herbal microneedle patches using two herbs found in nature, *Premna microphylla* and *Centella Asiatica*.<sup>199</sup> The microneedle patch actively shows excellent antioxidant and anti-inflammatory properties of asiaticoside (AS), a natural ingredient is *Centella asiatica*. AS hinders angiogenesis during the remodeling phase in addition to promoting angiogenesis during the inflammatory phase.<sup>200</sup> The preparation of Chinese herbal microneedle patches also serves as a booster for the global promotion of Chinese herbal medicine. In addition, Wang's team successfully manufactured a microneedle



Fig. 10 (A) Schematic illustrations of Fe-MSC-NVs/PDA MN patches for diabetic wound healing.<sup>189</sup> Copyright 2022 Wiley-VCH. (B) Schematic illustration of magnesium organic framework-based MN patches (denoted as MN-MOF-GO-Ag) for accelerating diabetic wound healing.<sup>194</sup> Copyright 2021 American Chemical Society. (C) Schematic diagram of the biomineralized melanin nanoparticle-loaded microneedle patches for the subcutaneous melanoma postoperative wound.<sup>195</sup> Copyright 2022 Wiley-VCH.

patch integrated with Mxenes to achieve a controlled release of AS, which is beneficial for wound healing.<sup>201</sup> The diabetic wound microenvironment is characterized by hyperglycemia, hypoxia, overproduction of oxidative stress and bacterial infection, making wound healing difficult.<sup>202</sup>

### 5.3 Delivering living cells and bioactive factors for skin regeneration

Growth factors, gene delivery, and cell therapy are some of the methods that have been used to speed up the healing of

non-healing wounds.<sup>23</sup> Growth factors such as the PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) have been found to have dysregulated biological activity in chronic trauma in both *in vitro* and *in vivo* studies.<sup>23,203,204</sup> By delivering the right amount of growth factors, the wound can be provided with a better environment for growth.<sup>205</sup> Cell-based therapeutic methods for healing wounds have also received attention. *In vivo*, the incorporation of fibroblasts, keratinocytes, and stem/progenitor cells significantly speeds up wound healing.<sup>23,206–208</sup>

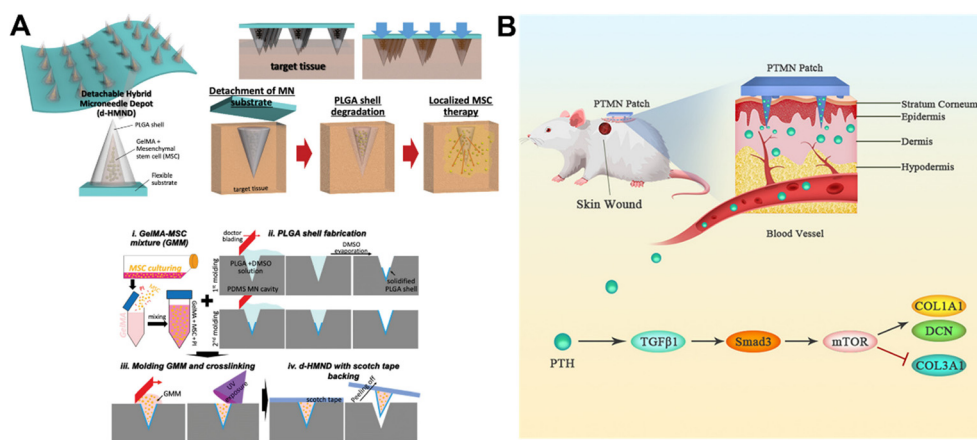


Fig. 11 (A) Conceptual diagram of the microneedle patch and the preparation process.<sup>210</sup> Copyright 2020 Wiley-VCH. (B) New polyvinyl alcohol microneedle patch releases the parathyroid hormone.<sup>214</sup> Copyright 2021 Elsevier.

Chen and his colleagues fabricated polymer microneedle patches for keratinocyte delivery. The delivery rate can reach 83.2%.<sup>209</sup> The design of microneedle patches loaded with mesenchymal stem cells (MSCs) for wound healing was first proposed by Kwangju Lee *et al.* (Fig. 11A).<sup>210</sup> Benefiting from the outer layer of the polylactic acid–ethanolic acid shell, the MSCs in the GelMA-MSC mixture within the microneedle tip remain viable. Results showed that the vitality and function of MSCs could be maintained up to 24 h, which increased wound closure rates and improved re-epithelialization.<sup>210</sup>

MengYuan and colleagues used a gelatin methacrylate microneedle patch to achieve controlled transdermal release of tazarotene and exosomes. Tazarotene is a retinoid that promotes angiogenesis and hair follicle and collagen regeneration.<sup>211</sup> The MCS-exosome is involved in skin regeneration by promoting macrophage polarization and reducing the release of pro-inflammatory factors.<sup>212</sup> Microneedle patches are used for the slow release of exosomes and tazarotene deep in the skin to promote cell migration and angiogenesis.<sup>213</sup> In addition, the researchers achieved a non-invasive sustained release of the parathyroid hormone in rats through the microneedle patches, which promoted wound healing by accelerating extracellular matrix deposition and improving the structure of the extracellular matrix (Fig. 11B).<sup>214</sup> Not only this but microneedle patches that deliver collagen to promote wound healing have also been developed.<sup>215,216</sup> Long *et al.* prepared the first recombinant human-derived collagen (rhCol III) and naproxen (Nap) loaded polylactic acid glycolic acid (PLGA) nanoparticle microneedle patch for the treatment of diabetic chronic wounds.<sup>217</sup> *In vitro* cell culture results show that microneedles loaded with rhCol III can effectively promote the proliferation and migration of fibroblasts and endothelial cells.<sup>217</sup>

## 6. Conclusions and prospects

Wound healing is affected by old age, a weakened immune system and malnutrition, which imposes a significant economic burden on society.<sup>127</sup> Functional dressings for various types of wounds have become increasingly available, but these wound dressings are expected to be able to monitor wound status in real time and provide personalized treatment. A new generation of smart wound dressings with real-time monitoring and on-demand treatment is currently under development to enable real-time tracking of the wound environment. Due to their powerful drug delivery capabilities, customizable microstructure and their superior biocompatibility, microneedle patches have great potential as wound dressings. This article discusses the current application of microneedle patches in promoting wound healing and smart wound management. The microneedle-based sensor enables real-time monitoring of a wide range of biomarkers, enabling early diagnosis of a variety of diseases such as Parkinson's disease and diabetes. However, microneedle-based sensors are still in the preliminary stages of exploration in smart wound management, although microneedle sensors have already realized the monitoring of inflammatory factors at the wound bed and the tracking of motion

sensing. The complex changes in the wound healing environment require them to realize real-time monitoring of more biomarkers and more intelligent wound management. In addition, enabling the monitoring of multiple markers means the interconnection of multiple sensors, and microneedle-based sensors are highly reproducible and stable. Low detection limits are a key requirement for medical problems. Microneedle patches as dressings to facilitate wound healing have undergone tremendous development, from designing individualized microstructures to meeting different adhesion requirements, to enabling the delivery of different functional substances. Based on the bionic, responsive, and conductive properties of microneedle patches, the application of microneedle patches in wound healing is described in three aspects. At the same time, a microneedle patch that promotes wound healing has achieved the delivery of various substances that promote wound healing, including antibacterial agents, living cells, and bioactive factors. However, the adhesion of the microneedle patches to the skin, the delivery efficiency, and the therapeutic effect are the main factors to be investigated. The skin and wounds on the skin are elastic tissues with complicated surface topography and counteracting forces, which can make penetration uneven.<sup>100</sup> Second, skin elasticity and thickness vary according to age, gender, and weight. These complex factors impose higher requirements on the design of microneedle patches. A phase III study of Zosano Pharmaceuticals' microneedle-delivered patch for sumatriptan (migraine) has recently been concluded. However, the FDA requested more data to address differences in the exposure of zolmitriptan and insufficient bridging of the pharmacokinetics of microneedle patches across batches when subjects received different microneedle patches.<sup>218,219</sup>

The smart microneedle patch combines on-demand drug delivery and real-time monitoring and is a new way forward for intelligent wound management. The therapeutic, diagnostic system should include controllable drug delivery patches, tiny electronic controllers, and high-sensitivity biosensors. The sensors send data to the control *via* bluetooth or WiFi after continuously monitoring different biomarkers in the wound environment. A microneedle patch-based system that personalizes treatment through early analysis and diagnosis. However, as far as the current research is concerned, more biomarkers related to wound healing are worth exploring. At the same time, the coordinated detection of multiple markers can provide more accurate data. As far as the existing research articles are concerned, the smart microneedle wound patch only realizes the monitoring of inflammatory factors and motion sensing. It is necessary to prepare microneedle patches with multiple monitoring properties.

## Author contributions

Fangfang Hu: data curation, writing and original draft preparation. Qian Gao, Jinxi Liu, and Wenting Chen: data collection and obtained the permission. Caiyun Zheng Que Bai, Na Sun,



and Wenhui Zhang: supervision. Fangfang Hu, Yanni Zhang, and Tingli Lu: writing, reviewing, and editing. All the authors participated in the conception and design, or analysis and interpretation of the data; drafting of the paper or revising it critically for intellectual content; and the final approval of the version to be published; and all authors agree to be accountable for all aspects of the work.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We acknowledge funding support from the National Natural Science Foundation of China (program no. 81803491), the Key Research and Development Program of Shaanxi (program no. 2021SF-106 and 2022SF-081), and the China Postdoctoral Science Foundation (no. 2021M702633). We appreciate the Experimental Center, College of Life Sciences of Northwestern Polytechnical University for supporting our research on the cell tests.

## References

- 1 S. O. Blacklow, J. Li, B. R. Freedman, M. Zeidi, C. Chen and D. J. Mooney, Bioinspired Mechanically Active Adhesive Dressings to Accelerate Wound Closure, *Sci. Adv.*, 2019, **5**, eaaw3963.
- 2 M. Farahani and A. Shafiee, Wound Healing: From Passive to Smart Dressings, *Adv. Healthcare Mater.*, 2021, **10**, 2100477.
- 3 C. Lindholm and R. Searle, Wound Management for the 21st Century: Combining Effectiveness and Efficiency, *Int. Wound J.*, 2016, **13**, 5–15.
- 4 M. Kerr, E. Barron, P. Chadwick, T. Evans, W. M. Kong, G. Rayman, M. Sutton-Smith, G. Todd, B. Young and W. J. Jeffcoate, The Cost of Diabetic Foot Ulcers and Amputations to the National Health Service in England, *Diabetic Med.*, 2019, **36**, 995–1002.
- 5 K. Raziyeve, Y. Kim, Z. Zharkinbekov, K. Kassymbek, S. Jimi and A. Saparov, Immunology of Acute and Chronic Wound Healing, *Biomolecules*, 2021, **11**, 700.
- 6 C. E. Fife, K. A. Eckert and M. J. Carter, Publicly Reported Wound Healing Rates: The Fantasy and the Reality, *Adv. Wound Care*, 2018, **7**, 77–94.
- 7 H. Derakhshandeh, *et al.*, A Wirelessly Controlled Smart Bandage with 3d-Printed Miniaturized Needle Arrays, *Adv. Funct. Mater.*, 2020, **30**, 1905544.
- 8 L. Barnum, M. Samandari, T. A. Schmidt and A. Tamayol, Microneedle Arrays for the Treatment of Chronic Wounds, *Expert Opin. Drug Delivery*, 2020, **17**, 1767–1780.
- 9 T. N. Demidova-Rice, M. R. Hamblin and I. M. Herman, Acute and Impaired Wound Healing: Pathophysiology and Current Methods for Drug Delivery, Part 1: Normal and Chronic Wounds: Biology, Causes, and Approaches to Care, *Adv. Skin Wound Care*, 2012, **25**, 304–314.
- 10 M. Samandari, *et al.*, Miniaturized Needle Array-Mediated Drug Delivery Accelerates Wound Healing, *Adv. Healthcare Mater.*, 2021, **10**, 2001800.
- 11 H. Sattar, I. S. Bajwa, R. ul Amin, J. Muhammad, M. F. Mushtaq, R. Kazmi, M. Akram, M. Ashraf and U. Shafi, Smart Wound Hydration Monitoring Using Biosensors and Fuzzy Inference System, *Wirel. Commun. Mob. Comput.*, 2019, **2019**, 1–15.
- 12 C. R. Kruse, K. Nuutila, C. C. Y. Lee, E. Kiwanuka, M. Singh, E. J. Caterson, E. Eriksson and J. A. Sorensen, The External Microenvironment of Healing Skin Wounds, *Wound Repair Regen.*, 2015, **23**, 456–464.
- 13 F. Mariani, M. Serafini, I. Gualandi, D. Arcangeli, F. Decataldo, L. Possanzini, M. Tessarolo, D. Tonelli, B. Fraboni and E. Scavetta, Advanced Wound Dressing for Real-Time Ph Monitoring, *ACS Sens.*, 2021, **6**, 2366–2377.
- 14 H. Teymourian, F. Tehrani, K. Mahato and J. Wang, Lab under the Skin: Microneedle Based Wearable Devices, *Adv. Healthcare Mater.*, 2021, **10**, 2002255.
- 15 A. W. C. Chua, Y. C. Khoo, B. K. Tan, K. C. Tan, C. L. Foo and S. J. Chong, Skin Tissue Engineering Advances in Severe Burns: Review and Therapeutic Applications, *Int. J. Burns Trauma*, 2016, **4**, DOI: [10.1186/s41038-016-0027-y](https://doi.org/10.1186/s41038-016-0027-y).
- 16 A. Moeini, P. Pedram, P. Makvandi, M. Malinconico and G. G. d'Ayala, Wound Healing and Antimicrobial Effect of Active Secondary Metabolites in Chitosan-Based Wound Dressings: A Review, *Carbohydr. Polym.*, 2020, **233**, 115839.
- 17 D. M. Supp and S. T. Boyce, Engineered Skin Substitutes: Practices and Potentials, *Clin. Dermatol.*, 2005, **23**, 403–412.
- 18 D. Breikreutz, N. Mirancea and R. Nischt, Basement Membranes in Skin: Unique Matrix Structures with Diverse Functions?, *Histochem. Cell Biol.*, 2009, **132**, 1–10.
- 19 Y. P. Liang, J. H. He and B. L. Guo, Functional Hydrogels as Wound Dressing to Enhance Wound Healing, *ACS Nano*, 2021, **15**, 12687–12722.
- 20 E. E. Tredget, B. Nedelec, P. G. Scott and A. Ghahary, Hypertrophic Scars, Keloids, and Contractures - the Cellular and Molecular Basis for Therapy, *Surg. Clin. North Am.*, 1997, **77**, 701–730.
- 21 B. M. Delavary, W. M. van der Veer, M. van Egmond, F. B. Niessen and R. H. J. Beelen, Macrophages in Skin Injury and Repair, *Immunobiology*, 2011, **216**, 753–762.
- 22 K. A. Bielefeld, S. Amini-Nik and B. A. Alman, Cutaneous Wound Healing: Recruiting Developmental Pathways for Regeneration, *Cell. Mol. Life Sci.*, 2013, **70**, 2059–2081.
- 23 H. S. Kim, X. Y. Sun, J. H. Lee, H. W. Kim, X. B. Fu and K. W. Leong, Advanced Drug Delivery Systems and Artificial Skin Grafts for Skin Wound Healing, *Adv. Drug Delivery Rev.*, 2019, **146**, 209–239.
- 24 M. E. Okur, I. D. Karantas, Z. Senyigit, N. U. Okur and P. I. Sifaka, Recent Trends on Wound Management: New Therapeutic Choices Based on Polymeric Carriers, *Asian J. Pharm. Sci.*, 2020, **15**, 661–684.

- 25 J. Li, J. Chen and R. Kirsner, Pathophysiology of Acute Wound Healing, *Clin. Dermatol.*, 2007, **25**, 9–18.
- 26 M. Rodrigues, N. Kosaric, C. A. Bonham and G. C. Gurtner, Wound Healing: A Cellular Perspective, *Physiol. Rev.*, 2019, **99**, 665–706.
- 27 E. M. Tottoli, R. Dorati, I. Genta, E. Chiesa, S. Pisani and B. Conti, Skin Wound Healing Process and New Emerging Technologies for Skin Wound Care and Regeneration, *Pharmaceutics*, 2020, **12**, 735.
- 28 Z. Wang, F. Rong, Z. Li, W. Li, K. Kaur and Y. Wang, Tailoring Gas-Releasing Nanoplatforams for Wound Treatment: An Emerging Approach, *Chem. Eng. J.*, 2023, **452**, 139297.
- 29 W. Dai, Y. C. Dong, T. Han, J. Wang, B. Gao, H. Guo, F. Xu, J. Li and Y. F. Ma, Microenvironmental Cue-Regulated Exosomes as Therapeutic Strategies for Improving Chronic Wound Healing, *Npg Asia, Materials*, 2022, **14**, 75.
- 30 G. Han and R. Ceille, Chronic Wound Healing: A Review of Current Management and Treatments, *Adv. Ther.*, 2017, **34**, 599–610.
- 31 P. Yang, S. Li, H. Zhang, X. Ding and Q. Tan, Lrg1 Accelerates Wound Healing in Diabetic Rats by Promoting Angiogenesis Via the Wnt/Beta-Catenin Signaling Pathway, *Int. J. Lower Extremity Wounds*, 2022, DOI: [10.1177/15347346221081610](https://doi.org/10.1177/15347346221081610).
- 32 C. C. Yan, *et al.*, Human Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes Accelerate Diabetic Wound Healing Via Ameliorating Oxidative Stress and Promoting Angiogenesis, *Front. Bioeng. Biotechnol.*, 2022, **10**, 7.
- 33 Q. Pang, D. Lou, S. J. Li, G. M. Wang, B. B. Qiao, S. R. Dong, L. Ma, C. Y. Gao and Z. H. Wu, Smart Flexible Electronics-Integrated Wound Dressing for Real-Time Monitoring and on-Demand Treatment of Infected Wounds, *Adv. Sci.*, 2020, **7**, 1902673.
- 34 Q. Wang, S. Ling, X. Liang, H. Wang, H. Lu and Y. Zhang, Self-Healable Multifunctional Electronic Tattoos Based on Silk and Graphene, *Adv. Funct. Mater.*, 2019, **29**, 1808695.
- 35 M. Qin, H. Guo, Z. Dai, X. Yan and X. Ning, Advances in Flexible and Wearable Ph Sensors for Wound Healing Monitoring, *J. Semicond.*, 2019, **40**, 111607.
- 36 S. D. Milne, I. Seoudi, H. Al Hamad, T. K. Talal, A. A. Anoop, N. Allahverdi, Z. Zakaria, R. Menzies and P. Connolly, A Wearable Wound Moisture Sensor as an Indicator for Wound Dressing Change: An Observational Study of Wound Moisture and Status, *Int. Wound J.*, 2016, **13**, 1309–1314.
- 37 L. Wang, Q. H. Hou, W. F. Zheng and X. Y. Jiang, Fluorescent and Antibacterial Aminobenzeneboronic Acid (Aba)-Modified Gold Nanoclusters for Self-Monitoring Residual Dosage and Smart Wound Care, *ACS Nano*, 2021, **15**, 17885–17894.
- 38 Q. Pang, D. Lou, S. Li, G. Wang, B. Qiao, S. Dong, L. Ma, C. Gao and Z. Wu, Smart Flexible Electronics-Integrated Wound Dressing for Real-Time Monitoring and on-Demand Treatment of Infected Wounds, *Adv. Sci.*, 2020, **7**, 1902673.
- 39 K. Zheng, *et al.*, Flexible Bicolorimetric Polyacrylamide/Chitosan Hydrogels for Smart Real-Time Monitoring and Promotion of Wound Healing, *Adv. Funct. Mater.*, 2021, **31**, 2102599.
- 40 Z. Zhang, H. Yan, B. Qiu, P. Ran, W. Cao, X. Jia, K. Huang and X. Li, Persistent Luminescence-Based Theranostics for Real-Time Monitoring and Simultaneously Launching Photodynamic Therapy of Bacterial Infections, *Small*, 2022, **18**, 2200813.
- 41 P. Salvo, V. Dini, F. Di Francesco and M. Romanelli, The Role of Biomedical Sensors in Wound Healing, *Wound Medicine*, 2015, **8**, 15–18.
- 42 P. Salvo, V. Dini, A. Kirchhain, A. Janowska, T. Oranges, A. Chiricozzi, T. Lomonaco, F. Di Francesco and M. Romanelli, Sensors and Biosensors for C-Reactive Protein, Temperature and Ph, and Their Applications for Monitoring Wound Healing: A Review, *Sensors*, 2017, **17**, 2952.
- 43 P. Mostafalu, *et al.*, Smart Bandage for Monitoring and Treatment of Chronic Wounds, *Small*, 2018, **14**, 1703509.
- 44 G. Xu, *et al.*, Battery-Free and Wireless Smart Wound Dressing for Wound Infection Monitoring and Electrically Controlled on-Demand Drug Delivery, *Adv. Funct. Mater.*, 2021, **31**, 2100852.
- 45 Y. N. Zhu, *et al.*, A Multifunctional Pro-Healing Zwitterionic Hydrogel for Simultaneous Optical Monitoring of Ph and Glucose in Diabetic Wound Treatment, *Adv. Funct. Mater.*, 2020, **30**, 1905493.
- 46 X. Zhang, R. Lv, L. Chen, R. Sun, Y. Zhang, R. Sheng, T. Du, Y. Li and Y. Qi, A Multifunctional Janus Electrospun Nanofiber Dressing with Biofluid Draining, Monitoring, and Antibacterial Properties for Wound Healing, *ACS Appl. Mater. Interfaces*, 2022, **14**, 12984–13000.
- 47 M. Tessarolo, L. Possanzini, I. Gualandi, F. Mariani, L. D. Torchia, D. Arcangeli, F. Melandri, E. Scavetta and B. Fraboni, Wireless Textile Moisture Sensor for Wound Care, *Frontiers Physics*, 2021, **9**, 616.
- 48 C. Cheng, Y. M. Qiu, S. M. Tang, B. Y. Lin, M. Z. Guo, B. B. Gao and B. F. He, Artificial Spider Silk Based Programmable Woven Textile for Efficient Wound Management, *Adv. Funct. Mater.*, 2022, **32**, 2107707.
- 49 N. Tang, Y. Zheng, D. Cui and H. Haick, Multifunctional Dressing for Wound Diagnosis and Rehabilitation, *Adv. Healthcare Mater.*, 2021, **10**, 2101292.
- 50 N. Tang, Y. Zheng, X. Jiang, C. Zhou, H. Jin, K. Jin, W. Wu and H. Haick, Wearable Sensors and Systems for Wound Healing-Related Ph and Temperature Detection, *Micromachines*, 2021, **12**, 430.
- 51 A. McLister, J. McHugh, J. Cundell and J. Davis, New Developments in Smart Bandage Technologies for Wound Diagnostics, *Adv. Mater.*, 2016, **28**, 5732–5737.
- 52 C. Watters, T. T. Yuan and K. P. Rumbaugh, Beneficial and Deleterious Bacterial-Host Interactions in Chronic Wound Pathophysiology, *Chronic Wound Care Manag. Res.*, 2015, **2**, 53–62.
- 53 R. Pourkarim, M. R. Farahpour and S. A. Rezaei, Comparison Effects of Platelet-Rich Plasma on Healing of Infected and Non-Infected Excision Wounds by the Modulation of the Expression of Inflammatory Mediators: Experimental Research, *Eur. J. Trauma Emerg. Surg.*, 2022, **48**, 3339–3347.

- 54 D. Braig, B. Kaiser, J. R. Thiele, H. Bannasch, K. Peter, G. B. Stark, H. G. Koch, S. U. Eisenhardt and A. Conformational, Change of C-Reactive Protein in Burn Wounds Unmasks Its Proinflammatory Properties, *Int. Immunol.*, 2014, **26**, 467–478.
- 55 S. RoyChoudhury, *et al.*, Continuous Monitoring of Wound Healing Using a Wearable Enzymatic Uric Acid Biosensor, *J. Electrochem. Soc.*, 2018, **165**, B3168–B3175.
- 56 X. Liu and P. B. Lillehoj, Embroidered Electrochemical Sensors on Gauze for Rapid Quantification of Wound Biomarkers, *Biosens. Bioelectron.*, 2017, **98**, 189–194.
- 57 A. Pal, D. Goswami, H. E. Cuellar, B. Castro, S. H. Kuang and R. V. Martinez, Early Detection and Monitoring of Chronic Wounds Using Low-Cost, Omniphobic Paper-Based Smart Bandages, *Biosens. Bioelectron.*, 2018, **117**, 696–705.
- 58 Y.-C. Du and W.-S. Ciou, A Sensor Gauze with Multi-Channel Moisture and Ph Monitoring for Chronic Wound Care, *IEEE Access*, 2019, **7**, 29185–29192.
- 59 H. S. Guo, *et al.*, Pro-Healing Zwitterionic Skin Sensor Enables Multi-Indicator Distinction and Continuous Real-Time Monitoring, *Adv. Funct. Mater.*, 2021, **31**, 2106406.
- 60 D. A. Jankowska, M. B. Bannwarth, C. Schulenburg, G. Faccio, K. Maniura-Weber, R. M. Rossi, L. Scherer, M. Richter and L. F. Boesel, Simultaneous Detection of Ph Value and Glucose Concentrations for Wound Monitoring Applications, *Biosens. Bioelectron.*, 2017, **87**, 312–319.
- 61 Y. Zhu, *et al.*, A Multifunctional Pro-Healing Zwitterionic Hydrogel for Simultaneous Optical Monitoring of Ph and Glucose in Diabetic Wound Treatment, *Adv. Funct. Mater.*, 2020, **30**, 1905493.
- 62 Y. Gao, *et al.*, A Flexible Multiplexed Immunosensor for Point-of-Care in Situ Wound Monitoring, *Sci. Adv.*, 2021, **7**, eabg9614.
- 63 M. Zheng, *et al.*, Skin-Inspired Gelatin-Based Flexible Bio-Electronic Hydrogel for Wound Healing Promotion and Motion Sensing, *Biomaterials*, 2021, **276**, 121026.
- 64 T. Waghule, G. Singhvi, S. K. Dubey, M. M. Pandey, G. Gupta, M. Singh and K. Dua, Microneedles: A Smart Approach and Increasing Potential for Transdermal Drug Delivery System, *Biomed. Pharmacother.*, 2019, **109**, 1249–1258.
- 65 H. Amani, M. A. Shahbazi, C. D'Amico, F. Fontana, S. Abbaszadeh and H. A. Santos, Microneedles for Painless Transdermal Immunotherapeutic Applications, *J. Controlled Release*, 2021, **330**, 185–217.
- 66 E. Larraneta, R. E. M. Lutton, A. D. Woolfson and R. F. Donnelly, Microneedle Arrays as Transdermal and Intradermal Drug Delivery Systems: Materials Science, Manufacture and Commercial Development, *Mater. Sci. Eng. R Rep.*, 2016, **104**, 1–32.
- 67 Y. W. Naguib, A. Kumar and Z. Cuin, The Effect of Microneedles on the Skin Permeability and Antitumor Activity of Topical 5-Fluorouracil, *Acta Pharm. Sin. B*, 2014, **4**, 94–99.
- 68 M.-C. Kearney, E. Caffarel-Salvador, S. J. Fallows, H. O. McCarthy and R. F. Donnelly, Microneedle-Mediated Delivery of Donepezil: Potential for Improved Treatment Options in Alzheimer's Disease, *Eur. J. Pharm. Biopharm.*, 2016, **103**, 43–50.
- 69 J.-Y. Kim, M.-R. Han, Y.-H. Kim, S.-W. Shin, S.-Y. Nam and J.-H. Park, Tip-Loaded Dissolving Microneedles for Transdermal Delivery of Donepezil Hydrochloride for Treatment of Alzheimer's Disease, *Eur. J. Pharm. Biopharm.*, 2016, **105**, 148–155.
- 70 N. U. Rehman, C. Song, J. Kim, I. Noh, Y.-S. Rhee and H. J. Chung, Pharmacokinetic Evaluation of a Novel Donepezil-Loaded Dissolving Microneedle Patch in Rats, *Pharmaceutics*, 2022, **14**, 5.
- 71 M. Kale, T. Kipping and A. K. Banga, Modulated Delivery of Donepezil Using a Combination of Skin Microporation and Iontophoresis, *Int. J. Pharm.*, 2020, **589**, 119853.
- 72 L. Dong, *et al.*, Au Nanocage-Strengthened Dissolving Microneedles for Chemo-Photothermal Combined Therapy of Superficial Skin Tumors, *ACS Appl. Mater. Interfaces*, 2018, **10**, 9247–9256.
- 73 A. M. V. Mohan, J. R. Windmiller, R. K. Mishra and J. Wang, Continuous Minimally-Invasive Alcohol Monitoring Using Microneedle Sensor Arrays, *Biosens. Bioelectron.*, 2017, **91**, 574–579.
- 74 S. A. Ranamukhaarachchi, C. Padeste, U. O. Hafeli, B. Stoeber and V. J. Cadarso, Design Considerations of a Hollow Microneedle-Optofluidic Biosensing Platform Incorporating Enzyme-Linked Assays, *J. Micromech. Microeng.*, 2018, **28**, 024002.
- 75 O. Hosu, S. Mirel, R. Sandulescu and C. Cristea, Minireview: Smart Tattoo, Microneedle, Point-of-Care, and Phone-Based Biosensors for Medical Screening, Diagnosis, and Monitoring, *Anal. Lett.*, 2019, **52**, 78–92.
- 76 O. Erdem, I. Es, G. A. Akceoglu, Y. Saylan and F. Inci, Recent Advances in Microneedle-Based Sensors for Sampling, Diagnosis and Monitoring of Chronic Diseases, *Biosensors-Basel*, 2021, **11**, 296.
- 77 G.-S. Liu, Y. Kong, Y. Wang, Y. Luo, X. Fan, X. Xie, B.-R. Yang and M. X. Wu, Microneedles for Transdermal Diagnostics: Recent Advances and New Horizons, *Biomaterials*, 2020, **232**, 119740.
- 78 S. Yao, Y. Luo and Y. Wang, Engineered Microneedles Arrays for Wound Healing, *Engineered Regeneration*, 2022, **3**, 232–240.
- 79 R. Y. He, H. Liu, T. S. Fang, Y. Niu, H. Q. Zhang, F. Han, B. Gao, F. Li and F. Xu, A Colorimetric Dermal Tattoo Biosensor Fabricated by Microneedle Patch for Multiplexed Detection of Health-Related Biomarkers, *Adv. Sci.*, 2021, **8**, 2103030.
- 80 J. Y. Shan, X. X. Zhang, B. Kong, Y. J. Zhu, Z. X. Gu, L. J. Ren and Y. J. Zhao, Coordination Polymer Nanozymes-Integrated Colorimetric Microneedle Patches for Intelligent Wound Infection Management, *Chem. Eng. J.*, 2022, **444**, 136640.
- 81 K. Lee, *et al.*, Non-Transdermal Microneedles for Advanced Drug Delivery, *Adv. Drug Delivery Rev.*, 2020, **165–166**, 41–59.
- 82 B. Gao, M. Guo, K. Lyu, T. Chu and B. He, Intelligent Silk Fibroin Based Microneedle Dressing (I-Smd), *Adv. Funct. Mater.*, 2021, **31**, 2006839.



- 83 M. Z. Guo, Y. Q. Wang, B. B. Gao and B. F. He, Shark Tooth-Inspired Microneedle Dressing for Intelligent Wound Management, *ACS Nano*, 2021, **15**, 15316–15327.
- 84 X. Zhang, G. Chen, Y. Yu, L. Sun and Y. Zhao, Bioinspired Adhesive and Antibacterial Microneedles for Versatile Transdermal Drug Delivery, *Research*, 2020, **2020**, DOI: [10.34133/2020/3672120](https://doi.org/10.34133/2020/3672120).
- 85 P. Makvandi, *et al.*, Bioinspired Microneedle Patches: Biomimetic Designs, Fabrication, and Biomedical Applications, *Matter*, 2022, **5**, 390–429.
- 86 X. Zhang, G. Chen, L. Sun, F. Ye, X. Shen and Y. Zhao, Claw-Inspired Microneedle Patches with Liquid Metal Encapsulation for Accelerating Incisional Wound Healing, *Chem. Eng. J.*, 2021, **406**, 126741.
- 87 M. Guo, Y. Wang, B. Gao and B. He, Shark Tooth-Inspired Microneedle Dressing for Intelligent Wound Management, *ACS Nano*, 2021, **15**, 15316–15327.
- 88 W. K. Cho, *et al.*, Microstructured Barbs on the North American Porcupine Quill Enable Easy Tissue Penetration and Difficult Removal, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 21289–21294.
- 89 Y. Deng, C. Yang, Y. Y. Zhu, W. Y. Liu, H. L. Li, L. P. Wang, W. Chen, Z. Wang and L. Wang, Lamprey-Teeth-Inspired Oriented Antibacterial Sericin Microneedles for Infected Wound Healing Improvement, *Nano Lett.*, 2022, **22**, 2702–2711.
- 90 D. Han, R. S. Morde, S. Mariani, A. A. La Mattina, E. Vignali, C. Yang, G. Barillaro and H. Lee, 4d Printing of a Bioinspired Microneedle Array with Backward-Facing Barbs for Enhanced Tissue Adhesion, *Adv. Funct. Mater.*, 2020, **30**, 1909197.
- 91 S. Y. Yang, E. D. O'Cearbhaill, G. C. Sisk, K. M. Park, W. K. Cho, M. Villiger, B. E. Bouma, B. Pomahac, J. M. Karp and A. Bio-Inspired, Swellable Microneedle Adhesive for Mechanical Interlocking with Tissue, *Nat. Commun.*, 2013, **4**, 1702.
- 92 E. Y. Jeon, J. Lee, B. J. Kim, K. I. Joo, K. H. Kim, G. Lim and H. J. Cha, Bio-Inspired Swellable Hydrogel-Forming Double-Layered Adhesive Microneedle Protein Patch for Regenerative Internal/External Surgical Closure, *Biomaterials*, 2019, **222**, 119439.
- 93 Y.-C. Chen and H. Yang, Octopus-Inspired Assembly of Nanosucker Arrays for Dry/Wet Adhesion, *ACS Nano*, 2017, **11**, 5332–5338.
- 94 K. Jiang, Y.-Z. Long, Z.-J. Chen, S.-L. Liu, Y.-Y. Huang, X. Jiang and Z.-Q. Huang, Airflow-Directed in Situ Electrospinning of a Medical Glue of Cyanoacrylate for Rapid Hemostasis in Liver Resection, *Nanoscale*, 2014, **6**, 7792–7798.
- 95 D. H. Park, S. B. Kim, K. D. Ahn, E. Y. Kim, Y. J. Kim and D. K. Han, In Vitro Degradation and Cytotoxicity of Alkyl 2-Cyanoacrylate Polymers for Application to Tissue Adhesives, *J. Appl. Polym. Sci.*, 2003, **89**, 3272–3278.
- 96 X. Zhao, B. Guo, H. Wu, Y. Liang and P. X. Ma, Injectable Antibacterial Conductive Nanocomposite Cryogels with Rapid Shape Recovery for Noncompressible Hemorrhage and Wound Healing, *Nat. Commun.*, 2018, **9**, 2784.
- 97 Y. Huang, X. Zhao, Z. Zhang, Y. Liang, Z. Yin, B. Chen, L. Bai, Y. Han and B. Guo, Degradable Gelatin-Based Ipn Cryogel Hemostat for Rapidly Stopping Deep Noncompressible Hemorrhage and Simultaneously Improving Wound Healing, *Chem. Mater.*, 2020, **32**, 6595–6610.
- 98 Z. Qiao, *et al.*, A Mussel-Inspired Supramolecular Hydrogel with Robust Tissue Anchor for Rapid Hemostasis of Arterial and Visceral Bleedings, *Bioact. Mater.*, 2021, **6**, 2829–2840.
- 99 X. Zhang, G. Chen, L. Cai, Y. Wang, L. Sun and Y. Zhao, Bioinspired Pagoda-Like Microneedle Patches with Strong Fixation and Hemostasis Capabilities, *Chem. Eng. J.*, 2021, **414**, 128905.
- 100 Y. Q. Wang, M. Z. Guo, B. F. He and B. B. Gao, Intelligent Patches for Wound Management: In Situ Sensing and Treatment, *Anal. Chem.*, 2021, **93**, 4687–4696.
- 101 M. C. Chen, M. H. Ling, K. W. Wang, Z. W. Lin, B. H. Lai and D. H. Chen, Near-Infrared Light-Responsive Composite Microneedles for on-Demand Transdermal Drug Delivery, *Biomacromolecules*, 2015, **16**, 1598–1607.
- 102 Z. Zheng, H. Ye, J. Wang, T. Zhang, Q. You, H. Li, R. He, Y. Chen, W. Zhang and Y. Cao, Visible-Light-Controllable Drug Release from Multilayer-Coated Microneedles, *J. Mater. Chem. B*, 2017, **5**, 7014–7017.
- 103 L. Fan, X. Zhang, M. Nie, Y. Xu, Y. Wang, L. Shang, Y. Zhao and Y. Zhao, Photothermal Responsive Microspheres-Triggered Separable Microneedles for Versatile Drug Delivery, *Adv. Funct. Mater.*, 2022, **32**, 2110746.
- 104 Y. Zhang, D. F. Wang, M. Y. Gao, B. Xu, J. Y. Zhu, W. J. Yu, D. P. Liu and G. H. Jiang, Separable Microneedles for near-Infrared Light-Triggered Transdermal Delivery of Metformin in Diabetic Rats, *ACS Biomater. Sci. Eng.*, 2018, **4**, 2879–2888.
- 105 S. A. Gaware, K. A. Rokade, P. Bala and S. N. Kale, Microneedles of Chitosan-Porous Carbon Nanocomposites: Stimuli (Ph and Electric Field)-Initiated Drug Delivery and Toxicological Studies, *J. Biomed. Mater. Res., Part A*, 2019, **107**, 1582–1596.
- 106 X. Zhang, G. Chen, X. Fu, Y. Wang and Y. Zhao, Magneto-Responsive Microneedle Robots for Intestinal Macromolecule Delivery, *Adv. Mater.*, 2021, **33**, 2104932.
- 107 Y. Zhang, D. N. Chai, M. Y. Gao, B. Xu and G. H. Jiang, Thermal Ablation of Separable Microneedles for Transdermal Delivery of Metformin on Diabetic Rats, *Int. J. Polym. Mater. Polym. Biomater.*, 2019, **68**, 850–858.
- 108 Y. Wang, H. Lu, M. Guo, J. Chu, B. Gao and B. He, Personalized and Programmable Microneedle Dressing for Promoting Wound Healing, *Adv. Healthcare Mater.*, 2022, **11**, 2101659.
- 109 Y. Q. Zhang, J. Q. Wang, J. C. Yu, D. Wen, A. R. Kahkoska, Y. Lu, X. D. Zhang, J. B. Buse and Z. Gu, Bioresponsive Microneedles with a Sheath Structure for H<sub>2</sub>O<sub>2</sub> and Ph Cascade-Triggered Insulin Delivery, *Small*, 2018, **14**, 1704181.
- 110 J. Yu, J. Wang, Y. Zhang, G. Chen, W. Mao, Y. Ye, A. R. Kahkoska, J. B. Buse, R. Langer and Z. Gu, Glucose-Responsive Insulin Patch for the Regulation of Blood

- Glucose in Mice and Minipigs, *Nat. Biomed. Eng.*, 2020, **4**, 499–506.
- 111 Y. Zhang, P. Feng, J. Yu, J. Yang, J. Zhao, J. Wang, Q. Shen and Z. Gu, Ros-Responsive Microneedle Patch for Acne Vulgaris Treatment, *Adv. Ther.*, 2018, **1**, 1800035.
  - 112 X. Yue, Q. Zhang and Z. Dai, Near-Infrared Light-Activatable Polymeric Nanoformulations for Combined Therapy and Imaging of Cancer, *Adv. Drug Delivery Rev.*, 2017, **115**, 155–170.
  - 113 P. Makvandi, *et al.*, Stimuli-Responsive Transdermal Microneedle Patches, *Mater. Today*, 2021, **47**, 206–222.
  - 114 S. Yao, Y. Wang, J. Chi, Y. Yu, Y. Zhao, Y. Luo and Y. Wang, Porous Mof Microneedle Array Patch with Photothermal Responsive Nitric Oxide Delivery for Wound Healing, *Adv. Sci.*, 2022, **9**, 2103449.
  - 115 M. B. Witte and A. Barbul, Role of Nitric Oxide in Wound Repair, *Am. J. Surg.*, 2002, **183**, 406–412.
  - 116 C. J. Ma, Y. He, X. Jin, Y. Zhang, X. Zhang, Y. Li, M. Xu, K. Liu, Y. Yao and F. Lu, Light-Regulated Nitric Oxide Release from Hydrogel-Forming Microneedles Integrated with Graphene Oxide for Biofilm-Infected-Wound Healing, *Biomater. Adv.*, 2022, **134**, 112555.
  - 117 S. Schreml, R. M. Szeimies, L. Prantl, S. Karrer, M. Landthaler and P. Babilas, Oxygen in Acute and Chronic Wound Healing, *Br. J. Dermatol.*, 2010, **163**, 257–268.
  - 118 W. L. Yip, Influence of Oxygen on Wound Healing, *Int. Wound J.*, 2015, **12**, 620–624.
  - 119 X. Zhang, G. Chen, Y. Liu, L. Sun, L. Sun and Y. Zhao, Black Phosphorus-Loaded Separable Microneedles as Responsive Oxygen Delivery Carriers for Wound Healing, *ACS Nano*, 2020, **14**, 5901–5908.
  - 120 Z. B. Sun, H. H. Xie, S. Y. Tang, X. F. Yu, Z. N. Guo, J. D. Shao, H. Zhang, H. Huang, H. Y. Wang and P. K. Chu, Ultrasmall Black Phosphorus Quantum Dots: Synthesis and Use as Photothermal Agents, *Angew. Chem., Int. Ed.*, 2015, **54**, 11526–11530.
  - 121 Y. Zeng, Y.-R. V. Shih, G. S. Baht and S. Varghese, In Vivo Sequestration of Innate Small Molecules to Promote Bone Healing, *Adv. Mater.*, 2020, **32**, 1906022.
  - 122 Z. Bonyanian, M. Walker, E. Du Toit and R. B. Rose-Meyer, Multiple Adenosine Receptor Subtypes Stimulate Wound Healing in Human Ea.Hy926 Endothelial Cells, *Purinergic Signalling*, 2019, **15**, 357–366.
  - 123 M. C. Montesinos, A. Desai, J. F. Chen, H. Yee, M. A. Schwarzschild, J. S. Fink and B. N. Cronstein, Adenosine Promotes Wound Healing and Mediates Angiogenesis in Response to Tissue Injury Via Occupancy of a(2a) Receptors, *Am. J. Pathol.*, 2002, **160**, 2009–2018.
  - 124 S. Wang, Z. Zhang, S. Wei, F. He, Z. Li, H.-H. Wang, Y. Huang and Z. Nie, Near-Infrared Light-Controllable Mxene Hydrogel for Tunable on-Demand Release of Therapeutic Proteins, *Acta Biomater.*, 2021, **130**, 138–148.
  - 125 P. Xue, *et al.*, Near-Infrared Light-Driven Shape-Morphing of Programmable Anisotropic Hydrogels Enabled by Mxene Nanosheets, *Angew. Chem., Int. Ed.*, 2021, **60**, 3390–3396.
  - 126 L. Y. Sun, L. Fan, F. K. Bian, G. P. Chen, Y. T. Wang and Y. J. Zhao, Mxene-Integrated Microneedle Patches with Innate Molecule Encapsulation for Wound Healing, *Research*, 2021, **2021**, 9838490.
  - 127 J. Chi, X. Zhang, C. Chen, C. Shao, Y. Zhao and Y. Wang, Antibacterial and Angiogenic Chitosan Microneedle Array Patch for Promoting Wound Healing, *Bioact. Mater.*, 2020, **5**, 253–259.
  - 128 D. Y. Shan, E. Gerhard, C. J. Zhang, J. W. Tierney, D. Xie, Z. W. Liu and J. Yang, Polymeric Biomaterials for Biophotonic Applications, *Bioact. Mater.*, 2018, **3**, 434–445.
  - 129 B. B. Gao, M. Z. Guo, K. Lyu, T. S. Chu and B. F. He, Intelligent Silk Fibroin Based Microneedle Dressing (I-Smd), *Adv. Funct. Mater.*, 2021, **31**, 2006839.
  - 130 Y. Ren, X. Yu, Z. Li, D. Liu and X. Xue, Fabrication of Ph-Responsive Ta-Keratin Bio-Composited Hydrogels Encapsulated with Photoluminescent Go Quantum Dots for Improved Bacterial Inhibition and Healing Efficacy in Wound Care Management: In Vivo Wound Evaluations, *J. Photochem. Photobiol., B*, 2020, **202**, 111676.
  - 131 A. Ullah, M. Jang, H. Khan, H. J. Choi, S. An, D. Kim, Y.-R. Kim, U.-K. Kim and G. M. Kim, Microneedle Array with a Ph-Responsive Polymer Coating and Its Application in Smart Drug Delivery for Wound Healing, *Sens. Actuators, B*, 2021, **345**, 130441.
  - 132 V. C. Ibekwe, H. M. Fadda, G. E. Parsons and A. W. Basit, A Comparative in Vitro Assessment of the Drug Release Performance of Ph-Responsive Polymers for Ileo-Colonic Delivery, *Int. J. Pharm.*, 2006, **308**, 52–60.
  - 133 Z. Guo, H. Liu, Z. Shi, L. Lin, Y. Li, M. Wang, G. Pan, Y. Lei and L. Xue, Responsive Hydrogel-Based Microneedle Dressing for Diabetic Wound Healing, *J. Mater. Chem. B*, 2022, **10**, 3501–3511.
  - 134 Y. Liu, M. Petreaca and M. Martins-Green, Cell and Molecular Mechanisms of Insulin-Induced Angiogenesis, *J. Cell. Mol. Med.*, 2009, **13**, 4492–4504.
  - 135 Y. Liu, M. Petreaca, M. Yao and M. Martins-Green, Cell and Molecular Mechanisms of Keratinocyte Function Stimulated by Insulin During Wound Healing, *BMC Cell Biol.*, 2009, **10**, 1–15.
  - 136 P. Yang, *et al.*, Insulin-Containing Wound Dressing Promotes Diabetic Wound Healing through Stabilizing Hif-1 Alpha, *Front. Bioeng. Biotechnol.*, 2020, **8**, 592833.
  - 137 M. Zhao, Electrical Fields in Wound Healing—an Overriding Signal That Directs Cell Migration, *Semin. Cell Dev. Biol.*, 2009, **20**, 674–682.
  - 138 K. Y. Nishimura, R. R. Isseroff and R. Nuccitelli, Human Keratinocytes Migrate to the Negative Pole in Direct Current Electric Fields Comparable to Those Measured in Mammalian Wounds, *J. Cell Sci.*, 1996, **109**, 199–207.
  - 139 L. F. Jaffe and J. W. Vanable, Jr., Electric Fields and Wound Healing, *Clin. Dermatol.*, 1984, **2**, 34–44.
  - 140 Y.-S. Sun, Electrical Stimulation for Wound-Healing: Simulation on the Effect of Electrode Configurations, *BioMed Res. Int.*, 2017, **2017**, 5289041.
  - 141 S. B. Rajendran, K. Challen, K. L. Wright and J. G. Hardy, Electrical Stimulation to Enhance Wound Healing, *J. Funct. Biomater.*, 2021, **12**, 40.

- 142 Y. Long, *et al.*, Effective Wound Healing Enabled by Discrete Alternative Electric Fields from Wearable Nanogenerators, *ACS Nano*, 2018, **12**, 12533–12540.
- 143 A. Guo, B. Song, B. Reid, Y. Gu, J. V. Forrester, C. A. B. Jahoda and M. Zhao, Effects of Physiological Electric Fields on Migration of Human Dermal Fibroblasts, *J. Invest. Dermatol.*, 2010, **130**, 2320–2327.
- 144 Y. Su, *et al.*, Dissolvable Microneedles Coupled with Nanofiber Dressings Eradicate Biofilms Via Effectively Delivering a Database-Designed Antimicrobial Peptide, *ACS Nano*, 2020, **14**, 11775–11786.
- 145 A. D. Permana, M. Mir, E. Utomo and R. F. Donnelly, Bacterially Sensitive Nanoparticle-Based Dissolving Microneedles of Doxycycline for Enhanced Treatment of Bacterial Biofilm Skin Infection: A Proof of Concept Study, *Int. J. Pharm.: X*, 2020, **2**, 100047.
- 146 H. C. Flemming and J. Wingender, The Biofilm Matrix, *Nat. Rev. Microbiol.*, 2010, **8**, 623–633.
- 147 R. Jamaledin, C. K. Y. Yiu, E. N. Zare, L.-N. Niu, R. Vecchione, G. Chen, Z. Gu, F. R. Tay and P. Makvandi, Advances in Antimicrobial Microneedle Patches for Combating Infections, *Adv. Mater.*, 2020, **32**, 2002129.
- 148 H. Koo, R. N. Allan, R. P. Howlin, P. Stoodley and L. Hall-Stoodley, Targeting Microbial Biofilms: Current and Prospective Therapeutic Strategies, *Nat. Rev. Microbiol.*, 2017, **15**, 740–755.
- 149 J. H. Xu, R. Danehy, H. W. Cai, Z. Ao, M. Pu, A. Nusawardhana, D. Rowe-Magnus and F. Guo, Microneedle Patch-Mediated Treatment of Bacterial Biofilms, *ACS Appl. Mater. Interfaces*, 2019, **11**, 14640–14646.
- 150 J. Ziesmer, P. Tajpara, N.-J. Hempel, M. Ehrstrom, K. Melican, L. Eidsmo and G. A. Sotiriou, Vancomycin-Loaded Microneedle Arrays against Methicillin-Resistant *Staphylococcus Aureus* Skin Infections, *Adv. Mater. Technol.*, 2021, **6**, 2001307.
- 151 K. Tsioris, W. K. Raja, E. M. Pritchard, B. Panilaitis, D. L. Kaplan and F. G. Omenetto, Fabrication of Silk Microneedles for Controlled-Release Drug Delivery, *Adv. Funct. Mater.*, 2012, **22**, 330–335.
- 152 S. Sillankorva, L. Pires, L. M. Pastrana and M. Banobre-Lopez, Antibiofilm Efficacy of the *Pseudomonas Aeruginosa* Pbnavirus Vb\_Paem-Sms29 Loaded onto Dissolving Polyvinyl Alcohol Microneedles, *Viruses-Basel*, 2022, **14**, 964.
- 153 I. Woodhouse, *et al.*, Flexible Microneedle Array Patch for Chronic Wound Oxygenation and Biofilm Eradication, *ACS Appl. Bio Mater.*, 2021, **4**, 5405–5415.
- 154 M. Mir, A. D. Permana, N. Ahmed, G. M. Khan, A. U. Rehman and R. F. Donnelly, Enhancement in Site-Specific Delivery of Carvacrol for Potential Treatment of Infected Wounds Using Infection Responsive Nanoparticles Loaded into Dissolving Microneedles: A Proof of Concept Study, *Eur. J. Pharm. Biopharm.*, 2020, **147**, 57–68.
- 155 A. Panda, A. Shettar, P. K. Sharma, M. A. Repka and S. N. Murthy, Development of Lysozyme Loaded Microneedles for Dermal Applications, *Int. J. Pharm.*, 2021, **593**, 120104.
- 156 M. S. Arshad, A. T. Zahra, S. Zafar, H. Zaman, A. Akhtar, M. M. Ayaz, I. Kucuk, M. Maniruzzaman, M. W. Chang and Z. Ahmad, Antibiofilm Effects of Macrolide Loaded Microneedle Patches: Prospects in Healing Infected Wounds, *Pharm. Res.*, 2021, **38**, 165–177.
- 157 X. Yu, J. Zhao and D. Fan, A Dissolving Microneedle Patch for Antibiotic/Enzymolysis/Photothermal Triple Therapy against Bacteria and Their Biofilms, *Chem. Eng. J.*, 2022, **437**, 135475.
- 158 L. E. G. Garcia, M. N. MacGregor, R. M. Visalakshan, N. Ninan, A. A. Cavallaro, A. D. Trinidad, Y. P. Zhao, A. J. D. Hayball and K. Vasilev, Self-Sterilizing Antibacterial Silver-Loaded Microneedles, *Chem. Commun.*, 2019, **55**, 171–174.
- 159 A. D. Permana, *et al.*, Selective Delivery of Silver Nanoparticles for Improved Treatment of Biofilm Skin Infection Using Bacteria-Responsive Microparticles Loaded into Dissolving Microneedles, *Mater. Sci. Eng., C*, 2021, **120**, 111786.
- 160 S. Yao, J. Chi, Y. Wang, Y. Zhao, Y. Luo and Y. Wang, Zn-Mof Encapsulated Antibacterial and Degradable Microneedles Array for Promoting Wound Healing, *Adv. Healthcare Mater.*, 2021, **10**, 2100056.
- 161 X. Yi, C. Wang, X. Yu, W. Su and Z. Yuan, Chitosan/Zinc Nitrate Microneedles for Bacterial Biofilm Eradication, *J. Biomed. Mater. Res., Part B*, 2021, **109**, 911–920.
- 162 T. Ning, *et al.*, Synergistically Detachable Microneedle Dressing for Programmed Treatment of Chronic Wounds, *Adv. Healthcare Mater.*, 2022, **11**, 2102180.
- 163 L. K. Jennings, *et al.*, Pel Is a Cationic Exopolysaccharide That Cross-Links Extracellular DNA in the *Pseudomonas Aeruginosa* Biofilm Matrix, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 11353–11358.
- 164 T. F. Bahamondez-Canas, L. A. Heersema and H. D. C. Smyth, Current Status of in Vitro Models and Assays for Susceptibility Testing for Wound Biofilm Infections, *Biomedicines*, 2019, **7**, 34.
- 165 P. Kaiser, J. Wachter and M. Windbergs, Therapy of Infected Wounds: Overcoming Clinical Challenges by Advanced Drug Delivery Systems, *Drug Delivery Transl. Res.*, 2021, **11**, 1545–1567.
- 166 Y. H. Yan, Y. Z. Li, Z. W. Zhang, X. H. Wang, Y. Z. Niu, S. H. Zhang, W. L. Xu and C. G. Ren, Advances of Peptides for Antibacterial Applications, *Colloids Surf., B*, 2021, **202**, 111682.
- 167 Y. J. Su, *et al.*, Dissolvable Microneedles Coupled with Nanofiber Dressings Eradicate Biofilms Via Effectively Delivering a Database-Designed Antimicrobial Peptide, *ACS Nano*, 2020, **14**, 11775–11786.
- 168 S. S. Khan, A. Mukherjee and N. Chandrasekaran, Studies on Interaction of Colloidal Silver Nanoparticles (Snps) with Five Different Bacterial Species, *Colloids Surf., B*, 2011, **87**, 129–138.
- 169 R. Sinha, R. Karan, A. Sinha and S. K. Khare, Interaction and Nanotoxic Effect of ZnO and Ag Nanoparticles on Mesophilic and Halophilic Bacterial Cells, *Bioresour. Technol.*, 2011, **102**, 1516–1520.



- 170 B. Wu, R. Huang, M. Sahu, X. Y. Feng, P. Biswas and Y. J. Tang, Bacterial Responses to Cu-Doped TiO<sub>2</sub> Nanoparticles, *Sci. Total Environ.*, 2010, **408**, 1755–1758.
- 171 W. Jiang, H. Mashayekhi and B. Xing, Bacterial Toxicity Comparison between Nano- and Micro-Scaled Oxide Particles, *Environmental Pollution*, 2009, **157**, 1619–1625.
- 172 M. J. Hajipour, K. M. Fromm, A. A. Ashkarran, D. J. de Aberasturi, I. R. de Larramendi, T. Rojo, V. Serpooshan, W. J. Parak and M. Mahmoudi, Antibacterial Properties of Nanoparticles, *Trends Biotechnol.*, 2012, **30**, 499–511.
- 173 K. Kalishwaralal, S. BarathManiKanth, S. R. K. Pandian, V. Deepak and S. Gurunathan, Silver Nanoparticles Impede the Biofilm Formation by *Pseudomonas Aeruginosa* and *Staphylococcus Epidermidis*, *Colloids Surf., B*, 2010, **79**, 340–344.
- 174 A. R. Shahverdi, A. Fakhimi, H. R. Shahverdi and S. Minaian, Synthesis and Effect of Silver Nanoparticles on the Antibacterial Activity of Different Antibiotics against *Staphylococcus Aureus* and *Escherichia Coli*, *Nanomedicine*, 2007, **3**, 168–171.
- 175 M. van der Zande, *et al.*, Distribution, Elimination, and Toxicity of Silver Nanoparticles and Silver Ions in Rats after 28-Day Oral Exposure, *ACS Nano*, 2012, **6**, 7427–7442.
- 176 M. F. Shen, F. Forghani, X. Q. Kong, D. H. Liu, X. Q. Ye, S. G. Chen and T. Ding, Antibacterial Applications of Metal-Organic Frameworks and Their Composites, *Compr. Rev. Food Sci. Food Saf.*, 2020, **19**, 1397–1419.
- 177 S. Yao, J. J. Chi, Y. T. Wang, Y. J. Zhao, Y. Luo and Y. A. Wang, Zn-Mof Encapsulated Antibacterial and Degradable Microneedles Array for Promoting Wound Healing, *Adv. Healthcare Mater.*, 2021, **10**, 2100056.
- 178 N. A. Kamel, S. L. Abd El-Messieh and N. M. Saleh, Chitosan/Banana Peel Powder Nanocomposites for Wound Dressing Application: Preparation and Characterization, *Mater. Sci. Eng., C*, 2017, **72**, 543–550.
- 179 M. Hosseiniadjad and S. M. Jafari, Evaluation of Different Factors Affecting Antimicrobial Properties of Chitosan, *Int. J. Biol. Macromol.*, 2016, **85**, 467–475.
- 180 G. F. Yuan, H. Lv, W. Y. Tang, X. J. Zhang and H. Y. Sun, Effect of Chitosan Coating Combined with Pomegranate Peel Extract on the Quality of Pacific White Shrimp During Iced Storage, *Food Control*, 2016, **59**, 818–823.
- 181 F. R. Tamara, C. Lin, F.-L. Mi and Y.-C. Ho, Antibacterial Effects of Chitosan/Cationic Peptide Nanoparticles, *Nanomaterials*, 2018, **8**, 88.
- 182 M. Tian, L. Zhou, C. Fan, L. Wang, X. Lin, Y. Wen, L. Su and H. Dong, Bimetal-Organic Framework/Gox-Based Hydrogel Dressings with Antibacterial and Inflammatory Modulation for Wound Healing, *Acta Biomater.*, 2022, **158**, 252–265.
- 183 S. Y. Kim and M. G. Nair, Macrophages in Wound Healing: Activation and Plasticity, *Immunol. Cell Biol.*, 2019, **97**, 258–267.
- 184 A. E. Boniakowski, A. S. Kimball, B. N. Jacobs, S. L. Kunkel and K. A. Gallagher, Macrophage-Mediated Inflammation in Normal and Diabetic Wound Healing, *J. Immunol.*, 2017, **199**, 17–24.
- 185 C. Dunnill, T. Patton, J. Brennan, J. Barrett, M. Dryden, J. Cooke, D. Leaper and N. T. Georgopoulos, Reactive Oxygen Species (Ros) and Wound Healing: The Functional Role of Ros and Emerging Ros-Modulating Technologies for Augmentation of the Healing Process, *Int. Wound J.*, 2017, **14**, 89–96.
- 186 H. Zhao, J. Huang, Y. Li, X. J. Lv, H. T. Zhou, H. R. Wang, Y. Y. Xu, C. Wang, J. Wang and Z. Liu, Ros-Scavenging Hydrogel to Promote Healing of Bacteria Infected Diabetic Wounds, *Biomaterials*, 2020, **258**, 120286.
- 187 H. Wu, F. Li, W. Shao, J. Gao and D. Ling, Promoting Angiogenesis in Oxidative Diabetic Wound Microenvironment Using a Nanozyme-Reinforced Self-Protecting Hydrogel, *ACS Cent. Sci.*, 2019, **5**, 477–485.
- 188 J. Zhu, Q. Jin, H. Zhao, W. Zhu, Z. Liu and Q. Chen, Reactive Oxygen Species Scavenging Sutures for Enhanced Wound Sealing and Repair, *Small Structures*, 2021, **2**, 2100002.
- 189 W. Ma, X. Zhang, Y. Liu, L. Fan, J. Gan, W. Liu, Y. Zhao and L. Sun, Polydopamine Decorated Microneedles with Fe-Msc-Derived Nanovesicles Encapsulation for Wound Healing, *Adv. Sci.*, 2022, **9**, 2103317.
- 190 X. Bao, J. Zhao, J. Sun, M. Hu and X. Yang, Polydopamine Nanoparticles as Efficient Scavengers for Reactive Oxygen Species in Periodontal Disease, *ACS Nano*, 2018, **12**, 8882–8892.
- 191 S. Sharma, D. Mittal, A. K. Verma and I. Roy, Copper-Gallic Acid Nanoscale Metal-Organic Framework for Combined Drug Delivery and Photodynamic Therapy, *ACS Appl. Bio Mater.*, 2019, **2**, 2092–2101.
- 192 A. Ahangarpour, H. Sharifinasab, H. Kalantari, M. A. Dehghani, N. S. Maram and F. Golfakhrabadi, Gallic Acid and Gallic Acid Nanoparticle Modulate Insulin Secretion Pancreatic Beta-Islets against Silica Nanoparticle-Induced Oxidative Damage, *Biol. Trace Elem. Res.*, 2022, **200**, 5159–5171.
- 193 D. L. Tran, P. L. Thi, T. T. H. Thi and K. D. Park, Novel Enzymatically Crosslinked Chitosan Hydrogels with Free-Radical-Scavenging Property and Promoted Cellular Behaviors under Hyperglycemia, *Prog. Nat. Sci.: Mater. Int.*, 2020, **30**, 661–668.
- 194 M. Yin, *et al.*, Multifunctional Magnesium Organic Framework-Based Microneedle Patch for Accelerating Diabetic Wound Healing, *ACS Nano*, 2021, **15**, 17842–17853.
- 195 Q. Lei, *et al.*, Microneedle Patches Integrated with Biomineralized Melanin Nanoparticles for Simultaneous Skin Tumor Photothermal Therapy and Wound Healing, *Adv. Funct. Mater.*, 2022, **32**, 2113269.
- 196 E. Di Mauro, O. Carpentier, S. I. Y. Sanchez, N. I. Ignoumba, M. Lalancette-Jean, J. Lefebvre, S. Zhang, C. F. O. Graeff, F. Cicoira and C. Santato, Resistive Switching Controlled by the Hydration Level in Thin Films of the Biopigment Eumelanin, *J. Mater. Chem. C*, 2016, **4**, 9544–9553.
- 197 Y. Liang, R. Li, H. Sun, J. Dan, Z. Su, Y. Kang, Q. Zhang, S. Shi, J. Wang and W. Zhang, Functionalized Natural

- Melanin Nanoparticle Mimics Natural Peroxidase for Total Antioxidant Capacity Determination, *Sens. Actuators, B*, 2022, **359**, 131541.
- 198 J. Zhou, W. Liu, X. Y. Zhao, Y. F. Xian, W. Wu, X. Zhang, N. N. Zhao, F. J. Xu and C. Y. Wang, Natural Melanin/Alginate Hydrogels Achieve Cardiac Repair through ROS Scavenging and Macrophage Polarization, *Adv. Sci.*, 2021, **8**, 2100505.
  - 199 J. Chi, L. Sun, L. Cai, L. Fan, C. Shao, L. Shang and Y. Zhao, Chinese Herb Microneedle Patch for Wound Healing, *Bioact. Mater.*, 2021, **6**, 3507–3514.
  - 200 J. Huang, X. Zhou, L. Xia, W. Liu, F. Guo, J. Liu and W. Liu, Inhibition of Hypertrophic Scar Formation with Oral Asiaticoside Treatment in a Rabbit Ear Scar Model, *Int. Wound J.*, 2021, **18**, 598–607.
  - 201 P. Wang, Y. Wang, Y. Yi, Y. Gong, H. Ji, Y. Gan, F. Xie, J. Fan and X. Wang, Mxenes-Integrated Microneedle Combined with Asiaticoside to Penetrate the Cuticle for Treatment of Diabetic Foot Ulcer, *J. Nanobiotechnol.*, 2022, **20**, 259.
  - 202 J. Shan, X. Zhang, Y. Cheng, C. Song, G. Chen, Z. Gu and Y. Zhao, Glucose Metabolism-Inspired Catalytic Patches for NIR-II Phototherapy of Diabetic Wound Infection, *Acta Biomater.*, 2023, **157**, 200–209.
  - 203 A. P. Veith, K. Henderson, A. Spencer, A. Univer and A. B. Baker, Therapeutic Strategies for Enhancing Angiogenesis in Wound Healing, *Adv. Drug Delivery Rev.*, 2019, **146**, 97–125.
  - 204 N. S. Greaves, K. J. Ashcroft, M. Baguneid and A. Bayat, Current Understanding of Molecular and Cellular Mechanisms in Fibroplasia and Angiogenesis During Acute Wound Healing, *J. Dermatol. Sci.*, 2013, **72**, 206–217.
  - 205 S. Yamakawa and K. Hayashida, Advances in Surgical Applications of Growth Factors for Wound Healing, *Int. J. Burns Trauma*, 2019, **7**, DOI: [10.1186/s41038-019-0148-1](https://doi.org/10.1186/s41038-019-0148-1).
  - 206 G. Mascré, S. Dekoninck, B. Drogat, K. K. Youssef, S. Brohee, P. A. Sotiropoulou, B. D. Simons and C. Blanpain, Distinct Contribution of Stem and Progenitor Cells to Epidermal Maintenance, *Nature*, 2012, **489**, 257–262.
  - 207 D. T. Woodley, Distinct Fibroblasts in the Papillary and Reticular Dermis: Implications for Wound Healing, *Dermatol. Clin.*, 2017, **35**, 95–100.
  - 208 L. Y. Liu, Y. H. Yu, Y. S. Hou, J. K. Chai, H. J. Duan, W. L. Chu, H. J. Zhang, Q. Hu and J. D. Du, Human Umbilical Cord Mesenchymal Stem Cells Transplantation Promotes Cutaneous Wound Healing of Severe Burned Rats, *PLoS One*, 2014, **9**, e88348.
  - 209 Y. H. Chen, D. C. Lin, E. Chern and Y. Y. Huang, The Use of Micro-Needle Arrays to Deliver Cells for Cellular Therapies, *Biomed. Microdevices*, 2020, **22**, 1–8.
  - 210 K. Lee, *et al.*, A Patch of Detachable Hybrid Microneedle Depot for Localized Delivery of Mesenchymal Stem Cells in Regeneration Therapy, *Adv. Funct. Mater.*, 2020, **30**, 2000086.
  - 211 Z. Zhu, Y. Liu, Y. Xue, X. Cheng, W. Zhao, J. Wang, R. He, Q. Wan and X. Pei, Tazarotene Released from Aligned Electrospun Membrane Facilitates Cutaneous Wound Healing by Promoting Angiogenesis, *ACS Appl. Mater. Interfaces*, 2019, **11**, 36141–36153.
  - 212 D. H. Ha, *et al.*, Mesenchymal Stem/Stromal Cell-Derived Exosomes for Immunomodulatory Therapeutics and Skin Regeneration, *Cells*, 2020, **9**, 1157.
  - 213 M. Yuan, *et al.*, Gelma/Pegda Microneedles Patch Loaded with HUVECs-Derived Exosomes and Tazarotene Promote Diabetic Wound Healing, *J. Nanobiotechnol.*, 2022, **20**, 147.
  - 214 Z. X. Yao, T. Xue, H. Xiong, C. A. D. Cai, X. D. Liu, F. Wu, S. Liu and C. Y. Fan, Promotion of Collagen Deposition During Skin Healing through Smad3/Mtor Pathway by Parathyroid Hormone-Loaded Microneedle, *Mater. Sci. Eng., C*, 2021, **119**, 111446.
  - 215 L.-y Long, W. Liu, L. Li, C. Hu, S. He, L. Lu, J. Wang, L. Yang and Y.-b Wang, Dissolving Microneedle-Encapsulated Drug-Loaded Nanoparticles and Recombinant Humanized Collagen Type III for the Treatment of Chronic Wound Via Anti-Inflammation and Enhanced Cell Proliferation and Angiogenesis, *Nanoscale*, 2022, **14**, 1285–1295.
  - 216 W. Sun, M. Inayathullah, M. A. C. Manoukian, A. V. Malkovskiy, S. Manickam, M. P. Marinkovich, A. T. Lane, L. Tayebi, A. M. Seifalian and J. Rajadas, Transdermal Delivery of Functional Collagen Via Polyvinylpyrrolidone Microneedles, *Ann. Biomed. Eng.*, 2015, **43**, 2978–2990.
  - 217 L. Y. Long, W. Q. Liu, L. Li, C. Hu, S. Y. He, L. Lu, J. Wang, L. Yang and Y. B. Wang, Dissolving Microneedle-Encapsulated Drug-Loaded Nanoparticles and Recombinant Humanized Collagen Type III for the Treatment of Chronic Wound Via Anti-Inflammation and Enhanced Cell Proliferation and Angiogenesis, *Nanoscale*, 2022, **14**, 1285–1295.
  - 218 B. Creelman, C. Frivold, S. Jessup, G. Saxon and C. Jarrahian, Manufacturing Readiness Assessment for Evaluation of the Microneedle Array Patch Industry: An Exploration of Barriers to Full-Scale Manufacturing, *Drug Delivery Transl. Res.*, 2022, **12**, 368–375.
  - 219 E. L. H. Spierings, J. L. Brandes, D. B. Kudrow, J. Weintraub, P. C. Schmidt, D. J. Kellerman and S. J. Tepper, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study of the Safety and Efficacy of Adam Zolmitriptan for the Acute Treatment of Migraine, *Cephalalgia*, 2018, **38**, 215–224.