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Conformable electrochemical devices for closed-loop wound management

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Chronic wounds arising from accidents, surgeries, or diseases impose a significant clinical and economic burden, underscoring the need for effective solutions to prevent severe complications. Recent advancements in materials science and electrochemical technology have facilitated the development of conformable electrochemical platforms for detection and management, incorporating monitoring, diagnosis, and treatment. Nevertheless, current wound detection and therapy systems face challenges related to the stability and specificity of sensor monitoring, as well as the need for on-site and comprehensive evaluation criteria to offer timely treatment guidance and follow-up care. This review provides a comprehensive overview of the closed-loop management system, emphasizing wound biomarker detection, wound assessment, and on-demand treatment, ultimately culminating in an integrated wound management approach by conformable electrochemical devices. Additionally, we explore the challenges, opportunities, and future prospects of soft and stretchable electrochemical biosensors, with the aim of enhancing the efficiency and timeliness of wound management.

KEYWORDS

wound management, conformable device, closed-loop, electrochemical biosensing, on-demand treatment

1 Introduction

Wounds resulting from accidents, surgeries, or chronic conditions pose a significant clinical challenge and impose a substantial economic burden on global healthcare systems. Effective wound management is not only about alleviating physical discomfort but also stands as a crucial healthcare necessity. Neglected or inadequately treated wounds have the potential to escalate into severe medical issues, including infections, sepsis, amputations, and, at times, even fatalities (Sen, 2021). According to a survey conducted by the World Health Organization, the issue of wounds has affected more than 305 million people around the world. It is estimated that by 2024, global expenditures related to wound care will reach \$80 billion (Yao et al., 2022). Traditional wound treatment, often involving dressing removal or sample examination, is time-consuming, expensive, and uncomfortable. A patient-friendly tool is needed to monitor disease progression, guide treatment, and reduce costs (Romanelli et al., 2013).

Recent advancements in materials fabrication, sensing techniques, and device integration strategies have opened up numerous opportunities in various healthcare management systems (Mathew et al., 2020; Sun et al., 2021). In particular, conformable electrochemical devices stand out due to their flexibility, breathability, biocompatibility, and

their capability to continuously analyze biomarkers in personalized wound management (Mirvakili and Langer, 2021; Tang et al., 2021). Electrochemical biosensors are cost-effective, portable, and seamlessly integration into electronic acquisition modules, making them promising for comprehensive evaluation of the wound progress and treatment in the intricate wound microenvironment. Furthermore, to enhance patient outcomes and achieve greater efficiency and precision in wound management, electrochemical devices are undergoing continuous evolution. They are shifting from single-function devices that primarily focus on biomarker sensing or treatment to more interconnected wound management systems (Mathew et al., 2020). This evolution is leading to the development of interconnected wound management systems, which seamlessly coordinate various facets of the wound healing process. These systems cover everything from biomarker detection, wound evaluation, and on-demand treatment, ultimately culminating in the creation of a closed-loop wound management system that seamlessly integrates all these modules. This logical progression in technology promises a more holistic and efficient approach to wound care, benefiting both patients and healthcare providers (Mathew et al., 2020; Mirvakili and Langer, 2021; Tang et al., 2021; Yang et al., 2023).

In this review, we provide an overview of recent advancements in closed-loop wound management systems utilizing conformable electrochemical devices. As illustrated in Figure 1, we begin by introducing the wound biomarkers and the associated electrochemical detection techniques. These techniques are designed to collect essential information through real-time monitoring or periodic detection, tailored to the unique characteristics of different biomarkers. Next, a comprehensive wound condition evaluation criteria and strategies were

introduced. Furthermore, we explore electrochemical-based wound treatment approaches, encompassing physical treatments and diverse drug delivery strategies. Our primary aim is to provide an extensive and in-depth perspective on the use of cutting-edge adaptable electrochemical devices in the field of wound management. This review advocates for an integrated closed-loop wound management platform that combines biomarker detection, holistic evaluation, and on-demand treatment, ultimately creating an adaptive and efficient approach to wound care.

2 Biomarkers detection

Wound environments encompass a multitude of measurable indicators crucial for comprehensive wound assessment and treatment guidance. These biomarkers provide valuable insights into the wound's condition and the healing process (Tang et al., 2021). To address this complexity, we provide a concise overview of current electrochemical detection techniques, categorizing them into two modes: real-time monitoring and regular assessment. Real-time monitoring is applied to holistic wound indicators like temperature, pH, and humidity, and small molecule metabolites (such as uric acid, nitric oxide, etc.), while regular detection is employed for biomarkers recognized by bioreceptors that can be detected by disposable devices, such as metabolites, cytokines, and enzymes. This classification allows for a targeted and tailored strategy in wound management, ensuring a cohesive approach to assessing and addressing wound conditions.

2.1 Brief introduction to electrochemical detection techniques

Electrochemical detection is a valuable tool for precisely converting wound markers into electrical signals in complex wound environments, ensuring high sensitivity and specificity. Electrochemical sensors stand out for their cost-effectiveness, user-friendliness, and portability compared to alternative methods, making them an ideal choice for *in vitro* diagnosis (Li et al., 2021). These sensors employ various techniques, including amperometric, voltammetric, potentiometric, and impedance methods. In amperometric methods, analyte concentration directly correlates with the measured current. Enzyme sensors, such as uricase-modified sensors for uric acid detection, are commonly used. Voltammetry, the most prevalent technique, captures redox currents in relation to analyte concentration. Potentiometric sensors detect potential shifts resulting from ion concentration changes, while impedance spectroscopy quantifies analytes based on their impedance response (Piro and Reisberg, 2017; Liu et al., 2021; Pollard et al., 2021). Wound related biomarkers and corresponding electrochemical detection methods are summarized in Table 1.

Electrochemical sensors can provide a versatile and efficient approach to monitor wound biomarkers through real-time monitoring as well as regular detection modes. These methods significantly contribute to enhancing wound management by offering precise insights into wound conditions and facilitating well-informed treatment decisions.

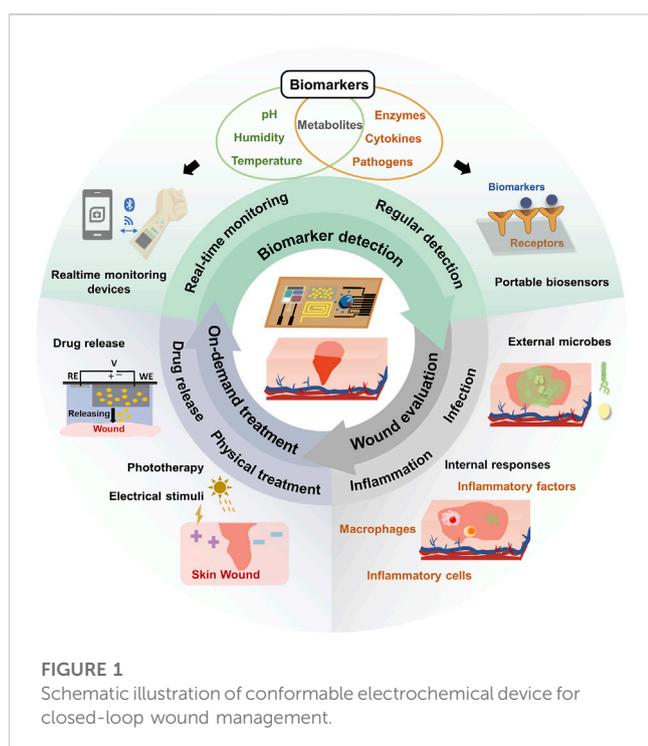


TABLE 1 Summary of wound related biomarkers and corresponding electrochemical detection methods.

	Biomarkers	Method	Sensing elements	Detection range	Data transfer	Reference	
Biomarkers for real-time detection	pH	Potentiometry	PEDOT	4–8	Bluetooth	Shirzaei Sani et al. (2023)	
		Potentiometry	PANI	5–9	Bluetooth	Yang et al. (2022)	
		Potentiometry	PANI	3–9	NFC	Xu et al. (2021)	
		Voltammetry	PEDOT:PSS	4–10	Bluetooth	Liu et al. (2021)	
		Potentiometry	PANI	4–9	Bluetooth	Gao et al. (2021)	
	Humidity	Impedance	PEDOT: PSS			NFC	Tessarolo et al. (2021)
		Capacitance	IFRep gel			Bluetooth	Yang et al. (2022)
	Uric acid	Voltammetry	UOx	0–300 μ M		Bluetooth	Pal et al. (2018), RoyChoudhury et al. (2018)
		Voltammetry	rGO/AuNPs	100–800 μ M		NFC	Xu et al. (2021)
		Voltammetry	chitosan/PB	0–1000 μ M		Bluetooth	Liu et al. (2021)
		Voltammetry	PB	0–100 μ M		Bluetooth	Shirzaei Sani et al. (2023)
		Voltammetry	PA/CNT	100–1000 μ M		None	Jarošová et al. (2019), Simoska et al. (2020)
		Voltammetry	CUAs	100–700 μ M		None	Simoska et al. (2020)
	NO	Voltammetry	CUAs	1–100 μ M		None	Simoska et al. (2020)
	PYO	Voltammetry	CUAs	1–250 μ M		None	Simoska et al. (2020)
Voltammetry		PA/CNT	1–118 μ M		None	Jarošová et al. (2019)	
Voltammetry		MXene/AuNPs/peptides	1–100 μ M		NFC	Shi et al. (2023)	
Biomarkers for regular detection	Cytokines (TNF- α , TGF- β 1, IL-6, IL-8)	Voltammetry	MB	TNF- α :0–2 ng/mL; TGF- β 1: 0–150 pg/mL; IL-6: 0–30 ng/mL; IL-8: 0–30 ng/mL		Bluetooth	Gao et al. (2021)
	Cathepsin, Deoxyribonuclease	Capacitance	IFRep gel	0–500 ng/mL		NFC	Yang et al. (2022)
	Sortase A	Voltammetry	MXene/AuNPs/peptides	1 pg/mL to 100 ng/mL		NFC	Shi et al. (2023)

PEDOT- poly(3,4-ethylenedioxythiophene); PANI- polyaniline; PEDOT: PSS- poly(3,4-ethylenedioxythiophene): Poly (styrenesulfonate); IFRep gel-Inflammation-responsive gel (IFRep gel); UOx- urate oxidase; PB- prussian blue; PA/CNT- Polyacrylamide-coated, carbon nanotube; CUAs- carbon ultramicroelectrode arrays; MB- methylene blue.

2.2 Biomarkers for real-time detection

Wound management is a multifaceted process involving various factors such as temperature, pH, and moisture levels, which serve as holistic biomarkers for real-time sensing. It's important to note that most holistic biomarkers are monitored in conjunction with other biomarkers to provide a comprehensive view of wound conditions from various perspectives. Additionally, small molecule metabolites, closely associated with inflammatory and infectious processes, can be continuously monitored as well. These metabolites are usually detected by using enzyme-based biosensors employing amperometric methods (e.g., glucose) or voltammetric methods.

When the integrity of skin is destroyed, many factors will lead to the change of temperature in and around the wound. It is found that the temperature is the highest in the unhealed and infected wounds, and it decreases with the healing of the wounds (Power et al., 2017; Gethin et al., 2021). Lou and colleagues, by monitoring the

temperature of the wound in real time, gets the specific situation of the wound (Lou et al., 2020). For instance, a sudden temperature increase or prolonged high temperature may indicate infection or delayed healing (Gianino et al., 2018; Prasad Mahindrakar et al., 2023). Wound pH is another critical element in the wound healing equation, significantly influencing essential processes like collagen formation, inflammation, angiogenesis, and tissue oxygen utilization (Romanelli et al., 2013; Pang et al., 2023; Derwin et al., 2023). Among the pH sensing materials, polyaniline (PANI) is reported as a type of widely used conductive polymer that can sensing pH change through the protonation-deprotonation pathway (Figure 2A). And, because of their reversible property of protonation-deprotonation reaction, PANI based sensors can continuously monitoring pH value in a wide pH range (Figure 2B). In the wound environment, moisture levels are equally vital. An adequately humid setting can promote tissue growth and collagen proliferation (Weller, 2009; Kruse et al.,

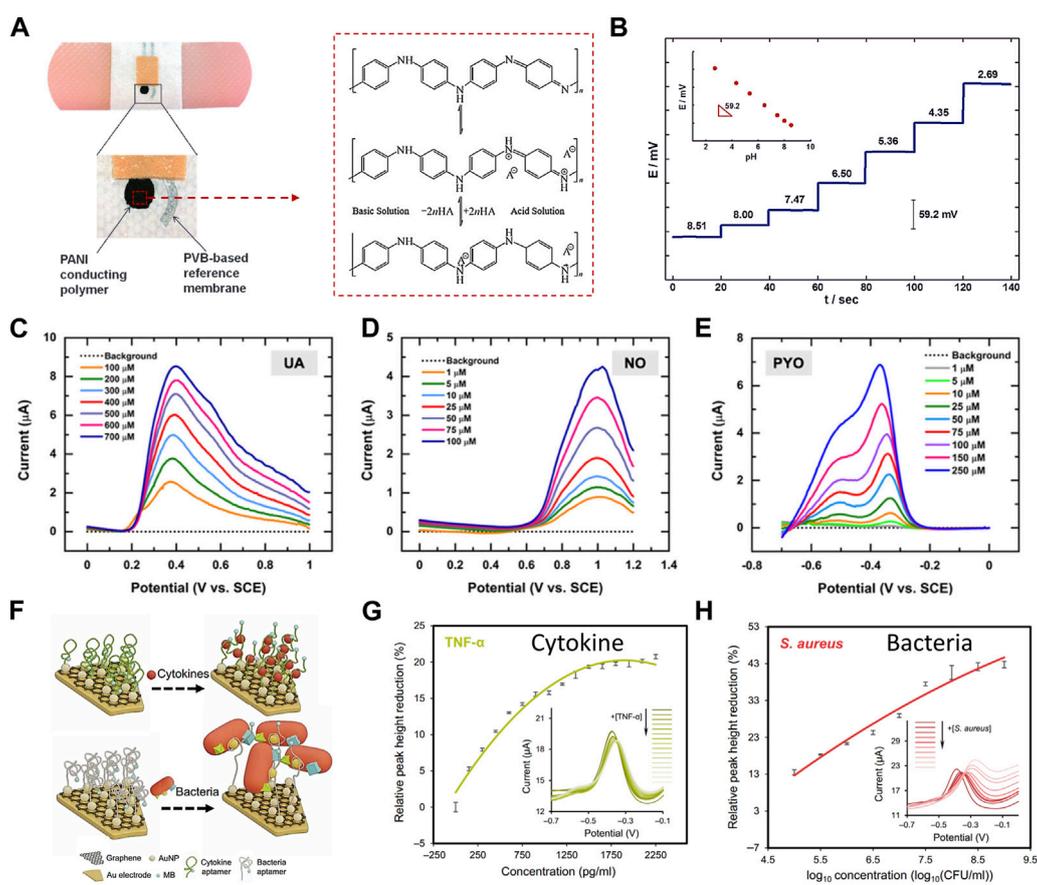


FIGURE 2

Real-time monitoring (A–E) and regular detection (F–H) of electrochemical devices for various wound biomarkers. (A) The images depict a printed potentiometric sensor on an adhesive bandage, and illustration of the polyaniline protonation-deprotonation pathway from base conditions (top structure) to acid conditions (bottom structure) (Cascioferro et al., 2014). (Copyright 2014 *Electroanalysis*) (B) The potentiometric time-trace of a pH bandage sensor ranges from pH 8.51 to 2.69, with an inset showing the EMF dependence versus pH for the PANI conducting polymer ISE (Jayaseelan et al., 2014). (Copyright 2014 *Electroanalysis*) Additionally, (C–E) display square wave voltammetric current responses (background subtracted) for several biologically relevant concentrations of (C) PYO, (D) NO, and (E) UA in simulated wound exudates (Simoska et al., 2020). (Copyright 2020 *ACS Sensors*) (F–H) Aptamer-based sensors for regular detection of cytokines and bacteria, (F) presents a schematic of the sensing mechanisms, and (G–H) show variations in relative peak height based on voltammetric spectra of the TNF-α and *S. aureus* sensors (Gao et al., 2021). (Copyright 2021 *Science Advances*).

2015), while facilitating the autolysis of necrotic tissue (Nuutila and Eriksson, 2021). However, excessive exudate may not necessarily be beneficial for wound healing, as it can hinder the process (Zhang et al., 2021; Zhang et al., 2022). Striking the right moisture balance is critical because both excessive and insufficient moisture can impede wound healing (Okan et al., 2007). Notably, pH is often monitored by potentiometry and Voltammetric technology, and humidity is often monitored by impedance and capacity.

The wound-environment interface contains electroactive small molecule metabolites, such as glucose, uric acid, and nitric oxide, closely linked to inflammation and infection. These metabolites significantly affect wound healing. Detecting and monitoring these metabolites offers valuable insights into wound conditions and informs appropriate treatments. For example, high glucose levels can harm blood vessels, impair nerve function, reduce circulation, and weaken the immune system, all vital for wound healing. Prolonged uncontrolled blood sugar can result in chronic wounds, which are more susceptible to infection due to impaired healing (Zhu et al., 2019). Uric acid (UA) serves as a critical indicator of wound severity, with its

concentration increasing as wounds become more severe. Excess uric acid levels can hinder healing by promoting inflammation, especially in chronically hypoxic wounds (Fernandez et al., 2012; Fernandez et al., 2014; Faruk Hossain and Slaughter, 2021). Nitric oxide (NO) has anti-inflammatory and antibacterial properties, regulates angiogenesis, and influences collagen deposition, playing a crucial role in various cell activities during wound healing. Wounds in the inflammatory stage and those infected by bacteria produce significant NO amounts (Schwentker et al., 2002; Schwentker and Billiar, 2003; Luo and Chen, 2005; Cinelli et al., 2019; Wu et al., 2021; Li et al., 2022). Bacterial metabolites with redox activity such as pyocyanin (PYO) serve as an infection indicator, which is also applied as biomarker for real-time detection. As shown in Figures 2C–E, UA, NO, and PYO with redox activity are able to be simultaneously detected in wound samples or simulators using a flexible carbon microelectrode array (CUAs) sensor. Square wave voltammetry (SWV) was employed to evaluate the sensor's response, determining the limits of detection (LODs) and linear dynamic range (LDR) in simulated wound fluid. It was found that the characteristic SWV current response of PYO and

uric acid increased with the increase of analyte concentration in the micromolar range determined by *in vitro* and *in vivo* concentrations (Simoska et al., 2020). As Figures 2F–H shows, a multiplex immunosensor can realize the in-situ analysis of wound microenvironment, inflammation and infection status through real-time quantitative evaluation of pro-inflammatory factor TNF- α and bacterial load. The concentration of TNF- α in wound fluid of unhealed ulcer is higher than that of healed ulcer. *Staphylococcus aureus* is a dominant species in all types of chronic wound samples. The peak current height of each adaptive sensor decreases with the increase of target concentration, in which the monitoring range of TNF- α is 0–2 ng/mL, and the range of *Staphylococcus aureus* is $0\text{--}1 \times 10^9$ colony forming unit (CFU)/ml, and it has been proved that it has good selectivity (Gao et al., 2021).

2.3 Biomarkers for regular detection

In contrast to the holistic biomarkers and some small molecule metabolites, there are specific biomarkers present in the wound interfaces that are related to both external microbes and internal physiological conditions and inflammatory responses. However, the recognition of these biomarkers is not reversible, and they can only be detected with disposable biosensors. Specific detection techniques are necessary to target these biomarkers and provide a precise evaluation of the wound conditions.

Cytokines are small molecular proteins, which are involved in the regulation and coordination of various cell types (Borena et al., 2015) and are very important in cell signal transduction. Its role may be promoting inflammation or inhibiting inflammation (Pilvenyte et al., 2023), strictly control the wound healing process (Efron et al., 2000; Werner and Grose, 2003). Therefore, it is very meaningful to monitor the change of cytokine expression level (Filik and Avan, 2020). Legrand and coworkers reported that tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-8 (IL-8) and transforming growth factor- β 1 (TGF- β 1) are used for wound assessment. Pro-inflammatory cytokines interleukin-1 (IL-1), IL-6 and TNF- α are upregulated in the inflammatory stage of wound healing (Legrand and Martino, 2022), and their concentrations in chronic wounds are higher than those in normal healing wounds (Gianino et al., 2018). TNF- α and IL-1 are necessary in the early stage of wound healing, but the persistent over-expression may lead to the aggravation of tissue damage through the over-activation of immune cells and their protease products (Efron and Moldawer, 2004). TNF- α has pleiotropic, growth regulating and differentiation effects on various cell types. It is a key regulator of inflammatory reaction and plays an important role in inflammation and infection (Pilvenyte et al., 2023). Three days after skin injury, the level of TNF- α in wound fluid reached its peak. IL-1 exists in two forms: IL-1 α and IL-1 β . IL-1 β is a pro-inflammatory cytokine, which can be induced by infections such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It can be detected in the wound environment within 24 h after injury, and its concentration reaches its peak within 24–72 h. Infections such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* can induce IL-1 β secretion (Efron and Moldawer, 2004; Barrientos et al., 2008; Pilvenyte et al., 2023). TGF- β plays an important role in inflammation, angiogenesis, epithelial re-formation and connective tissue regeneration. With the occurrence of traumatic

injury, its expression also increased. For these wound markers, electrochemical device such as aptamer modified.

Matrix metalloproteinases (MMPs) are the main proteases involved in wound healing, among which MMP-9, MMP-2 and tissue inhibitor of matrix metalloproteinases (TIMPs) are the most common components in wound exudates (Power et al., 2017). The contents of MMP-9 and MMP-2 decreased during wound healing (Tarlton et al., 1997). The balance of protease is very important for wound healing. Excessive protease activity will cause damage to extracellular matrix (ECM) and newly formed tissues, thus delaying the healing process. MMP-9 is produced by many kinds of cells and induced by cytokines, growth factors, stress or inflammation (Rayment et al., 2008). TIMPs is a tissue inhibitor of matrix metalloproteinases, which regulates the activity of MMPs (Behm et al., 2012; Lindley et al., 2016). According to the research, the long-term increase of matrix protease level and the decrease of TIMPs level or the abnormal ratio of matrix protease level to TIMPs level are related to wound nonunion, especially the decrease of MMP/TIMP ratio is a good prognostic indicator of wound behavior (Ladwig et al., 2002). Taking advantage of the proteinase activity, MMPs can be detected using substrate peptide-based biosensors. Using MMP-2 as an example, the peptide unit consists of two regions: one for self-assembly and one for bio-recognition. Ion nanochannels can then generate an electrochemical response in response to MMP activities (Wang et al., 2022).

Many pathogenic species, including *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli* and *Staphylococcus aureus*, are usually distributed in chronic wounds. Therefore, microbiological methods for pathogen identification can be used as qualitative indicators of infection (Simoska et al., 2020). The current research progress, aiming at the detection of bacteria, Enzymes such as lipase, hyaluronidase, antimicrobial peptides, antibacterial peptides, substances on the outer membrane of bacteria (such as lipopolysaccharide (LPS), peptidoglycan and lipopeptide), bacterial flagellin, bacterial DNA, etc., are used to monitor bacteria (Khoshroo et al., 2022; Wang et al., 2020).

3 Evaluation of the wound status

Despite the presence of a wide array of strategies and technologies in wearable chemical sensors for wound interfaces and non-invasive biofluids, the parameterization and calibration of these sensor modes have not received enough attention (Ronkainen et al., 2010). It is crucial to emphasize the collection and integration of data from multiplexed and multimodal sensors in the context of wound information. This is imperative for robust post-processing, particularly when considering the physiological (inflammation) and pathogenic (infection) processes at the wound interface (Sempionatto et al., 2022). The comprehensive interpretation of this multiplexed and multimodal data, whether derived from real-time monitoring or regular sensor readings, occupies an important position in the close-loop wound management systems.

3.1 Inflammation at the wound interfaces

The body's immune system plays a crucial role in initiating an inflammatory response as a protective mechanism at the wound

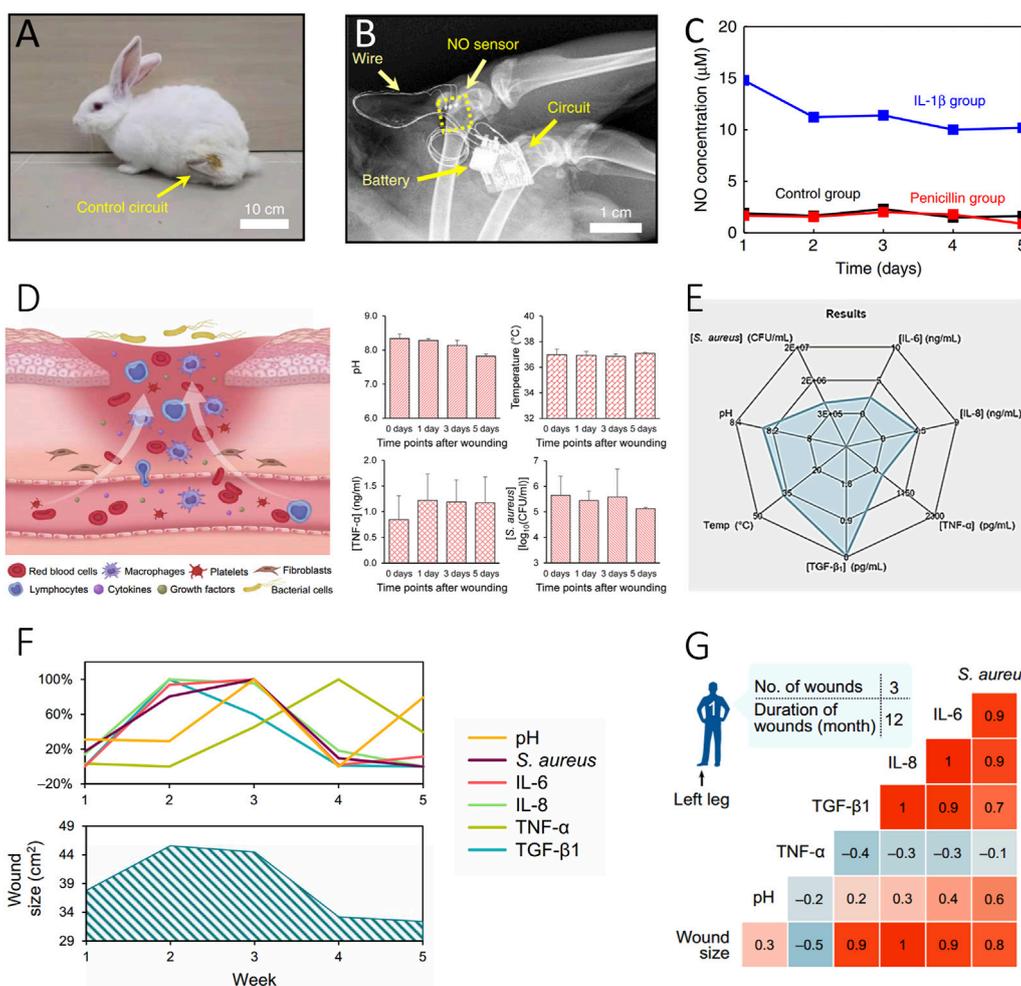


FIGURE 3

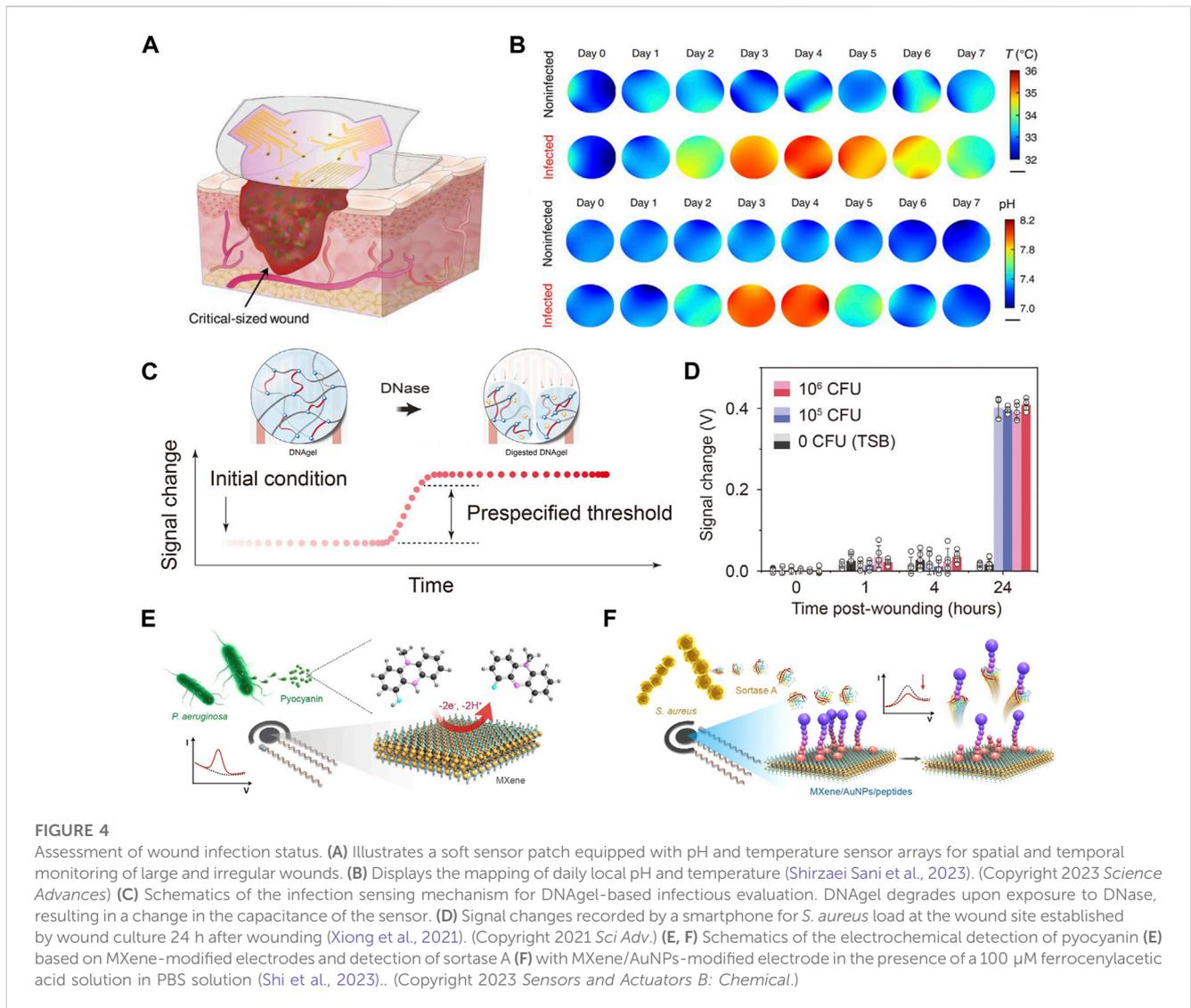
Evaluation of inflammatory status of wound. (A–C) Inflammatory Evaluation with a Real-Time NO Monitoring Device in the Puncture Cavity of New Zealand Rabbits (Li et al., 2020). (Copyright 2020 *Nature Communications*) (A) X-ray image and (B) the implanted NO sensor, wire connections, and wireless module. A photograph of the rabbit after NO sensor implantation with the wireless circuit secured on the thigh. (C) High NO concentration correlated with IL-1β-induced inflammation (blue), compared to the untreated (black) and penicillin-treated (red) groups. (D–G) Interpretation of Multiplexed Immunosensors with Wound Parameters (Gao et al., 2021). (Copyright 2021 *Science Advances*) (D) Illustration of the microenvironment of venous ulcers and *in situ* assessment of pH, temperature, mouse TNF-α, and *S. aureus* using Immunosensors. (E) Radar map depicting the integration of different inflammatory-related biomarkers, including TNF-α, IL-6, IL-8, TGF-β1, *S. aureus*, and pH sensors. (F, G) Interpretation of sensor-derived data analysis of wound exudate from a patient with a venous ulcer over a 5-week period (F) and the resulting correlation matrices (G).

interface. This response involves the participation of various signaling molecules, including metabolites, cytokines, and macrophages, which work in concert to regulate the immune response and coordinate the repair process (Razyeva et al., 2021; Zhao et al., 2016).

The assessment of inflammation holds paramount importance in effective wound management, with numerous biomarkers intricately involved in this process. NO plays a pivotal role in the regulation of the immune response by influencing key factors such as chemokines, IL-8, TGF-β1, monocytes, and neutrophils, etc., (Luo and Chen, 2005; Cinelli et al., 2019; Wu et al., 2021). In the proliferative stage of wound healing, NO promotes the proliferation of endothelial cells and mediates the production of vascular endothelial growth factor (VEGF) (Luo and Chen, 2005). A study by Li R. et al. illustrated a strong correlation between NO and cytokines, utilizing a real-time wireless NO monitoring platform (Li et al., 2020) (Figures 3A, B). Moreover, NO sensors placed in the

puncture cavity of New Zealand rabbits exhibited a robust correlation with the inflammatory cytokine IL-1β and proved adaptable for wound assessment (Figure 3C).

Considering the complex nature of conditions at the wound interface, the need for versatile and integrated in-situ multi-channel inflammatory cytokine detection platforms, along with holistic pH sensors, becomes evident for comprehensive wound condition assessment (Figure 3D). The Lim group's work showcases the integration of various types of inflammatory data using a flexible multiplexed immunosensor, allowing quantitative interpretation of cytokines like TNF-α, IL-6, IL-8, and the growth factor TGF-β1 through a radar map (Figure 3E) (Gao et al., 2021). This approach also revealed changes in these biomarkers closely correlated with different stages of wound recovery over a period of 5 weeks. The correlation of this inflammatory information with wound conditions offers valuable insights into the healing process



(Figures 3F, G). Ultimately, this integrated immune monitoring system serves as a powerful tool for real-time assessment of wound conditions, offering invaluable support for optimizing wound management and making informed treatment decisions.

3.2 Infection at the wound interfaces

In the context of chronic wounds, infections present significant challenges as external microorganisms release virulence metabolites. These metabolites cause changes in the overall wound environment and specific biomarker alterations. These alterations hold vital information for early warning and diagnostics, bridging the crucial link between infection and wound assessment to the on-demand treatment.

Holistic biomarkers such as temperature, pH, and other vital parameters can be utilized to evaluate infectious status. For temperature, distinct temperature changes were observed in wounds infected with various bacterial strains. Prolonged elevated temperatures may indicate infections, such as those caused by *Staphylococcus aureus*. A Flexible Wound Healing System (FWHS) incorporates a visual

indicator and an alarm for automatically detecting abnormal temperature changes exceeding the rectal temperature. This system, tested on both early and late infected wounds, demonstrated varying temperature fluctuations at different stages, confirming its early warning capabilities (Lou et al., 2020). In Gao group, wearable patches with pH and temperature sensor arrays were used to monitor the critical size of full-thickness infected wound defects in diabetic rats (Figure 4A). They observed that the infected wound showed a more uniform pH and temperature in regions 2 and 3 days after infection due to the formation of a uniform biofilm after infection. After treatment on the fourth day, the pH value and temperature value decreased significantly and returned to the level before infection on the seventh day, which indicated that the biofilm was destroyed and finally eliminated after treatment (Figure 4B) (Shirzaei Sani et al., 2023).

The virulence factors associated with conditional pathogens can serve as reliable criteria for assessing infection status (Clatworthy et al., 2007; Mota et al., 2021). For instance, the secretion of deoxyribonuclease (DNase) by bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* reflects

the occurrence of infection (Figure 4C). In this method, a reactive DNAgel with wound extrudes is employed. Elevated levels of DNase trigger the degradation of the DNA hydrogel, resulting in a change in the dielectric constant. This change can be utilized as an indicator to evaluate the infection status. When infection occurs, the bacterial reactive DNAgel contacts with DNase, and the bacterial reactive DNA hydrogel degrades, which leads to the change of dielectric constant in the area above the staggered electrodes, thus triggering the infection alarm on the smart phone. The capability to indicate wound infection *in vivo* was validated with an acute wound model in mice. The widely accepted clinical threshold for laboratory infection diagnosis, ranging from 10^5 to 10^6 colony-forming units (CFU), was employed. In the control group, minimal changes were observed. However, in wounds inoculated with live *Staphylococcus aureus* (10^5 and 10^6 CFU), a signal change of 0.4 V was detected after 24 h (Xiong et al., 2021) (Figure 4D).

In another study, two typical biomarkers, sortase A and pyocyanin, were employed to indicate infections caused by Gram-positive *Staphylococcus aureus* and Gram-negative *Pseudomonas aeruginosa*. Electrochemical differential pulse voltammetry was utilized for timely evaluation of wound infections and to distinguish between infection types. Results from animal experiments demonstrate the effectiveness of the smart bandage in conducting multi-biomarker analysis of wounds, enabling the early warning of wound infections (Figures 4E, F) (Shi et al., 2023).

The wound evaluation approaches mentioned above are based on specific biomarkers closely related to the status of wound conditions. However, the variation in these wound-related biomarkers is influenced by multiple factors within the complex wound environment. In such cases, artificial intelligence can analyze complex data, offering potential applications in early detection, diagnosis, treatment, prognosis prediction, and prognosis evaluation of wounds, contributing significantly to the field of wound care. Research has successfully integrated artificial intelligence technology into wound management, particularly in the classification of chronic wounds, including diabetic ulcers, lymphatic vessel wounds, surgical wounds, and pressure injuries (Sarp et al., 2021). This integration has facilitated accurate evaluations of wound area and the percentage of granulation tissue (PGT) (Howell et al., 2021), prediction of the healing stage of inflammatory wounds (Kalasin et al., 2022), and overall assessment and management of wounds (Barakat-Johnson et al., 2022). These advancements not only optimize the diagnosis and treatment workflow but also improve the efficiency of the entire wound care process.

4 On-demand wound management systems

The progress in the management of wounds has resulted in the emergence of precise, instantaneous, and dynamic on-demand treatment systems that cater to individual requirements (Verdolino et al., 2021; Vivcharenko et al., 2023). Traditional flexible electrochemical devices with singular monitoring functions are no longer adequate. To effectively address the needs of wound management, integrated closed-loop systems that amalgamate monitoring and controllable treatment systems are emerging as a superior option (Pollard et al., 2021).

These integrated closed-loop systems hold immense potential, encompassing diagnosis, early infection warning, treatment effect assessment, and long-term wound management (Liu et al., 2023). Recent years the application of physical treatment (i.g. electrical stimulation), controlled drug release, or combined treatment have been reported in closed-loop wound treatment (Bagherifard et al., 2016; Amjadi et al., 2018; Jiang et al., 2022).

4.1 Physical treatment

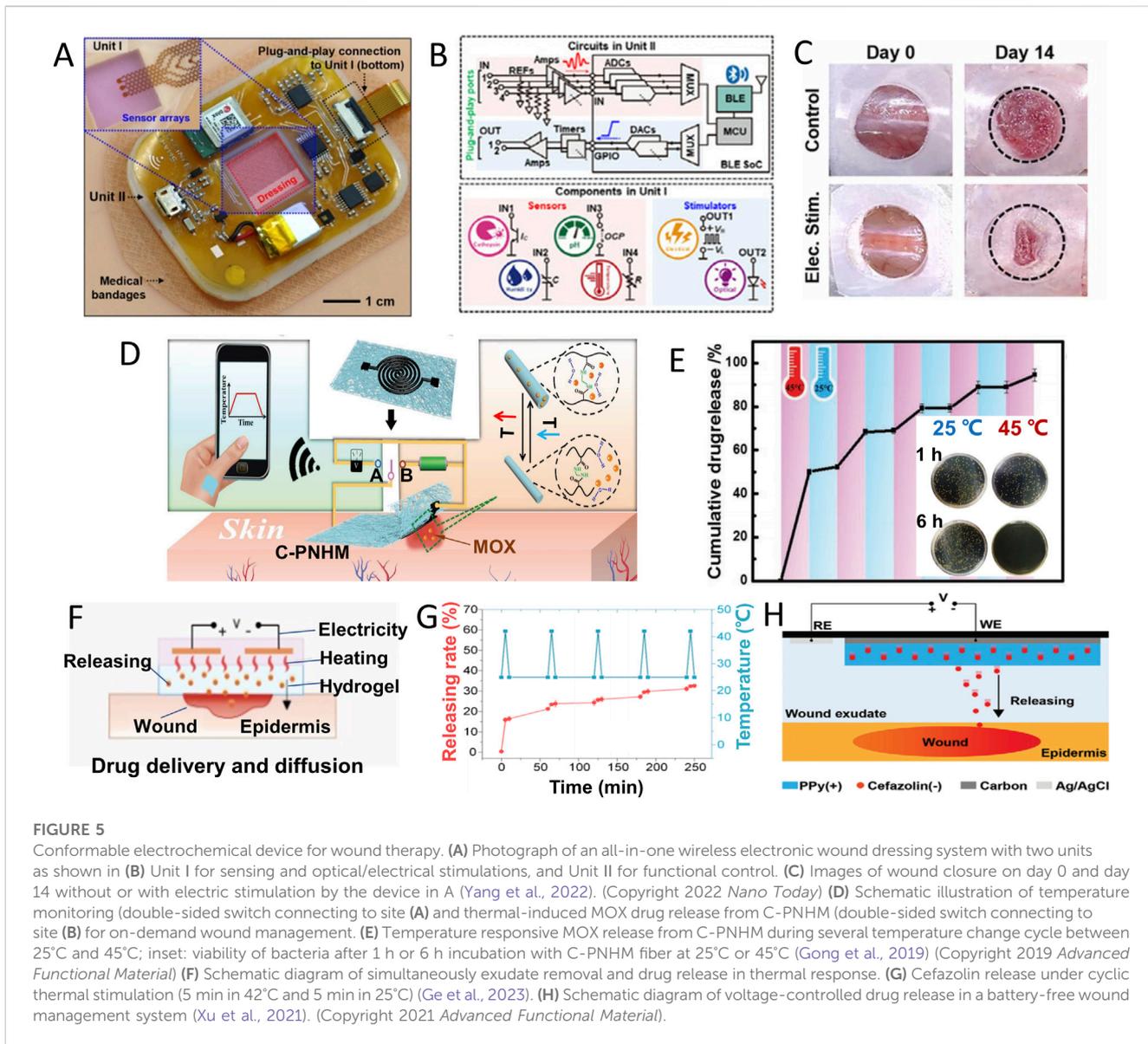
Electrical stimulation (ES) has exhibited its efficacy in regulating cellular proliferation and migration, mitigating inflammation, and expediting wound closure by emulating or amplifying the inherent electromagnetic field's influence induced by potassium (K^+) and sodium (Na^+) ions (Luo et al., 2021). Electrical stimulation application was found to accelerate wound healing and skin remodelling, with increased wound impedance and improved histological characteristics such as skin thickness and the number of skin appendages. Single-cell RNA sequencing (SCRNA-SEQ) analysis confirmed the activation of regeneration-promoting genes in monocytes and macrophages and followed by enhancing tissue regeneration, neovascularization, and skin recovery (Jiang et al., 2022). Yang and coworkers proposed a medic-free wound manage approach by a wireless electrochemical device (Figure 5A) that contains a unit for electrical/optical stimulations (Figure 5B). Figure 5C suggests the electronic dressing devices induced wound healing acceleration successfully with only physical treatment (Yang et al., 2022).

Furthermore, phototherapy, encompassing photodynamic therapy (PDT) and photothermal therapy (PTT), has been demonstrated to accelerate wound healing by impacting macrophage phenotypic metamorphosis, fostering tissue proliferation, and impeding bacterial functionalities, thereby restraining biofilm growth and microbial infections (Xu et al., 2022; Chen et al., 2023).

4.2 Controlled drug release treatment

In certain situations, physical treatments alone may not suffice for managing chronic wound conditions, particularly when dealing with infectious microbes. There is a clear need for specific drugs and controlled drug release strategies that can respond actively based on the information and feedback obtained through monitoring and simulation results. This integrated approach offers a more comprehensive and effective way to address the complex and evolving nature of chronic wounds, ensuring that treatment is tailored to individual needs (Luo et al., 2021; Jiang et al., 2022).

One common strategy is thermal-induced drug release, known for its ease of control. Gong et al., integrated a thermally responsive nanomesh film: Screen printing crosslinked poly (N- isopropylacrylamide -N- methacrylamide), with loaded moxifloxacin hydrochloride (MOX) and a dual-functional electrochemical device for wound management. As shown in Figure 5D, this device can monitor temperature changes when double-sided switch connects to site A, and the signal can be wirelessly transmitted to a mobile phone for infection determination. If an increase in temperature was confirmed by



infection, turning double-sided switch to site B can activate the heater function of device. The heater's temperature can be precisely controlled by adjusting the applied voltage, ensuring accurate MOX drug release from nanofibers (Figure 5E) for effective bacterial infection control (Gong et al., 2019).

Ge Z and coworkers added an exudate management module to optimize wound management. Self-pumping microfluidic channel, temperature and humidity sensor, liquid metal (LM) heating module and antibiotics-loaded thermosensitive hydrogel are integrated into wearable wound patch (Figure 5F). When the pulse voltage was applied to the LM heating coil, the exudate was removed through microfluidic channel, and the broad-spectrum antibiotic cefazolin was released from the temperature-sensitive hydrogel. The drug release rate at 42°C is significantly higher than that at 25°C, showing controllable and on-demand thermal response release characteristics (Figure 5G). Under the combined action of exudate removal and drug treatment, the wound temperature returned to normal level quickly due to a synergistic

effect (Ge et al., 2023). Xu and coworkers adopted conductive polymer and prepared a battery free electronically controlled drug release system offers low power consumption, cost-effectiveness, and rapid response (Figure 5H) (Xu et al., 2021).

Light serves as an optimal stimulus for precise drug delivery owing to its cleanliness, accuracy, and remote controllability. A comprehensive system comprising a temperature sensor, UV-responsive antibacterial hydrogel, and UV-LED enables the monitoring of wound temperature in real-time and the release of antibiotics as needed. Once the presence of infection was confirmed, the UV-LED (365 nm) is applied to activate the release of gentamicin (GS) and the release rate of GS escalates with prolonged exposure to UV irradiation. Upon the release of antibiotic, a gradual decrease in temperature can be observed. Subsequent cycles of UV irradiation maintained this pattern. Animal experiments validated the system's capability for real-time wound monitoring, infection detection, and effective treatment (Pang et al., 2020).

4.3 Combined wound treatment

The combination of electrical stimulation and drugs offers a comprehensive approach to wound management. A multi-channel electrochemical biosensor array is employed to monitor wound biomarkers and regulate drug release via electrodes. The positively charged chondroitin 4-sulfate (CS) hydrogel facilitates the controlled release of dual-function anti-inflammatory and antibacterial peptides (AMP). *In vitro* experiments validated the precise release of AMP and its potent antibacterial activity against diverse pathogens. After treatment, pH and temperature normalized by the fifth and sixth days. The combined treatment group exhibited the highest rate of wound closure, as evidenced by histopathological analysis revealing collagen deposition and the formation of granulation tissue (Shirzaei Sani et al., 2023).

Above all these treatment strategies are effective in different scenarios. Thermal stimulation drug release is common in wound management but comes with drawbacks like high energy consumption and the need for external components. In contrast, electric stimulation release is cost-effective and has low power consumption, although it's limited to charged drugs. Light, as a clean energy source, offers high temporal and spatial resolution and remote control for drug release. The choice of treatment methods is closely tied to specific wound conditions, underscoring the importance of closed-loop wound management (Armstrong et al., 2020; Jiang et al., 2022; Pang et al., 2023).

5 Discussion and perspectives

In summary, our review has provided an overview of closed-loop wound management systems based on conformable electrochemical devices. These systems encompass biomarker detection, wound evaluation, and on-demand treatment, offering a comprehensive and efficient approach to wound management. Wound healing is a complex process that demands a thorough understanding of its status. Utilizing various electrochemical techniques to assess multiple wound biomarkers from different perspectives is essential, forming a solid foundation for diagnosis and treatment. Different wound types present distinct microenvironments, requiring adjustments in monitoring parameters for more precise and detailed assessments. The choice of electrochemical strategies depends on the types of biomarkers, ranging from holistic environmental biomarkers requiring continuous monitoring to specific biomarkers necessitating regular detection. The integration of multi-channel electrochemical devices allows for comprehensive monitoring, including wound microflora and their metabolites, by combining various detection modes. This comprehensive evaluation of wound conditions enables the precise identification of infectious or inflammatory states, facilitating timely treatment. Implementing measures to prevent biological contamination of interfaces, enhance sensitivity and specificity, perform active biosensor calibration, reduce response times, lower detection limits, and advance equipment miniaturization, networking, and intelligence is crucial for optimizing electrochemical sensors.

Furthermore, these closed-loop systems can address the challenges posed by multidrug resistance associated with traditional antibiotics. Alternative therapies such as growth factors, NO, metal ions, antimicrobial peptides, and physical modalities like electrical stimulation, light therapy, ultrasound, and heat have emerged as promising options for promoting skin regeneration. Recent developments have seen the application of drug-controlled release, electrical stimulation, photobiological regulation, and other technical methods in closed-loop wound treatment. These advancements underscore the increasing need for innovative design and manufacturing technologies for wearable sensors.

The future of wound management is heading towards intelligent platforms that seamlessly integrate monitoring and treatment, creating a closed-loop for wound detection and treatment. This evolution not only depends on the development of sensing materials but also the incorporation of artificial intelligence algorithms capable of integrating the uncovered bioinformation at the sensor-wound interfaces. With this capability, precise wound models can be reconstructed into comprehensive profiles, enabling much more efficient wound management steps based on personalized situations. A promising approach involves integrating monitoring systems with controllable treatment systems to establish comprehensive closed-loop systems for detection, diagnosis, and treatment.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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