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# *Smart Wound Dressings Integrating Biosensors for Real-Time Monitoring of Wound Conditions*

Maged Naser [1], Mohamed M. Nasr [2], and Lamia H. Shehata [3]

[1] Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of ob/gyn,

[2] Consultant of General and Endoscopic Surgery (MD, FRCS)

[3] Care National Hospital, Department of Radiology

Corresponding Author: Maged Naser



**Abstract - Biosensors have paved the way for significant advancements in the management of chronic wounds. Following Clarke's introduction of the oxygen electrode, biosensors have transformed into sophisticated bandages that autonomously release medications to address wounds based on physiological indicators, such as pH or glucose levels, that signify pathogenic threats. Aptamer based biosensors have been instrumental in detecting and characterizing harmful bacteria in wounds, which frequently develop antibiotic-resistant biofilms.**

**Numerous functional polymers have played vital roles in the development of these biosensors. Starting with natural polymers like alginate, chitosan, and silk derived fibroin, known for their biodegradable and absorptive properties, progress has occurred in creating biocompatible synthetic polymers like polyurethane and polyethylene glycol, aimed at minimizing nonspecific binding of proteins and cells, thus making biosensors less painful or cumbersome for patients. Recently, polycaprolactone has been engineered, offering flexibility and an extensive surface-area-to volume ratio. There remains potential for further innovations in the production and application of biosensors for wound healing and this review emphasize the evolution from biomarker detection to smart dressings and the integration of machine learning in crafting personalized wound patches for prolonged use.**

**Keywords: bacteria, biofilm, chronic wounds, biosensors, DFU,hydrogels, polymers**

## I. Introduction

The healing of cutaneous wounds involves a sequence of spatial and temporal events leading to scar development and the restoration of the epithelial barrier. The initial phase of healing is hemostasis. During this phase, a clot comprising fibrin and platelets is formed to halt the bleeding. Platelets release factors that trigger an inflammatory response, attracting leukocytes to the wound area. Leukocytes, especially neutrophils, are the first responders, employing reactive oxygen species (ROS) to combat pathogens and prevent wound infection. This is

succeeded by monocytes that convert into proinflammatory macrophages at the injury site, which clear the damage caused by neutrophils through bacterial phagocytosis. Subsequently, anti inflammatory macrophages emerge, secreting cytokines and growth factors that facilitate healing. During the proliferative phase, fibroblasts infiltrate the wound, producing extracellular matrix (ECM) components essential for the structural and biochemical integrity of new tissue. Keratinocytes begin to proliferate and migrate to envelop the wound, crafting the epidermis, while endothelial cells generate new micro vessels within the wound tissue to supply nutrients and oxygen. This culminates in the formation

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of "granular appearing" granulation tissue. The concluding stage of wound healing is remodeling, where excess cells are eliminated through apoptosis, and surplus ECM derived healing tissue is cleared by phagocytes . The restructured wound tissue forms scar tissue.

A) Stages of wound healing. Wounds proceed through four stages: hemostasis, inflammation, proliferation, and remodeling. In chronic wounds, however, one or more of these phases can become disorganized, occur out of sequence, or inflammati on may remain unresolved.An alkaline pH in wounds (pH > 8) indicates protracted inflammation. Consequently, biosensors frequently target pH to monitor wound physiology orguide drug delivery in smart dressings.

B) Types of Biosensors in wound ealing A summary of various advancements in the detection of wound parameters. Typically, in biomarker oriented biosensors or 'smart' dressings, two or more technologies are amalgamated to either monitor multiple parameters simultaneously or coordinate the detection of a parameter with the signalling for medication release into the wound. This illustrates the pathway for acute wound healing, which can become disrupted, leading to inadequate healing; wounds fail to properly seal, the skin barrier remains unformed, and granulation tissue does not transition into scar tissue. Therefore, poor regulation of the intricate cellular and molecular mechanisms essential for effective healing can result in chronic wounds.

Chronic wounds are defined by ongoing inflammation, insufficient vascularization, and failure to reepithelialize. They often become colonized, leading to bacteria that form biofilms, which contributes to wound chronicity. Chronic wounds pose a global health risk, affecting approximately 8.2 million individuals and incurring costs of about $28.1…96.8 billion annually in the US alone. A significant type of chronic wound is diabetic foot ulcers (DFUs), which carry a 5year mortality rate comparable to that of cancer. Nearly 12% of DFU patients require amputation, followed by approximately a 50% 5year survival

rate post-amputation [1]. There exists an urgent demand for an effective treatment for DFUs, especially considering the rise in type IIdiabetes, which constitutes approximately 90–95% of all diabetes cases. Worldwide, diabetes impacts 387 million individuals, with 28 million of those in the United States. Additionally, pre-diabetes affects 316 million globally and 86 million in the U.S.[2,3 ] Numerous studies have been conducted to grasp the intricate complexities involved in chronic wound formation. However, these investigations have yet to adequately elucidate the multi-faceted complexities tied to the development or healing of chronic diabetic wounds. Various treatments, including chemical compounds, growth factors, living cell patches, ECM patches, and skin grafts, have been explored, but with limited success. Biosensors are innovative devices that capture and quantify biological or chemical elements in real-time. Typically, they incorporate a biological aspect, such as an enzyme or antibody, that interacts with the target substance to produce a measurable signal. The biosensor concept was initially introduced in 1906 by Michael Cremer, who showcased that the electric potential difference in a fluid compartment divided by a glass membrane directly correlates with the acid concentration in the liquid. [4,5 ] In 1922, the enzyme invertase was bioactively immobilized on aluminium hydroxide and charcoal. Years of pioneering research culminated in the invention of the 'Clark electrode' in 1956. Designed by Dr. Leland Clarke to deoxygenate solutions using glucose oxidase, which converts oxygen to hydrogen peroxide as a byproduct, he soon recognized its potential for detecting and quantifying glucose, thus creating the first biosensor.[4,5] Since that time, the field has significantly expanded, with technologies that transform signals from bio-analytes into electronic signals finding diverse applications in biology, including glucose monitoring biosensors utilized by diabetic patients, microbe-based immunosensors, surface plasmon resonance immunosensors, and nano biosensors.[6,7,8 ]

**1. How Do Biosensors Assist in Wound Monitoring?**

Various biosensors exist based on technology, including enzyme-based, electrochemical, aptamer, and optical biosensors . Chronic wounds are marked by elevated oxidative stress and extended periods of inflammation. Within the wound environment, particular physiological indicators provide essential information critical to the healing process and subsequent treatment.[9,10] Here, we outline the aforementioned technologies categorized by analytes (according to wound physiology) :

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### 1.1. pH Measurement

The pH level is a vital factor in the dynamics of wound healing. Chronic wounds exhibit a more alkaline state (pH 7–9) compared to acute healing wounds.[9,10,11,12 ] Biosensing patches are capable of measuring and transmitting the pH levels of wounds. For instance, [13] developed a microfluidic system utilizing hydrogel-based fibers that could be assembled into a wearable wound patch . This hydrogel, composed of a blend of alginate and glycerol, was linked to mesoporous silica particles treated with pH-responsive dyes. The fibers, with a diameter of 800 µm, demonstrated optimal response times when tested within a pH range of 6.5 to 9. In vitro assessments of the hydrogel containing pH-responsive beads in human-derived keratinocytes revealed no marked difference in cell viability compared to controls, except when pH-sensitive dye residues leaked from the fibers. The resultant fluorescence can be quantified and detected using smartphones, hence eliminating the need for expensive imaging techniques.[ 13,14] Another innovation involves a wound patch that detects pH levels and simultaneously releases medication at the wound site if abnormal pH values are recorded. Named ‘GelDerm’, this patch also employs an alginate and glycerol composite for the hydrogel, but is created using a 3D bioprinter instead of a microfluidic device. Ion exchange beads infused with pH-responsive dyes were incorporated at each corner of the patch, along with two drug-eluting scaffolds centrally positioned, providing a set concentration of gentamicin to combat infections from Pseudomonas aeruginosa (P. aeruginosa) and Staphylococcus aureus (S. aureus) . The patch accurately registered pH levels ranging from 4 to 9. The biocompatibility of the patches was evaluated using keratinocytes and skin fibroblasts, and both showed no discrepancies in viability when compared to control cases as there was no dye leakage from the GelDerm patch.[15] The color change is documented and measured via smartphone functionality, as the patch design is transparent. Biosensors have developed capabilities to monitor multiple physiological factors simultaneously (pH, glucose, oxygen, etc.), thereby enhancing treatment options.

### 1.2 Glucose Monitoring

Currently, approximately 415 million individuals are afflicted with diabetes globally, with 15–20% experiencing chronic wounds that can result in limb amputations. To address diabetic foot ulcers (DFUs) in humans, continuous glucose monitoring (CGM) systems, initially designed for diabetes treatment, have been modified for wound care applications. These biosensors provide real-time glucose level monitoring in wounds, as glucose levels directly impact bacterial proliferation and reflect the patient's physiological state. Since pH and glucose are among the most variable factors in wounds, recent years have seen the advent of biosensors that concurrently detect both parameters.[15] designed a sensor that features a polyphenyl boronic acid covalently attached to porous silicon films (pSi-PVPBA), which alter their thickness in reaction to changing pH and glucose levels in the wound. The polymer's thickness was assessed using interferometric reflectance spectroscopy on the composite film. The effective optical thickness was evaluated using chronic wound fluid collected from patients. The commonly available commercial glucose monitor typically measures glucose within the range of 0.6–33.3 mm and is unsuitable for wound fluid measurement due to its blood optimization. The change in effective optical thickness of the pSi-PVPBA was tested on wound fluid and on wound fluid spiked with 10 mm glucose, resulting in marked differences between non-spiked and spiked samples.[15,16] immobilized glucose-sensing enzymes, glucose oxidase, and horseradish peroxidase within an alginate matrix. Coupled to this was a pH-sensitive fluorescent dye, carboxynaphthofluorescein, creating an optical biosensor to track wound healing . The enzymes remained stable upon immobilization. The authors employed biocompatible sodium alginate as the hydrogel and evaluated its effectiveness on artificial wound fluid. The pH detection system also exhibited reversible signaling under varying pH conditions.[16,17] developed a zwitterionic hydrogel encapsulating phenol red for pH measurement, along with two enzymes, horseradish peroxidase and glucose oxidase, to simultaneously ascertain glucose levels in the wound. Variations in pH and glucose concentrations are monitored through smartphone images and analyzed within MATLAB . The authors demonstrated that both horseradish peroxidase and glucose oxidase displayed improved activity and stability when incorporated within the zwitterionic poly-carboxybetaine (PCB) hydrogel, noted for its biocompatibility.[17] In a more current study,[18] researchers have enhanced the functionality of their groundbreaking wound dressing, 'GelDerm', by integrating glucose sensors alongside antibiotic and growth factor-releasing elements. This advancement reportedly not only expanded GelDerm's capabilities for microbial assessment but also heightened its therapeutic effectiveness. The integration of a range of glucose sensors into the dressing was shown to allow for real-time monitoring of glucose levels at the wound site. These sensors functioned effectively across diverse temperature ranges and storage conditions. Additionally,

incorporating growth-factor-releasing components within GelDerm accelerated the wound-healing process. The enhanced GelDerm exhibited dual functionality; acting as a protective barrier against pathogens while also promoting wound healing, regardless of the infection status of the wound.[18]

### 1.3 Oxygen Monitoring

Oxygen is vital in the process of healing wounds, and biosensors designed to assess oxygen levels within injuries emerge as essential instruments. [19] outlined an electrochemical galvanic cell constructed on parylene-C, serving as an oxygen detector for injuries. Potassium hydroxide acts as the electrolyte, while silver and zinc were utilized as electrodes. The dressing was affixed to a poly(dimethyl siloxane) membrane. The oxygen levels present in the wound were transmitted via wireless telemetry or Bluetooth, transforming it into a wearable smart bandage. The smart bandage's efficacy in oxygen measurement exhibited a linear correlation between oxygen concentration and the current produced. Nevertheless, testing of the smart bandage occurred solely in a simulated wound environment. [19,20] merged oxygen detection and delivery to a wound by employing a parchment paper substrate embedded with a microfluidic network. The flexible parchment paper patch is enhanced by its coupling with a dermal regeneration matrix composed of collagen and glycosaminoglycan. Oxygen detection was executed through phosphorescence using a ruthenium compound, while potassium permanganate catalytic activity was applied on 3% hydrogen peroxide for oxygen delivery. The patches underwent both in vitro and in vivo assessments. L-929 mouse fibroblast cells were utilized for in vitro evaluations, revealing that the patches should be rinsed in Hank's buffered saline solution, followed by a full growth medium to mitigate cytotoxic effects. After rinsing, cell attachment was recorded at over 85%, indicating minimal cytotoxicity. For in vivo testing, 8 weeks -old male SKH1 (hairless) mouse was used with a miniature patch in a splinted excisional wound healing model. The healing rate of wounds with the oxygen-releasing patch was observed to be slower compared to the non-oxygen-releasing patch; however, both types of wounds were found to be closing by 14 days following surgery. [20,21] employed boron nanoparticles exhibiting oxygen-independent fluorescence alongside oxygen-dependent phosphorescence. The ratio between these two luminescence types was then used as a relative indicator of wound oxygenation. For in vivo examinations, 3 to 4 month-old female C57Bl/6 mice with full-thickness dermal wounds and one female Yorkshire swine with a full-thickness excisional wound were utilized. Acute wounds treated with the patch in mice demonstrated a reduction in wound area alongside an increase in the fluorescence to phosphorescence ratio over the course of three days following wounding. Since only one swine was incorporated into the porcine wound model, no definitive conclusions regarding wound closure were drawn; nevertheless, the researchers noted an enhancement in the oxygen partial pressure within the wound correlated with the rising fluorescence to phosphorescence ratio. [21]

Oxygen detection biosensors. A) The innovative dressing features an electrochemical galvanized cell constructed on parylene-C. Potassium hydroxide serves as the electrolyte, while silver and zinc are utilized as electrodes, and PDMS is incorporated as the polymer within the dressing. Oxygen concentrations in the wound are transmitted via wireless telemetry or Bluetooth, transforming the setup into a wearable smart bandage. Reproduced with permission.[19] B) Crafted with a microfluidic system, this advanced bandage consists of parchment paper linked to a dermal regeneration matrix formulated with collagen and glycosaminoglycan, allowing for flexibility in the bandage. Potassium permanganate is employed as a catalyst on 3% hydrogen peroxide for oxygen release.[20] C) VeCare integrates the identification of inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin-6, interleukin-8, growth factor TGF-β, along with the detection of S. aureus, as well as temperature and pressure in venous ulcers. The wound fluid is gathered through a microfluidic apparatus and analyzed using aptamers tailored for each biomarker.[22] D) The ‘Three-in-one’ adhesive strip enables sampling of P. aeruginosa and S. aureus presence. The duration from sampling to confirmation via Raman spectroscopy, post-culture growth, is 8 hours—considerably shorter than PCR or colony culture.

### 1.4 Biomarker Identification

In recent years, biosensors have been utilized to recognize specific biomarkers that reflect wound healing progress. Cytokines, growth factors, and proteases linked to inflammation, along with lactic and uric acid, and bacterial metabolites can be quantified through biosensor frameworks. This facilitates the evaluation of wound advancement and the detection of potential issues. [22] developed a dressing (VeCare) that merges the recognition of inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin-6, interleukin-8, growth factor TGF-β, S. aureus detection, and assessment of temperature and pressure in venous ulcers.

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The wound fluid is seized by a microfluidic mechanism and examined using aptamers designed for each biomarker . Graphene and gold nanoparticle composite served as electrodes for the electrochemical analysis of aptamers engaged with wound fluids. [22] Remarked on the aptasensors' commendable long-term stability over four weeks, exhibiting drifts under 5%. Elements from an open-source universal wireless electrochemical detector created [23] were integrated into the design, incorporating a potentiostat for pH sensing and a microcontroller for wireless electrochemical evaluation of various wound parameters. [23] incorporated temperature sensing in the design using a Wheatstone bridge differential amplifier setup by measuring resistance. The competency of the biomarker analytical dressing was assessed on full-thickness excisional wounds in 10-12-week-old male Institute of Cancer Research outbred mice. The patch effectively monitored pH, temperature, mouse TNF-α, and S. aureus, along with a decrease in pH coinciding with re-epithelialization observed over five days of post-wounding observation. All data were collected and relayed through custom-built MATLAB applications. [22,24] designed wearable carbon ultramicroelectrode arrays (CUAs) on flexible multi-component substrates derived from polymethylmethacrylate dissolved in chlorobenzene. This biosensor detects three biomarkers: pyocyanin, a metabolite from the common wound pathogen P. aeruginosa, uric acid, and nitric oxide. Biomarker data were gathered using square wave voltammetry, where CUAs acted as an electrode, alongside UV-Vis measurements specifically for pyocyanin and nitric oxide. The patch was evaluated on wound fluid simulant with RAW 264.7 macrophage cells and demonstrated an increasing current correlated with rising concentrations of pyocyanin, uric acid, and nitric oxide as seen in square wave voltammetry data. [24] Can also detect bacterial load, especially pathogenic bacteria like Escherichia coli (E. coli), S. aureus, and P. aeruginosa via biosensors. [25] developed a "Three-in-one" adhesive strip for simultaneously detecting the presence of S. aureus and P. aeruginosa in wounds. The adhesive strip samples the bacteria from the wound and is afterward analyzed through Raman characterization of the bacteria sampled on gold nano stars situated between two layers of graphene. The analytical functionality of the "Three-In-One" adhesive strip was tested in a mouse burn wound model. Seven-week-old male BALB/c mice were utilized to create skin burn wounds, which were then infected with 1 × 106 cfu mL−1 of P. aeruginosa and S. aureus. Readings for quantifying P. aeruginosa and S. aureus were found to align with other Raman spectroscopy applications for bacterial count identification, additionally, this approach was determined to be simpler and more time-efficient than traditional methods such as colony culture and PCR . [25]

**1.5 Smart Dressings**

Recent developments in biosensor technology have enabled the incorporation of sensors into wound dressings, referred to as "smart dressings." These dressings can track changes in the wound, helping to address infections promptly. They monitor several factors, including temperature, moisture, pH, bacterial presence, and uric acid concentration, particularly in chronic wounds.[15,26] A specific design featured a smart bandage using a Candida-derived uricase enzyme linked to a Prussian blue transducer. This electrode, made with a solution of BSA, glutaraldehyde, and uricase, was coated with a biocompatible chitosan layer to prevent harmful substances from leaching into the wound. Uricase helps convert uric acid into hydrogen peroxide, which Prussian blue reduces, producing a current that reflects uric acid levels. This current was captured by both a wearable potentiostat and a CHI 440 electrochemical analyzer, delivering consistent measurements. However, the study lacked biocompatibility tests with cell cultures or animal models.[26] Chronoamperometric biosensors of this kind can monitor chronic wounds and send reports for timely interventions.[27] Another study created silica nanoparticles loaded with chlorhexidine within an alginate hydrogel. These nanoparticles release chlorhexidine when exposed to alkaline wound conditions, demonstrating significant antibacterial effects against common wound bacteria like E. coli and S. aureus. The cytotoxicity of these nanoparticles was assessed using normal human dermal fibroblasts, showing similar cell viability to the control group. [10,27] Additionally, a proof-of-concept protocol used a machine learning algorithm for sensing based on images and wound biomarkers to track wound healing. This biomarker sensor comprised a nanofiber composite on a polyethylene surface, designed to measure levels of TNF-α, TGF-β, and VEGF through an electrochemical response. Testing was conducted on patients with chronic venous leg ulcers, with wound status evaluated using the Bates Jensen Wound Assessment Tool. This design utilises machine learning for wound care, requiring fewer images since the pre-trained model assesses wound characteristics like colour and margins, tailored to individual patients.[28]

Smart dressings are used for wound biosensing. A) A 3D printed smart bandage includes an immobilized uricase enzyme that measures uric acid levels in the wound. A Prussian blue working electrode helps convert uric acid into hydrogen peroxide, producing

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a current that reflects the uric acid concentration.[34] B) chlorhexidine-dispensing silica nanoparticles are created. The antibiotic releases only when the pH is alkaline, which occurs in chronic wounds. The data shows that a single microemulsion coating on the silica nanoparticles is more effective for drug release than double coating. [27] C) A biomarker sensor is designed with a composite of nanofibers on a polyethylene surface. This composite is filled with antibodies to measure TNF-α, TGF-β, and VEGF levels using electrochemical signals. The sensor is innovative, as it utilizes machine learning on light and thermal images of venous ulcers to assess wound progress.[28]

**Table 1.**

**Classification of biosensors customized for addressing challenges in wound healing.**

| Type of sensor | Analyte | Biocomponent / Sensor | References |
|---|---|---|---|
| Aptamer | TNF-α, IL6, IL8, TGF-β, *S.aureus* | Aptamers | [22] |
| Enzyme | glucose | glucose oxidase, horseradish peroxidase | [16] |
| | glucose | glucose oxidase, horseradish peroxidase | [17] |
| Electrochemical | oxygen | parylene-C | [19] |
| | pH | potentiostat | [22, 23] |
| | temperature | Wheatstone bridge differential amplifier | [23,23] |
| | uric acid | uricase on a polymer matrix | [11] |
| | uric acid | uricase enzyme coupled with a catalytic Prussian blue transducer | [26] |
| | pyocyanin, uric acid, nitric oxide | carbon ultramicroelectrode arrays | [24] |
| Optical | pH, glucose | polyphenylboronic acid covalently bonded to porous silicon films | [15] |
| | pH | carboxynaphthofluorescein | [16] |
| | pH | phenol red | [17] |
| | pH | fluorescein isothiocyanate | [27] |
| | pH | brilliant yellow dye encapsulated in anion exchange resin beads | [13] |
| | pH | GelDerm colorimetric measurement | [14] |

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| Type of sensor | Analyte | Biocomponent / Sensor | References |
|---|---|---|---|
| | oxygen | ruthenium compounds | [20] |
| | oxygen | boron nanoparticles | [21] |
| | *S.aureus* and *P.aeruginosa* | gold nanostars held between two pieces of graphene | [25] |
| Antibody | TNF-α, TGF -β and VEGF | nanofiber composite loaded with antibodies | [10] |

## 2. Polymers in Wound Biosensing and Management

The fields of wound treatment and tissue engineering have experienced remarkable progress with the incorporation of both natural and synthetic polymers in the realm of wound sensing and management.[29] This review emphasizes the application of diverse natural biopolymers, such as alginate, gelatine, silk fibroin, chitosan, and cellulose, in wound sensing technologies. Additionally, synthetic polymers like polyurethane, polyvinyl alcohol, polyethylene glycol, and polycaprolactone are examined regarding their contribution to wound sensing techniques. The exceptional attributes of these polymers—including biocompatibility, biodegradability, and customizable material characteristics—position them as promising options for both wound treatment and sensing applications (Table 2 ). Numerous instances of polymer-based biosensors are introduced to demonstrate their effectiveness in wound surveillance, infection identification, and healing processes.

**Table 2.**

**Functional polymers in biosensor fabrication.**

| Polymers in wound dressing | Advantages |
|---|---|
| **Natural polymers** | |
| Alginate | cost-effective, forms ionotropic hydrogels |
| Gelatin | RGD peptides, tissue adhesiveness, thermo-sensitivity |
| Silk Fibroin | bioactive, widely available, absorptive, cost-effective |
| Chitosan | non-toxic, biodegradable, electronic conductivity |
| Cellulose | biodegradable, biocompatible, low cytotoxicity |

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| Polymers in wound dressing | Advantages |
|---|---|
| **Synthetic polymers** | |
| Polyurethane | biocompatible, biodegradable |
| polyvinyl alcohol | non-toxic, biocompatible, elastic, water absorption |
| Polyethylene Glycol | hydrophilic, biocompatible, inert in aqueous media, reduces nonspecific binding of proteins and cells |
| Polycaprolactone | biodegradable, biocompatible, high plasticity, ductility, large surface-area-to-volume ratio |

Natural polymers provide numerous advantages, including widespread accessibility, elevated bioactivity, compatibility with biological systems, environmental friendliness, and enhanced cytocompatibility, closely resembling the native extracellular matrix (ECM). Nevertheless, natural polymers face challenges like high production costs, restricted tunability of their physical, chemical, and mechanical traits, and the potential to provoke an immune response owing to their protein content. Furthermore, natural polymer-based products may exhibit substantial variability from batch to batch because of their intricate chemistry. Conversely, synthetic polymers, with their well-defined chemical frameworks, allow extensive physical, chemical, mechanical, and surface modifications tailored to specific uses, alongside being affordable, biocompatible, and less susceptible to systemic degradation or immune reactions. Indeed, synthetic polymers are generally biologically inert, which may limit their biological applicability.[30,31] Thus, the selection of materials for biological applications, such as wound treatment and sensing, is dictated by the specific demands of the application, as a universal solution remains elusive. Frequently, a combination of natural and synthetic polymers is utilized in a controlled manner to create composite materials that merge the beneficial properties of both types of components.

### 2.1 Natural Polymers

#### 2.1.1 Alginate-Based Wound Biosensors

Alginate, an economical biopolymer obtained from brown algae and certain bacteria, has been thoroughly investigated due to its distinctive structure and attributes.[ 32,33,34] In summary, alginate is widely accessible, non-toxic, highly compatible with biological systems, easily adjustable, and demonstrates significant absorption, swelling, and antibacterial properties. These features render alginate particularly suitable for wound healing applications. Notably, its ability to create ionotropic hydrogels when crosslinked by divalent or trivalent cations makes it an exceptional foundational material for sensing technologies.[35,36]Biosensors that utilize ionotropic alginate hydrogels permit the target analyte to interact within the hydrogel, culminating in the production of measurable signals using enzymes, nanoparticles, or responsive polymers. Importantly, these biosensors have shown excellent performance in discerning glucose and lactate in actual samples such as human sweat and blood, highlighting their remarkable sensitivity.[37,38] Furthermore, considerable advancements in this area have led to the development of an advanced smart bandage designed for chronic wound monitoring .[39] The ultra-thin bandage, measuring less than 3 mm, includes pH and temperature sensors, a microheater with a 20-ohm resistance, and drug carriers made from thermo-responsive poly(N-isopropyl acrylamide) (PNIPAM) within an alginate hydrogel patch. An electronic patch manages drug release triggered by sensor data through thermal activation. This technology allows for real-time monitoring of wounds, identifying infections directly at the site, and releasing drugs as needed, making it very useful for healthcare. The pH sensor, built on a flexible parylene base, shows a linear response with a sensitivity of -50 mV per pH unit. Carbon/polyaniline (PANI) and silver/silver chloride serve as the working and reference

electrodes, respectively, with PANI acting as a positive exchange membrane. When the pH sensor detects changes, it prompts the hydrogel to release antibacterial medication. A Bluetooth module within the electronic patch enables wireless control of sensor information and drug delivery. The bandage's performance was verified through various tests, including in vitro bacterial studies, drug release tests, scratch wound healing assessments, and biocompatibility tests on human cells. [39] Besides pH, the platform can incorporate other sensors, medications, and growth factors to address specific healing needs. However, its use on chronic wounds in animal models has yet to be tested in real-life scenarios.

Natural polymer-based systems are being developed for wound biosensing and antibacterial applications. Alginate-based polymers are being assessed for their antibacterial qualities in managing wounds. This includes a diffusion test comparing a hydrogel that releases antibacterial agents with a control hydrogel that does not contain antibiotics. Biofilm presence is visualised on both the control and antibacterial patches, highlighting live bacteria in green. A CFU assay examines the relationship between S. aureus and the antibiotic cefazolin. In an in vitro setup, S. aureus cultures are monitored in real-time for pH changes, which also activates a heater. The integration of these components is demonstrated with a patch being applied to the author's hand. [39] Gelatine-based bio-electronic hydrogels are explored for their ability to speed up wound healing through electrical stimulation. An in vivo study on SPF rats with full-thickness skin injuries investigates wound healing. The experimental design tracks the reduction in wound size over ten days across different treatments. On day 20, histological and immunohistochemical analyses are performed, marking fibroblasts, blood vessels, neutrophils, collagen, and certain growth factors.[40] Chitosan-based platforms are used for detecting bacteria and monitoring diabetic wounds. The design involves lectin-functionalised chitosan nanoparticles with crystal violet, which clump together in the presence of bacteria, contrasting with non-bacterial samples.[41] The ultra-slim CS-GO sensor features gold micro gap electrodes and uses linear sweep voltammetry to measure the response of human dermal fibroblasts to different glucose levels, ensuring accurate results across a wide range. Data is presented as mean ± standard deviation from three tests.

**2.1.2 Gelatine-BasedWoundBiosensors**

Gelatine, a form of denatured collagen, is commonly used in tissue engineering and wound healing. Its RGD peptides contribute to tissue adhesion and sensitivity to temperature. [42,43] Because of its strong biocompatibility, gelatine is a great choice for various biosensor applications. It offers excellent hemostatic, antimicrobial, and anti-inflammatory benefits while promoting cell movement, growth, blood vessel formation, and skin layer growth, making it highly effective for wound healing and repair.For over forty years [44,45,46] , gelatine-based biosensors have been effectively used to detect substances like glucose, proteases, and hydrogen peroxide. Recent research has highlighted their use in monitoring wound conditions.[40] For example, a new technique using N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) was developed to create a bioinspired 3D scaffold made from gelatine. This scaffold incorporated a water-dispersible conducting polymer complex called poly(3,4-ethylenedioxythiophene)-poly(styrene sulfonate) (PEDOT:PSS) and carboxyl-functionalized multi-walled carbon nanotubes (MWCNTs-COOH). Named 'MESGel,' this gelatine-based structure was designed to provide mechanical flexibility, electroactivity, and self-healing abilities. Its creation was achieved using a simple ‘one-pot’ method that combined physical doping and chemical crosslinking, leading to a complex 3D network within the hydrogel. In wound care, MESGel has transformed treatment by combining motion sensing with promoting skin healing through electrical stimulation, as shown in studies with rat models having full-thickness skin defects. MESGel has significantly reduced wound size and improved tissue healing by promoting collagen formation, blood vessel growth, and skin regeneration. Its ability to support the growth of Chinese hamster lung (CHL) cells [40] further highlights this synergy between electroactivity and bioelectronics.[47] However, its effectiveness in chronic wound models in animals still requires more study. [41] In another study, researchers developed a colour-changing pH sensor using a polyelectrolyte complex method. By combining polyampholytic gelatine with sodium alginate, they created a high-molecular-weight hydrogel bead. This bead used gallic acid, a natural antioxidant, as a visible indicator for detecting infections in wounds. In acidic conditions, it remained pale yellow or off-white but changed colour swiftly in basic conditions (above pH 7.4), signalling bacterial infection. This colour change was quick, providing immediate feedback. Beyond its visual function, the hydrogel bead also demonstrated significant antioxidant properties, showed no toxicity to cells, and effectively absorbed wound fluids. [41] However, like MESGel, its performance in chronic wound animal models is still untested.

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### 2.1.3 Silk Fibroin-Based Wound Biosensors

SF-based biosensors have proven useful in monitoring health, aiding wound healing, and tracking temperature changes, demonstrating their practical applications.[48] One innovative colorimetric SF biosensor can detect reactive oxygen species (ROS) in wounds, providing visible signals for prompt treatments. [49] In a study, researchers used electrospinning to create nanofibrous silk fibroin mats that contained Amplex red dye. These mats allow real-time monitoring of oxidative stress in wounds by converting Amplex into resorufin in the presence of hydrogen peroxide. Tests showed that hydrogen peroxide concentrations as low as 25 µM, combined with horse radish peroxidase, produced a noticeable color change. The mats were found to be compatible with human keratinocytes in laboratory conditions. In live tests on diabetic mice with non-chronic wounds, the mats changed colour from white to red after 24 hours, showing their ability to accurately measure oxidative stress in wounds. These sensing mats offer a straightforward method for tracking oxidative stress and ROS levels directly at the wound site, marking a new direction in wound monitoring and personalised treatment strategies. However, their effectiveness in chronic wound models still needs more research.

### 2.1.4 Chitosan-Based Wound Biosensors

Chitosan (CS), made from chitin, shows great potential in healthcare because it is non-toxic, biodegradable, and has good mechanical and electrical properties.[50,51] CS has strong anti-microbial effects and encourages cell growth, migration, and tissue regeneration, making it a strong candidate for wound care. Its unique properties can aid all stages of wound healing, potentially improving the overall effectiveness of wound biosensors.Although research on CS-based wound biosensors is still developing, the possibilities are exciting. One study achieved a composite biosensor using CS to detect bacterial infections at the point of care, while another confirmed that CS-based biosensors could effectively monitor diabetic wounds. The earlier study presented a point-of-care technology using lectin-coated chitosan nanoparticles with crystal violet to detect important bacterial infections. These nanoparticles, measuring less than 200 nm in diameter, acted as the main sensing material. When they came into contact with bacteria, they clumped together, forming visible aggregates that contrasted with samples lacking bacteria. This clumping provided a clear sign of bacterial presence. The technology only needed a 100 µL sample and was thoroughly tested in various environments, such as saline, simulated urine, artificial sputum, respiratory swabs, and wound swabs. The results showed high sensitivity and specificity, with a detection limit of 105 CFU mL−1. This innovative technology greatly improved infection detection, offering quick, accessible diagnostics with promising potential for real-world medical use. [52] However, further studies on the platform's compatibility with cells and testing in chronic wound animal models are necessary. The second study proposed a biosensor array made of ultra-thin layers of Chitosan-Graphene Oxide (CS-GO), featuring gold-based electrodes measuring 60 µm. The cross-linked GO improved the stability of the chitosan in water while allowing for easy microfabrication. The biosensor patch was evaluated by monitoring human dermal fibroblast (HDF) cells on the CS-GO surface. Cyclic voltammetry of this setup showed consistent peak increases during the growth of HDF cells over 96 hours. This increase related directly to how quickly the cells were growing, highlighting its usefulness in tracking cell health and responses to different stimuli. The sensor could accurately measure glucose levels from 1 to 20 mm, with a sensitivity of 0.17 µA mm −1. These results demonstrated the potential of this sensor for various uses, including glucose monitoring, tracking cell growth at wound sites, and assessing wounds in diabetic patients.[53] However, in vivo testing of the sensor patch in chronic wound animal models is still needed.

### 2.1.5 Cellulose-Based Wound Biosensors

Cellulose is the most abundant polymer on earth, sourced from plants and bacteria.[54] Its qualities, such as biodegradability, biocompatibility, and low toxicity, make it ideal for many biomedical uses, including biosensors and wound dressings.[55,56] Cellulose absorbs well, swells quickly, retains exudate, and is versatile and flexible, making it suitable for wound applications. Its properties can be adjusted, allowing for the creation of customizable biosensors, including those for monitoring wounds. Several studies have investigated cellulose-based biosensors for tracking wounds. One such study explored a colorimetric method using peptide-linked cotton cellulose nanocrystals to detect human neutrophil elastase, an important marker in chronic wounds. The study presented a colorimetric method for detecting HNE using peptide-linked cellulose nanomaterials (CCN). The process involved attaching a specific HNE tripeptide substrate, n-Succinyl-Alanine–Alanine–Valine–para-nitroanilide (Suc-Ala–Ala–Val–pNA), to glycine-esterified CCN. The resulting CCN tripeptide links showed significantly greater visible HNE activity than similar structures

on paper.[57] When para-nitroaniline (pNA) was released enzymatically from the glycine-CCN conjugate, reactive dyes enhanced the color response, increasing chromogen absorption. This colorimetric method could detect HNE at levels found in chronic wound fluid (0.05 U mL−1 HNE). Although this research adds valuable knowledge to colorimetric HNE detection using cellulose, especially for wound care, the cytocompatibility and performance of this system in chronic wound animal models still need evaluation. Such assessments are essential for understanding how effective this detection system is in actual wound healing.

Another study developed a biosensor made of peptide and cellulose to detect high levels of human neutrophil elastase (HNE) in chronic wounds.[58] It focused on a peptide-cellulose conjugate biosensor that utilized the unique properties of TEMPO-oxidized nano fibrillated cellulose (tNFC) to find increased HNE levels in chronic wounds. The design featured a fluorescent peptide HNE substrate, n-succinyl-Ala-Pro-Ala-7-amino-4-methyl-coumarin, attached to the cellulose surface with a polyethylene glycol linker. The small crystallite size of tNFC set it apart from other cellulose materials, giving it a larger specific surface area and a higher volume ratio. This structure improved HNE access to enzyme substrates by reducing steric hindrance. Additionally, tNFC's natural porosity made it more effective than other substrates, emphasizing its potential for biosensor use. The combination of a small crystallite size and a higher sensor count within the tNFC framework offered great sensitivity. This biosensor may serve as a strong candidate for creating point-of-care diagnostic tools to detect high protease levels, particularly HNE, in chronic wounds and could have wider applications. However, further research on the cytocompatibility of this material and its performance in chronic wound animal models remains necessary.

Researchers have developed functional scaffolds by mixing cellulose nanocrystals (CNCs) and polyvinyl alcohol (PVA) to effectively immobilize biological probes.[59] The study showed that CNCs/PVA nanocomposites could be transformed into strong, water-insoluble scaffolds with a large surface area through a simple dip-coating method, followed by drying and heating. This process took advantage of the many surface hydroxyl groups in both CNCs and PVA, which can be modified with acrylate functional groups. This modification allowed for the addition of a high concentration of fluorescent sensor motifs using thiolene reactions. The resulting sensor films displayed quick, noticeable changes in fluorescence intensity with pH changes, providing an almost immediate response. This method was also used to detect protease activity. A Förster-type resonance energy transfer chromophore pair was included in the scaffold through a peptide sequence, allowing the cleavage of the protein linker by specific enzymes. This cleavage caused the chromophores to separate, triggering a ‘turn-on’ effect that increased the previously low fluorescence. A standard benchtop spectrometer measured the rise in fluorescence intensity, successfully identifying trypsin at levels often seen in abnormal proteolytic activity, common in wound fluids. The combination of CNCs and PVA in these multifunctional scaffolds highlighted their potential for fluorescence-based sensing and opened up new avenues for research. However, areas like cytocompatibility and performance in chronic wound animal models still need further study.

### 2.2 Synthetic Polymers

#### 2.2.1 Polyurethane-Based Wound Biosensors

Polyurethane (PU) is widely used in medical applications, such as wound dressings and bio-adhesives,[60,61] because of its biocompatibility and biodegradability. PU absorbs and retains water well, is gas permeable, and is flexible and elastic. This makes it useful for delivering growth factors and antibiotics, aiding in wound healing, and forming a barrier against bacteria. [62] PU also allows for a high degree of customization in its physical, chemical, and mechanical properties, and it has been used to create biosensors for monitoring wounds. Recent studies have highlighted the potential of PU-polydopamine (PDA) nanofiber composites for biosensor applications, particularly in smart wound dressings for quick testing.[63,64] One study introduced an easy method using electrospinning to produce receptor-free PU-integrated PDA nanofiber biosensors. These nanofibers quickly changed color from blue to red, providing a sensitive way to detect E. coli. The creation of nanofibers through electrospinning allowed for the simple detection of E. coli without complicated receptors, based on color changes. This process led to improved interaction between PDA and E. coli, resulting in notable sensitivity for detecting bacteria. The PU-PDA nanofiber system showed exceptional sensitivity, allowing for fast and clear color changes that can be easily seen by the naked eye when E. coli is present.

This biosensor uses electrospinning to make nanofibers that simplify the detection of E. coli without needing complex receptors. The electrospinning process causes diacetylene monomers to assemble on their own, which improves how PDA macromolecules

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interact with E. coli. This stronger interaction leads to high sensitivity in detecting bacteria. The PU-PDA nanofiber system is particularly effective, showing quick and clear color changes that are visible to the naked eye when E. coli is detected. This versatile biosensor design offers potential for various uses and opens up new research avenues in analyzing extracellular polymeric substances (EPS), contributing significantly to biosensing and detection technologies. However, important factors like the biosensor's compatibility with cells and its performance in chronic wound models still need investigation. Additionally, a new biosensor for uric acid (UA) has been created using a layer-by-layer (LbL) method, forming an electrode with specific polymers and xerogel materials. [65] This study introduced a new way to create a first-generation amperometric biosensor to detect UA using the LbL approach. It involved detailed examination and improvement of each layer, which included an outer polyurethane (PU) membrane for selectivity, an inner electro polymer with special properties, and a dual-layer xerogel structure. This thorough analysis revealed how PU's hydrophobic nature affects UA movement and provided insights into how each layer contributes to the biosensor's function. The study resulted in an optimized design that combined hydroxyl-methyl triethoxy silane (HMTES) xerogels, a polyluminol-aniline electro polymer, and 100% hydrophobic polyurethane, greatly improving UA detection capabilities. These advancements led to enhanced sensitivity of 0.8 nA μm−1 and a linear response range for UA concentrations from 100 to 700 μm. The biosensor quickly responds in about 10 seconds, with low detection limits under 10 μm and excellent selectivity against common interferences. By carefully adjusting the LbL design and using selected materials, this research sets a strong base for future biosensor developments. However, further studies are needed to explore the biosensor's compatibility with cells and its performance in chronic wound models, which will improve the overall understanding and potential of this biosensing method.

### 2.2.2 Polyvinyl Alcohol-Based Wound Biosensors

Polyvinyl alcohol (PVA) hydrogels are increasingly used in medical settings, particularly for temporary skin protection and burn dressings.[66] Their popularity stems from their safety, compatibility with biological tissues, flexibility, and ability to absorb water.[] Additionally, PVA's features, such as strong water retention, resistance to chemicals, and good strength, make it suitable for wound care. In wound biosensor technology, PVA is often combined with other polymers to identify wound biomarkers. For instance, researchers designed an electrochemical method to monitor wounds using the enzyme uricase to detect uric acid.[67] This technique involves encapsulating uricase in a specific polymer matrix to enhance its detection capabilities. To improve electron transfer during the process, a redox compound known as ferrocene carboxylic acid was added. The modified uricase showed significantly better performance in detecting uric acid compared to methods where it was simply attached. The biosensor provided consistent results across relevant concentration levels, specifically between 12 and 100 μm. Moreover, the stability of the biosensor was carefully assessed over 48 hours, maintaining 90% of its activity for up to five days. This biosensor successfully measured uric acid in fluids from sweat and wounds, displaying a recovery rate of around 102–107%. This innovative research marks a substantial advancement, offering an effective method for tracking uric acid, a key indicator of wound healing status. The combination of immobilising enzymes, efficient electron transfer, and continuous monitoring makes this biosensor a valuable tool in wound management and clinical diagnostics. However, further investigation into the cytocompatibility of this platform and its performance in chronic wound models is necessary.

In another study, researchers developed a smart wound dressing equipped with antibacterial and bio chromic features by incorporating an anthocyanin probe into a composite of carboxymethyl cellulose and PVA, alongside a potassium aluminium sulfate mordant.[11] This dressing functions like an aerogel and effectively monitors wound healing. It detects changes in pH levels within simulated wound environments, allowing for visible colour changes. The anthocyanin probe, a soluble dye, was integrated into the carboxymethyl cellulose/PVA matrix through the addition of the mordant. This integration improved the sensing capabilities of the dressing, enabling real-time monitoring. When exposed to a fluid that mimics wound conditions with a lower pH, the anthocyanin underwent a colour shift, changing the absorption spectrum from 592 to 446 nm. The halochromic reaction of anthocyanin caused noticeable changes in colour, shifting from purple to a vibrant pink. Further studies evaluated the cytotoxicity and antibacterial properties of the developed aerogel-like dressing. This research marked a significant step forward in wound care technology by combining wound healing monitoring and antibacterial action in one product. This innovation represents a key development in the design of wound dressings, introducing a colour-changing sensor that enhances monitoring and showcases the potential of natural

resources for innovative medical diagnostics. However, applying this research to a chronic wound model for in vivo testing needs further investigation.

### 2.2.3 Polyethylene glycol

The study used photolithography to attach a FRET peptide to a specially patterned hydrogel made of polyethylene diacrylate (PEGDA). The main goal was to detect MMP-2 and MMP-9 enzymes, which are essential for assessing wound severity. By fixing the FRET peptide sequence Dabcyl-Gly-Pro-Leu-Gly-Met-Trp-Ser-Arg-Lys (FITC)-Cys, which is cleaved between Gly and Met by MMP-2 or MMP-9, an increase in hydrogel fluorescence could be measured as an indicator of protease levels. This hydrogel biosensor shows great potential for detecting important proteases in chronic wounds, but further research is needed to explore its compatibility with cells and its effectiveness in a chronic wound model. In another study, a PEG hydrogel was used to attach a probe for creating smart sensor films that respond quickly to hypochlorous acid (HClO).[86] The research introduced a new luminescence probe, Eu(L)3(DPBT), based on Eu3+ complexes, designed for time-gated luminescence detection of HClO both in lab tests and in living organisms. This probe showed rapid and highly selective responses to HClO while keeping low toxicity. By incorporating the probe into a PEG hydrogel matrix, new sensor films were created. These films can be applied to the skin, allowing real-time monitoring of HClO levels in non-chronic wounds in mice, helping to distinguish between infected and acute wounds.[68] This innovative approach has promise as a diagnostic and therapeutic tool for wound management. However, measuring intracellular HClO is challenging due to the complex nature of sample conditions, local probe concentrations, and variations in excitation. Additionally, evaluating this biosensor in a chronic wound model is another area that requires future research.

### 2.2.4 Polycaprolactone-Based Wound Biosensors

PCL is strong and can be easily used to make biosensors. In biosensing, researchers created enhanced electrospun PCL nanofibers that have a large surface area. These fibers were modified with carbon quantum dots (CQDs) to produce a strong fluorescence signal.[69] The resulting biosensor uses aptamers and CQDs to quickly and affordably detect S. aureus bacteria in wounds. The CQDs, made from orto-phenylenediamine (OPD), emit a distinct yellow light. The process involved cross-linking to combine CQDs with polymer nanofibers, highlighting their integration with the polymer chains. This new aptasensor is selective, reproducible, stable, and compatible with fibroblast L929 cells, making it effective for identifying bacteria in infected wounds. In tests on non-chronic skin wounds in mice, the sensor showed increased fluorescence under UV light after two hours, demonstrating its effectiveness. The sensor can detect bacteria in a range from 10 to 108 CFU mL−1, with a detection limit of 10 CFU mL−1. The study suggests this platform could adapt to detect other microbes or viruses with the right modifications. However, further research is needed to confirm its performance in different wound types and its clinical potential.The use of natural and synthetic polymers in wound biosensing has improved wound care significantly. These advanced materials and biosensors enhance the monitoring of wounds, the detection of infections, and overall healing outcomes. Ongoing research into combining polymer-based biosensors with smart technologies could change how wound care is practiced and improve patients' quality of life. Polycaprolactone (PCL) is a type of synthetic polyester known for being biodegradable and biocompatible. It has useful properties like high elasticity, low melting point, and ductility.[70]

### A. Synthetic polymers

including polylactic acid (PLA), polyglycolic acid (PGA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polycaprolactone (PCL), offer benefits like finer scaffold fibres, increased porosity, and adjustable mechanical strength. However, these materials may lack essential biological qualities. The polymers used in scaffolding break down over time into smaller molecules. Unlike natural biocompatible materials, synthetic polymers can release toxic substances during degradation, which may harm cells and tissues. If these acidic by-products are not managed properly, they can lead to inflammation, irritation, or toxicity by lowering the pH in the surrounding area. It is crucial for these breakdown products to be non-toxic or effectively removed from the wound site to prevent complications. Otherwise, harmful by-products can hinder the healing process, resulting in delayed tissue regeneration or ongoing inflammation. The speed at which a nanofiber scaffold breaks down is essential for effective wound healing. Ideally, the scaffold should degrade at a rate that aligns with the wound's natural healing process. If it breaks down too quickly, it may not provide enough support for the new tissue, leading to complications such as wound collapse or improper healing. On the

other hand, if the scaffold degrades too slowly, it can hinder tissue regeneration. To reduce toxicity and achieve the right degradation rate, researchers often create hybrid polymers by mixing natural and synthetic materials. These scaffolds are designed to decompose in a way that encourages tissue growth while preventing the buildup of harmful degradation products. By combining natural and synthetic polymers, composites can be developed that take advantage of the strengths of both types. Natural polymers offer biocompatibility, biodegradability, and biological activity, while synthetic polymers provide better mechanical strength and uniform quality. This combined approach aims to produce materials that are more effective for tissue engineering. Electrospinning is a popular method for making nanofibrous scaffolds, but some natural polymers, like chitosan, cannot be easily spun into films on their own. To overcome this limitation, natural polymers are often mixed with synthetic fibres or other natural fibres to maximize their benefits.

**3. Methods for loading drugs onto nanofibrous scaffolds**

Physical adsorption method The physical adsorption method allows drugs to attach to the surface of scaffolds without any chemical reactions, relying instead on forces like electrostatic and van der Waals interactions. In this process, the drug is first dissolved in a solvent, and then the nanofibrous scaffolds are placed in this solution, enabling the drug to stick to the scaffold's surface. A key benefit of this method is its simplicity, as it does not change the drug’s chemical structure or its effectiveness. Since there are no chemical bonds formed, the drug remains physically active. However, this approach can lead to quicker drug release rates due to its limited loading capacity and weaker interactions with the scaffold.

(1)The physical adsorption method involves attaching drugs to the scaffold surface using natural interactions such as van der Waals forces and electrostatic forces. To begin, the drug is dissolved in a solvent, creating a drug solution, into which the nanofibrous scaffold is submerged. This process results in a drug-loaded scaffold that relies on physical bonds. The method preserves the drug's structure and properties. However, the drug is released quickly at the wound site, making it impossible to achieve sustained release. The chemical conjugation method links a drug to a molecular scaffold through a chemical reaction that forms stable bonds like covalent, ester, or amide bonds. For this to occur, either the drug or scaffold must contain a reactive functional group or be modified to include one. Under specific conditions, such as appropriate temperature and time, the drug binds to the scaffold. This results in a drug-loaded scaffold with strong chemical bonds, but the drug's original properties may change. This method allows for slow and ongoing release of the drug at the wound site and enables the loading of multiple drugs onto the scaffold. The coating method involves applying a drug or drug-carrier composite to the surface of a scaffold. The drug is dissolved to create a drug solution. The nanofibrous scaffold can then be sprayed, roll-coated, or brush-coated to apply the drug. This method maintains the original properties of the drug, but the lack of chemical bonding means that the drug is released quickly. However, it is also possible to load multiple drugs onto the scaffold using this method. The co-blending electrospinning method is another approach for drug loading.

(2)Both the drug and the scaffold are properly dissolved in suitable solvents. These solutions are then combined to form a mixture. This mixture undergoes electrospinning to create nanofibres. The result is nanofibrous scaffolds that are chemically bonded with the drug. These scaffolds are more mechanically stable compared to those made by other techniques. However, the drug's chemical make-up and properties can be affected by the chemical bonding, temperature changes, and exposure to light. This approach allows for a slow and steady release of the drug, and it also enables the incorporation of multiple drugs into the scaffolds. Image created using BioRender.com.

**A.The chemical conjugation method**

Focuses on loading drugs onto scaffolds through stable chemical bonds. It requires either the drug or the scaffold to have reactive functional groups, or the introduction of such groups through modification. This technique ensures that the drug remains securely attached to the scaffold, allowing for a slow and extended release rate and the possibility of loading several drugs. However, it can change the drug’s basic chemical structure and needs strict reaction conditions and elaborate preparation steps.

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**B.CoatingMethod**

This method involves applying the drug or its carrier directly to the scaffold's surface. Similar to physical adsorption, the drug is dissolved in a solvent. The scaffold can then be either immersed in or sprayed with this solution, or it can be coated on with a brush. While this approach leads to weak interactions between the scaffold and the drug, resulting in a quick release rate, it also allows for easy loading of multiple drugs. It is suitable for both small and large molecules.Co-blending Electrospinning MethodIn this method, the drug and scaffold materials are combined and electrospun to create nanofiber scaffolds that contain the drug. The process entails dissolving both materials in suitable solvents, mixing them, and then electrospinning the mixture to produce nanofibers that distribute the drug evenly. This approach allows for a slow and steady release of the drug while enhancing the scaffold's mechanical properties. However, controlling the release rates and maintaining drug stability can be challenging due to changes in temperature or exposure to light during electrospinning. Additionally, the lengthy process can make scaling up production difficult.

**C. Enhancing cell migration and blood vessel growth.**

Fibroblasts play a crucial role in wound healing as they grow, move, and release collagen and other key substances for tissue repair. Growth factors such as VEGF, TGF-β, FGF, and EGF are vital for these processes. Wang et al. created a scaffold with dual growth factors (EGF/bFGF) in a mouse model, leading to better collagen production and new blood vessel formation.[71] Essential vitamins A, C, E, B12, and B2 also support wound healing, contributing to collagen formation, fibroblast growth, and inflammation control.[72,73,74] Sayeed Farzanfar et al. designed a poly(caprolactone)/gelatine scaffold containing vitamin B12. Their cell studies indicated a significant increase in L929 cell growth after one and three days. After 14 days, the dressings with vitamin B12 showed a much higher wound closure rate compared to those without it [75]. Curcumin,[76] known for its beneficial properties, encourages fibroblast growth and collagen deposition. Jose et al. demonstrated that curcumin-loaded cellulose nanofibers enhanced fibroblast movement in chronic wound models.[77]

**D. Neovascularization**

Neovascularization is a crucial part of wound healing, and nanofiber scaffolds significantly aid this process. By delivering substances that promote blood vessel formation—like collagen, growth factors, and cytokines—these scaffolds enhance blood flow to the wound, speeding up healing. Common additives to boost angiogenesis include VEGF, FGF, PDGF, and TGF-β. Cytokines such as IL-8 and MCP-1[78] encourage the movement and growth of endothelial cells, further advancing blood vessel formation. Collagen proteins are particularly useful due to their compatibility with the body, creating favourable conditions for new blood vessels to develop.[79] Zhan and colleagues developed a multifunctional nanofiber that combines antibacterial and angiogenic properties, incorporating chitosan, copper, and a decellularized Wharton's jelly matrix.[80] Their findings highlight the potential of nanofiber scaffolds in enhancing neovascularization and accelerating wound healing.

**4. Multi-response intelligent stimuli responsive drug delivery systems based on nanofibrous scaffolds**

**4.1 Nanofibrous scaffold-based drug delivery systems** represent an innovative approach in tissue engineering, especially for wound healing. These smart dressings are designed to release medication in response to specific biological signals or environmental changes in a controlled manner. This targeted release aims to improve the effectiveness and safety of treatments. The polymers used in these scaffolds are essential to their function as they respond to different stimuli, including pH, temperature, light, electric fields, and magnetic fields.[81,82]

**4.2 pH-responsive nanofibrous scaffolds** are specifically designed to release drugs when there are changes in the surrounding pH. [83] These systems utilise polymers with functional groups, such as carboxyl and amine groups, that either ionise or protonate in response to pH shifts. This ionisation or protonation causes the polymer chains to either expand or contract, altering the scaffold's pore structure. [83]For instance, polyethyleneimine (PEI) shrinks in alkaline conditions due to deprotonation and expands in acidic conditions as a result of protonation.[84]Certain polymers, such as N-isopropylacrylamide (NIPAM), can switch from hydrophobic to hydrophilic depending on pH levels, influencing drug release. Changes in pH may also lead to the degradation of polymer structures or break chemical bonds sensitive to acidity or alkalinity, enhancing drug delivery. This targeted approach improves

treatment effectiveness and reduces side effects, particularly in areas like tumours or inflamed tissues. Koohzad et al. developed a nanofibrous structure that adheres to drugs through electrostatic forces, enabling a slow release of medication at alkaline wound sites. Altinbasak et al. [85] created a pH-responsive nanofiber scaffold using a polymer with an acrylate backbone, protected by a hydrolysable and acid-sensitive trimethoxy benzaldehyde sidechain. This scaffold shifts from hydrophobic to hydrophilic at a relevant extracellular pH of 6.5 in tumours, leading to hydrolysis of side chains and a threefold increase in fibre diameter, which allows for drug release.[86]

**4.3 Temperature-responsive nanofibrous scaffolds**

release medication based on temperature changes through phase transitions or by weakening the bonds that hold the drug and scaffold together. These scaffolds use temperature-sensitive polymers that undergo phase transitions near their upper or lower critical solution temperatures. For instance, poly(N-isopropylacrylamide) (PNIPAM) has a lower critical solution temperature (LCST) around 32 °C, above which it becomes hydrophobic, causing the scaffold to contract and release the drug. Increased temperatures can also expand the polymer, [87] altering the scaffold's pore structure and enhancing drug diffusion. Biodegradable polymers like polylactic acid (PLA) and polycaprolactone (PCL) may degrade at high temperatures, releasing drugs as they break down. Higher temperatures can also weaken interactions between the drug and polymer, promoting drug release.[88] Wang Xiaocheng et al. combined the temperature-responsive properties of PNIPAM hydrogels with the photothermal abilities of MXene nanosheets to deliver vascular endothelial growth factor (VEGF) in a controlled manner, promoting endothelial cell activity.[89] Liang Yuting et al. created a dual-responsive nanofiber by grafting the pH- and temperature-sensitive polymer polyethyleneimine-N-isopropyl acrylamide (PEI-NIPAM) onto cellulose nanofibers. At 37 °C, this nanofiber showed an accumulated drug release rate of 59.45%.[84]

(1) pH responsive scaffolds are created to release medication based on changes in pH levels. These scaffolds have specific functional groups, like carboxyl or amine, that are linked to the drug. In acidic environments, these groups protonate and the scaffold expands, allowing the drug to be released at the wound site. In alkaline conditions, the scaffold shrinks, which stops the drug from being released. Depending on the pH, the scaffold can be hydrophilic or hydrophobic, impacting drug release.

(2) Temperature-responsive scaffolds are designed to release drugs when the temperature changes at the healing site. As the temperature varies, the scaffold expands or contracts, influencing drug release. Temperature fluctuations can also break the bonds between the drug and the scaffold, determining if the drug is released.

Photoresponsive nanofibrous scaffolds release medication when exposed to light. They use several mechanisms like charge transfer and photothermal effects. These scaffolds contain polymers with chemical linkages that respond to light. When illuminated, these bonds break, causing the scaffold to collapse and release the medication. Some materials change structure under light, altering drug release. Light can also cause charge transfer, which affects how the drug interacts with the polymer, aiding in release. Additionally, light can generate localised heat, which helps release the drug through thermal expansion or degradation.[88-93] For example, scaffolds with gold nanoparticles use surface plasmon resonance to create heat for drug release when exposed to light.[114] Lin-Jin et al. developed vitamin E-containing MXene nanoribbon fibres that allow for adjustable temperature-responsive drug release. [95]

(1) Photoresponsive scaffolds change how they release materials based on light exposure. a-Different light levels can affect the scaffold's stability. b -Light can

(2) cause charge transfer. c-Photothermal lead to expansion or d-shrinkage, or e- even destroy parts of the scaffold. It can also trigger changes in molecular structure and break the bonds connecting the scaffold to the drug, influencing how drugs are released where they are needed.

(3) Electroresponsive scaffolds rely on electric fields to control drug release. When an electric field is applied, it guides the movement of drug molecules through a specific path. This process involves changing the attachment of drug molecules and breaking the bonds between the scaffold and the drug, which impacts the release of the medication.

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(4) Magnetic responsive scaffolds react differently to magnetic fields. Applying a magnetic field during their operation can cause changes in shape, heat effects, and the breaking of bonds with the drug. These reactions affect how medication is released at the site of healing.

**4.4 Electro responsive nanofiber drug delivery systems**

Use electric fields to control medication release through techniques like electrostriction, electro-osmosis, and charge-controlled desorption.

a-Electrostriction allows some polymers to change shape under an electric field, which alters the scaffold's pore structure and affects drug release.

b-Electric charge-controlled desorption means that the drug can be released or absorbed depending on the electric field's influence on the charge distribution between the drug and the polymer.[96]

c-Electro-osmosis involves the drug moving in the direction of the electric field due to charged drug molecules or ions within the scaffold.[97]

d-Electrolysis allows for changes in the polymer scaffold's structure. The drug can be released through hydrolysis or by breaking chemical bonds, a process triggered by an electric field.

Alexa-Maria Croitoru et al. created a quercetin-loaded poly(lactic acid)/graphene oxide micro-scaffold using electrospinning. The introduction of an electric field led to an impressive 8640-fold increase in the rate of quercetin release.[96] These techniques present a chance for precise and effective drug delivery by allowing controlled release in response to electrical stimulation.

**4.5 Magnetic-responsive nanofiber drug delivery systems** often integrate magnetic nanoparticles with magnetic-responsive polymers through copolymerization or physical mixing. These materials respond to a magnetic field in various ways, including changes in size, temperature, movement, and chemical bonds.[98-101] For instance, Yonggang Zhang and colleagues developed a nanofiber scaffold capable of controlled drug release when exposed to an alternating magnetic field. This scaffold featured a layered structure of hydroxyapatite and Fe3O4 [102]. Similarly, Die Dong and his team created a drug delivery system using cellulose nanofibers embedded with Fe3O4 nanoparticles [98], allowing for magnetic control of drug release. Such systems could enhance targeted drug delivery, improving treatment outcomes while reducing side effects.

**4.6 Hydrogel-based nanofibrous scaffolds** are currently being tested in clinical trials. One notable example is the FibDex dressing, produced by UPM-Kymmene Corporation, which aids wound healing by maintaining moisture. This dressing easily separates from the wound once healing is complete. [103]The field of drug-carrying nanofiber dressings remains underdeveloped, presenting an opportunity for further innovation. Another cellulose-based dressing is made from bacterial cellulose, similar to a 3D printing process performed by certain bacteria. [36] This dressing is highly porous and supports tissue growth, proving effective in treating burns, chronic ulcers, and surgical wounds in both pre-clinical and clinical studies.[104,05]

**4.7 Nanozymes are synthetic enzymes** that imitate the work of natural enzymes, effectively replacing them by replicating the 103catalytic site environment. Under normal conditions, bacteria live harmlessly on human skin, but damaged skin can lead to infections. Natural enzymes are effective and environmentally friendly, but their use can be limited. [106] During bacterial infections, neutrophils produce toxic reactive oxygen species from hydrogen peroxide using the enzyme myeloperoxidase.[107] Inspired by these natural processes, researchers are creating nanozymes that can attack microbes and disrupt biofilms.[108.109] Nanozymes offer multiple benefits, such as high surface energy, effective electron transport, adjustable catalytic efficiency, and improved stability. They can be modified for better compatibility with biological systems and are cost-effective, stable, and suitable for large-scale manufacturing. These materials have potential in treating bacterial infections and aiding wound healing. Unlike traditional antibiotics that target bacterial functions and can fail due to mutations and resistance, nanozymes generate harmful Reactive Oxygen Species (ROS) through their oxidoreductase activity.[110] Bacteria find it challenging to deal with ROS damage, making nanozymes more resistant to developing resistance. By attaching specific molecules, like aptamers, to nanozymes, targeted antibacterial effects can be achieved. Antimicrobial peptides or cell-penetrating peptides can also be bonded to nanozymes to

effectively reach bacterial cells. Nucleic acid probes and antibodies can provide targeted action against microbes using nanozymes. For instance, photoacid molecules can change charge in response to UV light, while Molybdenum Disulfide can be integrated into nanozymes to enhance binding to specific types of bacteria, whether gram-positive or gram-negative.[111]

The production of nanozymes involves straightforward chemical methods, making them affordable and mass-producible. Various forms exist, including metal-based, metal oxide-based, carbon-based, and those made from metal-organic frameworks or covalent-organic frameworks.[112] Nanozymes utilize enzyme-like functions, such as peroxidase and oxidase, to quickly produce harmful free radicals and manage ROS levels, which leads to antibacterial outcomes. Their main antibacterial actions stem from their ability to catalyse reactions and disrupt biofilms and bacteria directly. To boost their effectiveness, glucose oxidase can be enclosed in metal-organic frameworks, enabling a pH-controlled glucose-H2O2-hydroxyl radical reaction with antibacterial properties.[113] Some nanozymes, like TiO2 nanotubes and black phosphorus, can be activated by light to enhance ROS production and antibacterial performance.[114,115] Nanozymes with deoxyribonuclease-like activity can degrade environmental DNA in biofilms, while hydroperoxidase-like nanozymes can disrupt bacterial communication and inhibit biofilm formation.[116,117] Additionally, designs that exploit the features of the biofilm environment, such as negative charge, low pH, and high glutathione levels, further enhance antibacterial effectiveness.

**4.8 Metal-based nanozymes** are frequently produced due to their excellent electronic properties, ease of preparation, high surface energy, and effectiveness in photothermal conversion.[118,119] However, metals like silver, cobalt, and copper can be toxic, making it necessary to improve their selectivity and safety.[120,121] Commonly used examples include gold and graphitic carbon nitride-based nanozymes, while less desirable metals exhibit high toxicity and a tendency to clump together. Metal oxide nanozymes are materials with special properties that enable them to act like natural enzymes. They effectively break down hydrogen peroxide into reactive oxygen species (ROS). These nanozymes can induce oxidative stress, damaging proteins, nucleic acids, bacterial membranes, and biofilms.

**4.9 Chalcogenide-based nanozymes**, made from metal sulfides, offer advantages such as efficient electron interactions and cost-effectiveness. Common examples include molybdenum disulfide (MoS2), copper sulfide (CuS), and iron disulfide (FeS2). They have excellent photothermal and photodynamic characteristics, can respond to changes in pH, and are generally less toxic and more environmentally friendly than metal oxides.

**4.10 Carbon-based nanozymes** benefit from surface modifications and have good compatibility and catalytic abilities. They are increasingly used in nanozyme applications. Carbon dots, carbon nanotubes, graphene nanotubes, and fullerenes (Buckyballs) are notable for their ability to produce ROS.

**4.11 Gold nanoparticles** exhibit stable catalytic, optical, electrical, and biological properties in various forms.[122] Smaller gold nanoparticles tend to be more active due to their larger surface area, which aids in the generation of ROS through peroxidase (POD) activity, making them beneficial for treating infected wounds.[123]

**4.12 Graphitic carbon nitride** (gC3N4) is a non-toxic polymer known for its durability and enzyme-like activity.[124,125] While it is not directly used for wound infections, combining it with antibacterial agents shows promise.[120] Wang et al. prepared a g-C3N4@AuNPs nanocomposite (CNA), , nanocomposite has been developed to catalyse the production of highly toxic hydroxyl radicals at low hydrogen peroxide concentrations, effectively breaking down biofilms and killing bacteria without harming surrounding tissue.[123] This composite remains active in the acidic environment of wounds and is effective against both Gram-positive and Gram-negative bacteria, helping to reduce lung inflammation caused by methicillin-resistant Staphylococcus aureus (MRSA).[120]Despite their potential, metal nanomaterials, especially silver nanoparticles, face challenges like toxicity and clumping, which diminish their effectiveness.[126,127] To address these issues, a hybrid material was created by combining silver nanoparticles with ultrathin black phosphorus nanosheets. This hybrid reduces toxicity by controlling the release of silver ions and enhances photocatalytic activity by preventing the recombination of electrons and holes.Hydrogels are being explored as stable carriers for metal nanozymes. These three-dimensional structures keep wounds moist and support healing. Recent studies focus on developing nanobiocomposites using hydrogels such as carboxymethyl cellulose, lignin-agarose, and sodium alginate.[128,133]Jia and colleagues used tannic acid with silver nanoparticles to develop a self-coagulating hydrogel nanozyme. This nanozyme

enhances mechanical properties, electrical conductivity, and antibacterial effectiveness against E. coli by generating hydroxyl radicals from hydrogen peroxide.[134]

Metal oxide nanomaterials have unique redox and optoelectronic qualities that grant them catalytic abilities similar to natural enzymes [135]. These materials can effectively break down hydrogen peroxide into reactive oxygen species (ROS) [136] , which are highly reactive and can harm proteins, nucleic acids, and bacterial cell membranes. Their enzymatic activity often changes with pH, making them useful in specific environments, such as infected wounds.Researchers have explored various metal oxide nanozymes for antibacterial action. Examples include $Fe_3O_4$ [137], CuO [138], $CeO_2$ [139-141], $V_2O_5$[142], $Tb_4O_7$[143], and ZnO[144]. Combining metal oxides with tailored drug carriers increases antibacterial effectiveness, allows for controlled activation, and offers multifunctionality.ROS can disintegrate bacterial biofilms into proteins, polysaccharides, and nucleic acids. For instance, $Fe_3O_4$ metal nanoparticles show peroxidase-like activity, breaking down hydrogen peroxide.[107] However, ROS are short-lived and not selective for bacteria. To enhance sterilisation, reducing the time ROS take to reach bacteria is crucial. Ji and his team created a targeted delivery system using hyaluronic acid-encapsulated graphene-mesoporous silica nanosheets and $Fe_3O_4$ nanoparticles to deliver ascorbic acid effectively. They aimed to maintain ROS levels during transfer and efficiently eliminate biofilms on-site.[145] External factors like pH and light can further activate nanozymes. For example, visible light can trigger CuO nanorods to increase ROS production, improving their antibacterial performance.[138] The pH dependency of nanozymes may limit their use in infected wounds. Under neutral pH, substances like adenosine triphosphate can enhance the activity of citrate-modified $Fe_3O_4$ nanozymes, boosting their antibacterial power [138]. Vanadium oxide nanodots (VOxNDs), exhibit dual-enzyme activity [146], effectively targeting drug-resistant bacteria. Combining photothermal therapy and photodynamic therapy with nanozyme treatment can also enhance antibacterial effects and promote faster wound healing.[141]

**4.13 Chalcogenide-based nanozymes** particularly metal sulfide nanomaterials, provide advantages such as good electron optics, physicochemical properties, functional structures, and affordability. Their excellent photodynamic capabilities make them suitable for effective and safe antibacterial applications in wound healing.2D nanomaterials made from metal sulfides are more eco-friendly compared to traditional metal or metal oxide materials. However, there are concerns regarding their safety, as they can dissolve and release harmful heavy metals. It is crucial to improve the stability and safety of these materials for treating infected wounds.[147] Molybdenum disulfide ($MoS_2$), copper sulfide (CuS), and iron disulfide ($FeS_2$) are extensively researched because of their natural enzyme-like catalytic properties. [148,149] While chalcogenides have this catalytic activity, it is not enough for effective antibacterial treatments. Most studies focus on enhancing their catalytic performance or combining them with other methods. Metal sulfides also have natural optical properties that allow for efficient photocatalytic and photothermal applications in sterilization. Yi et al. created PEG-functionalised molybdenum disulfide nanoflowers (PEG-$MoS_2$ NFs) using a one-pot hydrothermal process. This combination of peroxidase-like and photothermal activity reduces treatment time and shows a better affinity for hydrogen peroxide than horseradish peroxidase. This formulation effectively kills ampicillin-resistant E. coli and B. subtilis endospores.[114] Yu et al. employed PEG-$MoS_2$ NFs as a coating for titanium dioxide ($TiO_2$) nanotubes, which have a high specific surface area and excellent electron transport. Coating $TiO_2$ nanotubes enhances the peroxidase-like activity of $MoS_2$ while reducing the bandgap of $TiO_2$, thereby improving photo response and increasing reactive oxygen species production.[150]Natural organosulfur compounds have been used to fight bacterial infections for some time, but their low water solubility and difficult mass production limit their biomedical applications.[151] Xu et al. used a solvothermal method to convert these natural compounds into inorganic sulfur compounds, resulting in a nanomaterial with antibacterial properties 500 times stronger than those derived from garlic.[149] In a different study, Nain et al. produced copper sulfide nanocrystals (BSA-CuS NCs) by heating an alkaline solution with $Cu^{2+}$ and bovine serum albumin without needing an extra sulfur source. BSA-CuS NCs showed more than a 60-fold increase in antibacterial effectiveness when exposed to near-infrared laser irradiation compared to non-irradiated conditions.[176]

**4.14 Carbon-based nanomaterials** including carbon dots, carbon nanotubes, carbon nitride, fullerenes, and graphene, have been widely studied for their catalytic applications [110].These materials are biocompatible and undergo surface modifications, making them suitable for nanozyme applications. They contain oxygen functional groups that contribute to their intrinsic peroxidase, catalase, hydrolase, and superoxide dismutase activities, making them viable options for treating and preventing infections.

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**4.15 Carbon dots (CDs)** which are made of zero-dimensional carbon, are stable, biocompatible, and possess excellent optical properties.[152,153] They effectively combat E. coli through light-induced sterilization, generating superoxide ions in visible light and achieving over 100% bactericidal efficiency. Various precursors, such as S. cerevisiae and ampicillin, can be used to produce CDs that selectively stain bacteria and assess their survival, disrupt cell membranes, and target several bacteria, including S. aureus and Listeria monocytogenes.[154] Langlin and colleagues created a Fe/N-doped chitosan-chelated carbon dot-based nanozyme that offers several benefits, including strong antibacterial properties, effective peroxidase-like activity, great stability, and high compatibility with biological systems. This innovation helps speed up wound healing. [155,156]

**4.16 Carbon nanotubes** (CNTs) are altered for better catalytic performance due to their low toxicity and potential uses in medicine. When oxidised, CNTs develop surface groups that act as active or inhibitory sites, known as oxide-rich CNTs (o-CNTs). Techniques like treating with 2-bromo-1-acetophenone enhance peroxidase action, which helps generate reactive oxygen species (ROS), reduces bacterial inflammation, and inhibits bacterial growth.[110]

**4.17 Graphene-based nanozymes** possess antibacterial properties affected by various factors, such as their layers, structure, and electron transport capacity.[156] In the presence of low concentrations of H2O2, graphene quantum dots (GQDs) convert it into hydroxyl radicals, enhancing their antibacterial effects.[157,158] Functionalised GQDs can also provide combined sterilisation through photothermal, photodynamic, and multivalent interactions when exposed to light.Metal-Organic Frameworks (MOFs) are created through coordination chemistry, which combines organic ligands with metal ions or clusters to form porous coordination polymers that are highly crystalline and permeable. MOFs with enzyme-like functions can be designed by strategically selecting metal nodes and organic ligands.[159] Due to their versatile coordination chemistry,[160,161] MOFs can be customised for various uses, including sensing, biomedicine, gas adsorption, and catalysis.[162,166] They are being explored for antibacterial applications, particularly in wound treatment. By encapsulating natural enzymes in their structure, MOFs protect these enzymes from external factors, maintaining their activity. However, the preferred pH for nanozymes is typically 3–4, which poses challenges for their effectiveness in the acidic conditions of infected wounds.[167]In general, 2D MOFs exhibit superior catalytic activity compared to 3D MOFs because of their larger surface area. An example includes Cu-TCPP(Fe)-encapsulated glucose oxidase (GOx), developed by Liu et al., which can initiate self-activating cascades. GOx converts glucose into gluconic acid and H2O2, lowering the pH and boosting catalytic activity in wounds. Li et al. used a co-precipitation method to create a multilayer film of GOx and Hn on MnCO3, followed by the removal of MnCO3 to produce Microreactors (MRs). These MRs demonstrate strong antibacterial activity and improved glucose affinity in slightly acidic conditions. Although metal-based nanozymes are effective catalysts, they face issues like aggregation and safety concerns.[168]

Combining metal nanoparticles with MOFs can enhance stability and reaction rates while reducing aggregation.[169] Hu et al. synthesised ultrasmall gold nanoparticles (UsAuNPs) on thin 2D MOFs through in situ reduction. MOFs serve as an excellent platform for UsAuNPs, which are prone to aggregation despite their advantages. The UsAuNPs/MOFs exhibit enhanced stability that can reduce mass transfer resistance and improve reaction speed.[170]COF-based nanozymes are new, porous materials that can be adjusted, are stable, environmentally friendly, and non-toxic.[171-173] In medicine, researchers are studying COF-based nanomaterials for various uses, including as carriers for antibiotics and in photodetection and photocatalysis.[174,175,176] For instance, Zhang and colleagues developed a photosensitizer containing COF that improved light conversion and effectively fought bacteria like E. coli and S. aureus. Li's team showcased a COF nanozyme that produced hydrogen peroxide while protecting healthy cells. [177]Additionally, Zhang et al. introduced a new nanozyme that used a COF to create enzyme-binding pockets, leading to impressive antibacterial outcomes through reactive oxygen species (ROS) production.[202] Nanozymes show great promise in wound healing due to their ability to generate ROS for antibacterial effects and tissue regeneration. Research on using nanozymes in clinical trials for wound healing is still early, focusing on their effectiveness, safety, and compatibility with the body. Key challenges include ensuring a steady release at wound sites, decreasing toxicity, and enhancing compatibility.[178] Further investigation is needed to address the unwanted breakdown of nanozymes within the body.[179] Prussian Blue Nanoparticles, now FDA-approved for their ROS scavenging abilities, indicate that many FDA-approved nanozymes are safe for animal use.[180] Iron oxide nanoparticles have a history as clinical MR contrast agents, making iron oxide-based nanozymes appealing for medical

purposes. Other biocompatible nanoparticles, such as graphene oxide and metal-organic frameworks, are also under thorough examination.[181]

**5. Electroactive polymers**

Electroactive polymers offer a promising new approach in wound care and skin tissue engineering. They can speed up wound healing through electrical stimulation, which encourages cell movement, growth, collagen production, and new blood vessel formation, all vital for tissue repair.[182] Normally, human skin maintains a transepithelial potential similar to a battery.[183] When skin is damaged, this potential changes, creating a current at the wound's edge. This current helps direct cells to the wound center, aiding the healing process and influencing cell division.[212] Researchers found that applying an external electric field to the wound area can further boost healing rates.[184-186] They also revealed enhanced antibacterial effects and potential for controlled drug delivery.[187] EAPs' improved conductivity allows for direct electrical stimulation at the wound site and regulated delivery of drugs or biological agents using electrical signals. Incorporating EAPs into wound dressings combines their unique properties to provide antimicrobial, antioxidant, and electroactive benefits, offering a comprehensive strategy for accelerating wound healing. To create the best dressings, a combination of synthetic and natural polymers can be used.The safety and compatibility of electroactive polymers (EAPs) are still being researched in clinical settings. As a result, the rules guiding their use in treatments are evolving, and currently, there are no EAP-based therapies approved for clinical use.

**6. PEDOT**

Poly(3,4-ethylenedioxythiophene), or PEDOT, is a conductive polymer known for its great electrical conductivity. While it has not been used alone, it has been combined with other materials for wound healing. Research has shown that PEDOT can be incorporated into conductive hydrogels, which combine the benefits of hydrogels and EAPs. These gels have antioxidant qualities that help maintain a healthy cellular environment, are biocompatible, and their conductive nature significantly speeds up the wound healing process.[50] PEDOT is frequently studied, particularly in combination with PSS, because this combination enhances wound healing. The conductivity of PEDOT, along with PSS's ease of processing and mechanical flexibility, makes it ideal for biomedical use.[52] This improvement in healing is linked to the polymer's ability to encourage blood vessel formation, as seen in studies showing increased levels of VEGF and a modest rise in TGF-β1.[189,190]

**7. PEDOT:PSS**

PEDOT:PSS has shown minimal toxic effects on body cells, such as macrophages, and does not trigger inflammation, highlighting its compatibility. [52] Its hydrogel form has proven effective in both lab and clinical settings, showing strong potential for medical applications. With its excellent conductivity, water solubility, and cell compatibility, [190-193] PEDOT:PSS stands out as a promising material for advanced wound dressings and medical devices, providing a safe method to enhance healing without harming skin. [194] These findings open the door for more research on PEDOT:PSS in treating chronic wounds. [51] Additionally, PEDOT:PSS hydrogels and fibers can be developed into soft, self-healing bioelectronic devices.[68,69]

**8. Polypyrrole**

(PPy) is utilized in hydrogels, ectro spunel fibers, and composites with natural polymers like chitosan and collagen for wound care. Research shows that nanofibers made with 10% PPy have improved cell adhesion, growth, and proliferation compared to other materials. Composite nanofibers combining PPy with other polymers enhance flexibility, breathability, and wettability in wound dressings. Electrical stimulation caused by mechanical motions and positive charges on the PPy surface can eliminate over 96% of bacteria by disrupting their cell membranes. Studies also indicate that electrical stimulation boosts the expression of growth factors, leading to quicker wound healing. This suggests new possibilities for designing wearable electrotherapy devices aimed at chronic wounds.[55]

**9. Polyaniline**

(PANI) is another conductive polymer that can be made into different forms, such as nanofibers and films, or integrated into other materials like hydrogels. Research has shown that PANI improves healing and boosts collagen and granulation tissue at wound sites while reducing inflammation.

**10. Natural polymers and synthetic polymers**

Combining natural polymers like chitosan, gelatine, collagen, alginate, and silk fibroin with synthetic polymers can enhance both electrical conductivity and biocompatibility.[56]

**11. Microfluidics in wound healing**

Microfluidics plays a significant role in wound healing by improving the delivery of medications. These devices allow for the controlled release of drugs in response to specific triggers, enhancing treatment effectiveness. They can replicate the conditions of wounds in a lab setting, providing valuable insights into the healing process and helping to develop new therapies. Microfluidics also enhance cell culture and tissue engineering by delivering essential nutrients and growth factors in a precise manner. With integrated sensors, these devices can monitor wound conditions in real time, allowing healthcare providers to adjust treatment strategies as needed, ultimately leading to better patient outcomes. The combination of personalized medicine and microfluidics presents a promising approach for creating targeted wound care solutions. However, as of now, there are no clinically approved treatments using this technology due to challenges such as standardization, scalability, and a lack of sufficient human clinical trials to demonstrate safety and efficacy.

**12. Personalized therapeutics**

focuses on developing treatment plans tailored to an individual's genetic profile, lifestyle, and specific wound characteristics, thus enhancing healing effectiveness. This method leverages genomic and proteomic analysis to identify specific markers and create targeted therapies. Drug delivery systems can release medications at the ideal time for maximum impact. Autologous stem cell therapy uses the patient's own cells to encourage tissue repair, which helps reduce immune rejection. Advanced monitoring technologies provide immediate feedback, enabling ongoing adjustments to treatment to improve healing conditions. While substantial progress has been made in cancer treatment and pharmacogenomics, personalized therapeutics in wound healing is still largely experimental, with widespread clinical use yet to be realised.

## II. Conclusion

Current research is focused on improving biosensor technology for monitoring wounds. This includes creating smaller, wearable biosensors, merging different sensing technologies into one device, and integrating biosensors with advanced data analysis and artificial intelligence for live wound assessments and tailored treatment suggestions. Various polymers have been employed in biosensors for wound healing. The trend has shifted towards multi-component biosensors and innovative smart dressings that use machine learning to determine the stage of a wound, allowing for personalised dressings tailored to each patient. This customisation is particularly beneficial for individuals with chronic wounds. Common polymers used in these biosensors include PEG, PU, PLGA, and PVA, selected based on their compatibility, mechanical properties, and specific design needs. Overall, the history of biosensors in wound healing has progressed from basic enzyme sensors to more advanced technologies. These tools are crucial in managing wounds, enabling healthcare providers to track wound conditions, spot complications, and make informed treatment decisions that promote effective healing.

**Conflict of Interest**

All authors declare no conflicts of interest.

**Author Contribution**

Authors have equally participated and shared every item of the work.

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