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Review

Nanozyme-based wearable biosensors for application in healthcare

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SUMMARY

Recent years have witnessed tremendous advances in wearable sensors, which play an essential role in personalized healthcare for their ability for real-time sensing and detection of human health information. Nanozymes, capable of mimicking the functions of natural enzymes and addressing their limitations, possess unique advantages such as structural stability, low cost, and ease of mass production, making them particularly beneficial for constructing recognition units in wearable biosensors. In this review, we aim to delineate the latest advancements in nanozymes for the development of wearable biosensors, focusing on key developments in nanozyme immobilization strategies, detection technologies, and biomedical applications. The review also highlights the current challenges and future perspectives. Ultimately, it aims to provide insights for future research endeavors in this rapidly evolving area.

INTRODUCTION

In recent years, the surge in aging-related concerns and health issues has led to a notable increase in demand for personalized diagnostics and health monitoring.[1,2] Traditional healthcare systems require samples to be collected and analyzed using sophisticated laboratory equipment, which is time-consuming and expensive, and cannot meet the needs for routine health monitoring and point-of-care testing. Wearable biosensors have garnered widespread attention due to their non-invasive and real-time monitoring capabilities, holding the potential to transform traditional medical models.[3] These biosensors, which are flexible and adaptable to the human body, are designed to sense, detect, and transmit information, offering insights into an individual's health by tracking a range of physiological parameters.[4] Currently, many wearable biosensors have been developed for the analysis of various biofluids, such as saliva,[5] tears,[6] sweat,[7] and interstitial fluid.[8] The target analytes include chemical and biological markers, such as metabolites,[9] nutrients,[10] drugs,[11] and pH values.[12] These devices enable non-invasive diagnostic assessments during daily activities, providing a promising approach for the early screening and diagnosis of diseases.

Natural enzymes are essential components in the development of wearable sensors because they serve as crucial recognition elements that catalyze a series of chemical or biochemical reactions, generating detectable signals upon exposure to specific analytes. Natural enzymes have been used to prepare a variety of wearable sensors.[13,14] However, natural enzymes have several drawbacks, including high cost, low stability, and challenges in storage, which limit their functionality under extreme pH and temperature conditions. These shortcomings have led to the rapid emergence of artificial nanozymes.[15] In contrast to natural enzymes, artificial nanozymes possess excellent enzyme-mimicking activity, along with low cost, high stability, batch production capabilities, and ease of storage.[16,17] The distinctive advantages of nanozymes make them highly attractive for the development of wearable devices. Nanozyme-based wearable sensors are continuously being developed, offering opportunities for rapid detection of analytes, such as glucose,[18] lactate,[19] and others. The integration of nanozymes and wearable devices combines the strengths of both, providing significant potential for health monitoring and advancing personalized healthcare (Figure 1).

Although there are already thematic reviews on nanozyme-based sensors and their various applications,[20–22] few have focused on integrated analytical systems composed of nanozymes and wearable devices. Against this backdrop, this review first introduces the immobilization strategies of nanozymes on wearable device interfaces, aiming to provide insights into the construction of wearable biosensors. Subsequently, the article explores the detection technologies required to build wearable sensors using nanozymes. To bridge the gap between theoretical research and the practical application of wearable devices, this review then comprehensively summarizes and analyzes the latest advancements in nanozyme-based wearable device for biomedical applications. Finally, it discusses the current challenges and future directions of nanozymes in the development of wearable sensors for healthcare. This article aims to elucidate the current status and latest advancements of nanozymes in the field of wearable sensing, which are of great research significance and application value for the design of novel nanozyme

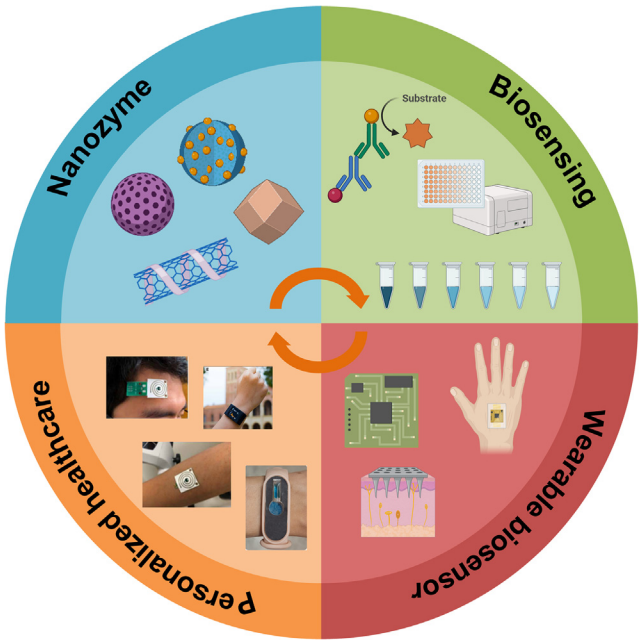

Figure 1. An overview of nanozyme-based wearable biosensor for healthcare

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materials and the development of next-generation wearable sensors. We anticipate that this review will provide new inspiration for the development of nanozyme-based wearable sensors and the expansion of wearable sensor applications.

IMMOBILIZATION STRATEGIES OF NANOZYME IN WEARABLE BIOSENSOR

Wearable biosensors rely on sensitive elements to generate chemical reactions with target analytes for detection. Nanozymes, with their enzyme-mimicking activity, serve as the sensitive elements of sensors to catalyze the reaction of the analytes. However, the functionality of wearable sensors is often challenged by mechanical deformation and bending caused by body movement. In nanozyme-based wearable biosensors, the development of effective immobilization strategies is pivotal for maintaining the stability and activity of nanozymes. These strategies not only preserve the enzymatic functionality under dynamic conditions but also enhance the sensitivity and accuracy of detection. Rationally designed immobilization methods can optimize the catalytic activity of nanozymes, thereby enabling efficient signal amplification, which is particularly critical for the detection of low-concentration analytes. Consequently, the immobilization strategy for nanozymes plays a crucial role in determining the overall performance of wearable sensors. Various immobilization approaches for integrating nanozymes into wearable biosensors are illustrated in Figure 2, showcasing their potential to enhance sensor functionality in real-world applications.

PHYSICAL ADSORPTION

Physical adsorption is widely used for immobilizing nanozymes by employing non-covalent interactions such as hydrogen bonding, van der Waals forces, and electrostatic forces to bind the nanozymes to the substrate surface. This approach offers several advantages, including simplicity, minimal requirements for additional materials, and compatibility with electronic devices, facilitating the miniaturization of wearable sensors. Furthermore, the non-covalent interactions during the immobilization process ensure minimal impact on the activity of nanozymes, making it a widely adopted method in wearable device construction.

A frequently used technique for physical adsorption is the drop-casting method. In this approach, nanozymes are dissolved in an appropriate solvent to create a solution, which is subsequently applied to the substrate—such as paper or the detection area of an electrode. Upon solvent evaporation, the nanozymes adhere to the substrate surface, forming a thin coating. For instance, Barman et al. prepared a self-powered multifunctional dressing by drop-cast bismuth telluride nanoplates (Bi_2Te_3 NPs) onto the bottom of carbon fiber fabrics to controllably generate H_2O_2.[23] Physical vapor deposition is also an effective method for immobilizing nanozymes, capable of controlling the deposition process and optimizing the catalytic performance of nanozymes. For instance, Li et al. prepared nickel oxide electrodes using physical vapor deposition, which could increase the number of active sites for catalysis.[24] In addition, printing techniques offer significant advantages, particularly for the large-scale production of flexible sensors. For instance, Hu et al. prepared a batch of Co-single-atom nanozyme (SAE)-based flexible sensors based on electrohydrodynamic jet technology.[25]

However, as a reversible process, physical adsorption is inherently prone to challenges such as weak fixation and detachment of nanozymes from the substrate. Therefore, nanomaterials with adhesive properties have been used for the immobilization of nanozymes. For instance, Smutok et al. used porous Nafion membrane to immobilize hemin and gold nanoparticle (Au NP)-modified carbon microfibers nanozyme.[26] Liu et al. constructed an electrochemical H_2O_2 detection platform by modifying MoS_2/Au NS nanozyme with the Nafion solution, which improved the nanozyme stability.[27] Furthermore, physical adsorption has inherent limitations, such as uneven distribution of nanozymes, potential exposure, and deactivation of the enzyme layer. Addressing these challenges requires careful optimization of the adsorption process and exploration of complementary strategies to improve the overall performance of wearable sensors.

ENTRAPMENT

The entrapment method involves mixing nanozymes with polymer monomers and encapsulating them within the spatial structure of the polymer during the polymerization process. The resulting entrapped carriers, such as natural gels[28] and resins,[29] typically feature a porous structure. These porous polymeric materials provide a protective microenvironment for the nanozymes, preserving their enzymatic activity while

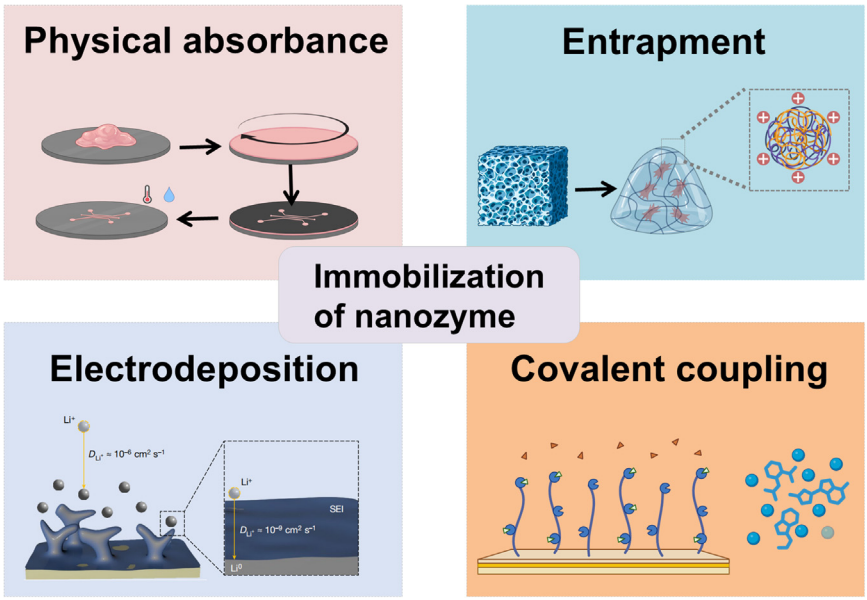

Figure 2. Strategies for immobilization of nanozymes in wearable biosensors

Electrodeposition: Reproduced with permission.[36] Copyright 2023, Spring nature.

maintaining access to reaction substrates. This capability results in excellent immobilization performance, making the entrapment method highly versatile and widely applied in wearable devices for health monitoring,[30] antimicrobial applications,[31] and tumor treatment.[32]

Hydrogels are among the most commonly utilized materials for nanozyme immobilization due to their high loading capacity and structural flexibility, allowing them to accommodate substantial quantities of functional materials. Wearable devices often require long-term attachment to the human skin; thus, ensuring biocompatibility and minimizing irritation from nanomaterials is critical. Agarose hydrogels, in particular, have gained popularity in nanozyme encapsulation owing to their excellent hydrophilicity, straightforward functionalization, and non-toxic gelation process that does not require hazardous initiators.

For instance, Zhou et al. encapsulated CuFe metal-organic framework (MOF) within agarose hydrogel to create a patch for vitamin C detection[33] (Figure 3A), whereas the same group encapsulated N-doped C-dots in agarose hydrogel to develop a bracelet for monitoring UV radiation exposure[34] (Figure 3B). Beyond agarose, other monomers have been utilized to prepare hydrogels for nanozyme encapsulation. Xu et al. used acrylamide monomers to fabricate hydrogels for encapsulating tannic acid-silver ion (Ta-Ag) nanozymes for skin applications[31] (Figure 3C). The Ta-Ag nanozymes, uniformly dispersed within the matrix of sodium alginate and polyacrylamide, confer a dermis-like structure to the flexible sensor. Similarly, Liu et al. synthesized conductive hydrogels by polymerizing hydroxyethyl methacrylate to encapsulate Prussian blue (PB) nanozymes with reactive oxygen species scavenging activities for preventing ocular surface diseases[29] (Figure 3D).

Despite its advantages, the entrapment method has certain limitations. Although encapsulation within porous carriers such as gels protects nanozymes from external environmental factors, it can also hinder the enzyme's reaction rate. Additionally, the selective permeability of porous carriers, which permits only small molecules to diffuse through, restricts the method's applicability to nanozymes acting on large-molecule substrates. To overcome this limitation and ensure optimal catalytic efficiency, careful tuning of the size of the carrier and nanozyme is necessary to fully leverage the catalytic performance of the nanozyme. For instance, Jia et al. designed an ultrasmall mussel-inspired tannic acid chelated-Ag nanozyme with peroxidase-like activity, which could induce acrylic-acid-based hydrogel self-setting without requiring an external aid, providing the hydrogels with long-term and repeatable adhesiveness.[28]

ELECTRODEPOSITION

Electrodeposition is a versatile technique for material deposition onto substrates through electrochemical processes. The method involves applying a voltage or current across a solid conductive interface, facilitating oxidation or reduction of the target material from an electrolyte solution. This process results in the formation of a functional film or coating on the surface of the anode or cathode. One of the key advantages of electrodeposition lies in its precise controllability. By adjusting parameters such as voltage, current, deposition time, and electrolyte composition, the thickness,[35] morphology,[36] and growth orientation[37] of the deposited layer can be finely tuned. Furthermore, electrodeposition is compatible with various electrode materials, making it particularly suitable for the fabrication of nanostructures in sensing applications.

In the context of wearable devices, electrodeposition serves as an effective method for immobilizing nanozymes, thereby enhancing detection stability. For instance, Li et al. successfully employed electrodeposition to generate high-performance nanozymes by depositing PB onto Au fibers, enabling wearable monitoring of hydrogen peroxide and uric acid (UA).[38] Similarly, the deposition of noble metals and their alloy nanoparticles onto electrode surfaces via electrodeposition has been shown to significantly enhance enzyme detection performance, thus improving the sensitivity of wearable sensors. For example, Zhao et al. developed a gold electrode coated with platinum nanoparticles (Pt NPs) through electrodeposition, improving the electrochemical performance of a wearable sensing system for monitoring sweat metabolites[39] (Figure 4A). Additionally, Nyein et al. enhanced glucose detection by electrodepositing gold and PB onto carbon electrode, demonstrating the potential

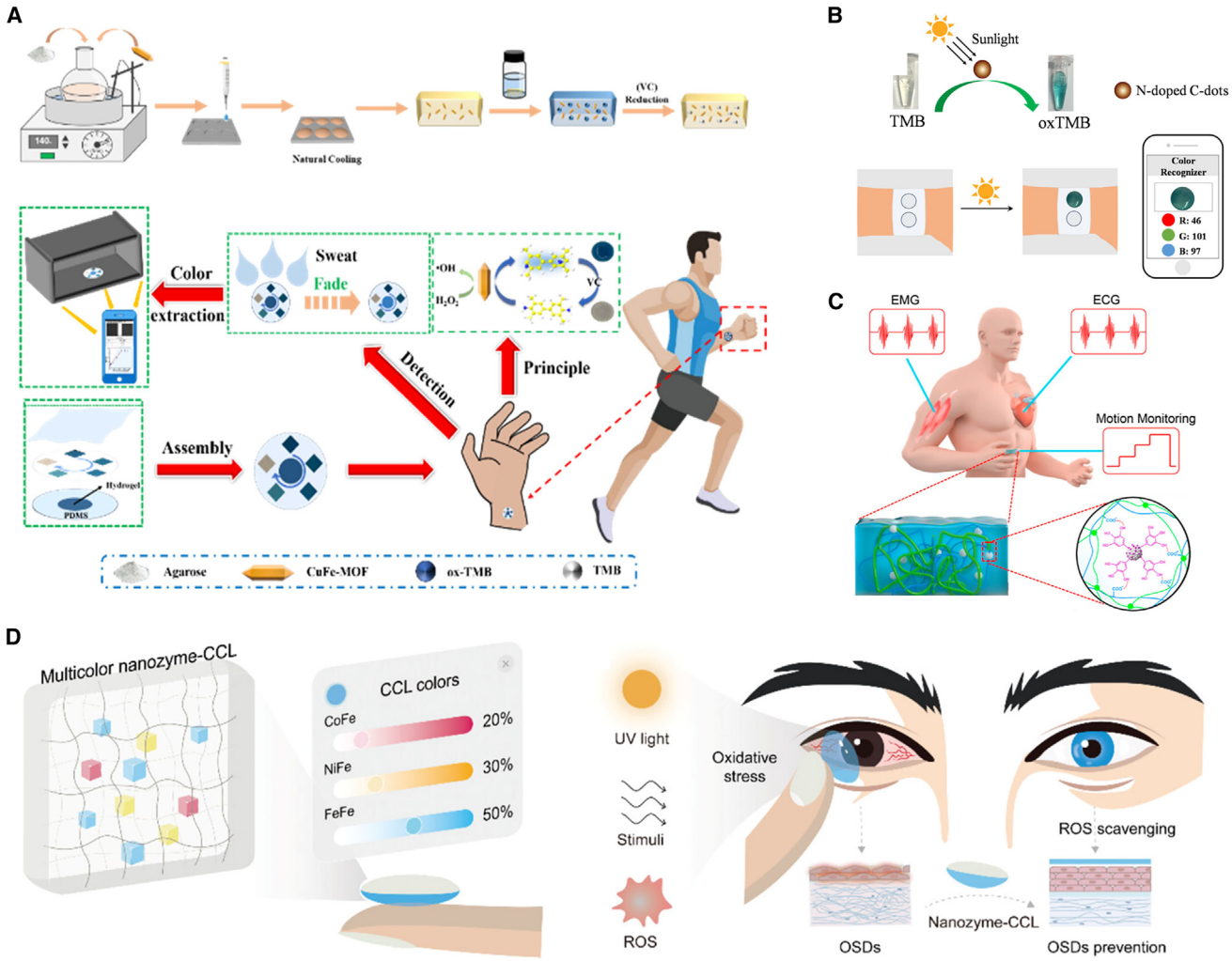

Figure 3. Immobilization of nanozymes by entrapment for developing wearable biosensors

(A) Entrapment of CuFe metal-organic framework nanozyme in a hydrogel patch for visual detection of vitamin C. Reproduced with permission.[33] Copyright 2024, American Chemical Society.

(B) Entrapment of nitrogen-doped carbon dots in a hydrogel for monitoring of UV radiation exposure. Reproduced with permission.[34] Copyright 2024, Elsevier.

(C) Entrapment of Ta-Ag nanozymes in a conductive hydrogel for skin application. Reproduced with permission.[31] Copyright 2024, American Chemical Society.

(D) Entrapment of Prussian blue (PB) nanozyme in a conductive hydrogel for ocular surface disease prevention. Reproduced with permission.[29] Copyright 2023, Wiley-VCH.

of this technique in wearable biosensing systems (Figure 4B).[40] The versatility, precision, and adaptability of electrodeposition make it a powerful tool for integrating nanozymes and enhancing the performance of wearable sensing platforms. As wearable devices continue to evolve, electrodeposition offers promising avenues for the development of highly sensitive and stable wearable biosensors.

COVALENT COUPLING

The covalent bonding method is a fixation technique that employs covalent bonds to couple functional modifiers with groups on the carrier surface.[41] The immobilization process typically involves two main steps. First, the carrier surface is activated and pretreated through physical, chemical, or electrochemical methods to introduce reactive functional groups. In the second step, nanozymes undergo crosslinking reactions with the functional groups on a crosslinking agent, forming stable covalent bonds. This process firmly anchors the functional nanozymes onto the pretreated carrier surface, ensuring robust immobilization.[42,43]

The primary advantage of the covalent coupling lies in its ability to provide a highly stable and durable fixation, minimizing the detachment of nanozymes. For example, glutaraldehyde crosslinking strategy is commonly used to immobilize nanozymes.[44] In addition, covalent coupling has been reported to promote the stability and long-term functionality of nanozymes. For example, Xu et al. prepared Fe-MOFs with intrinsic peroxidase-like activity

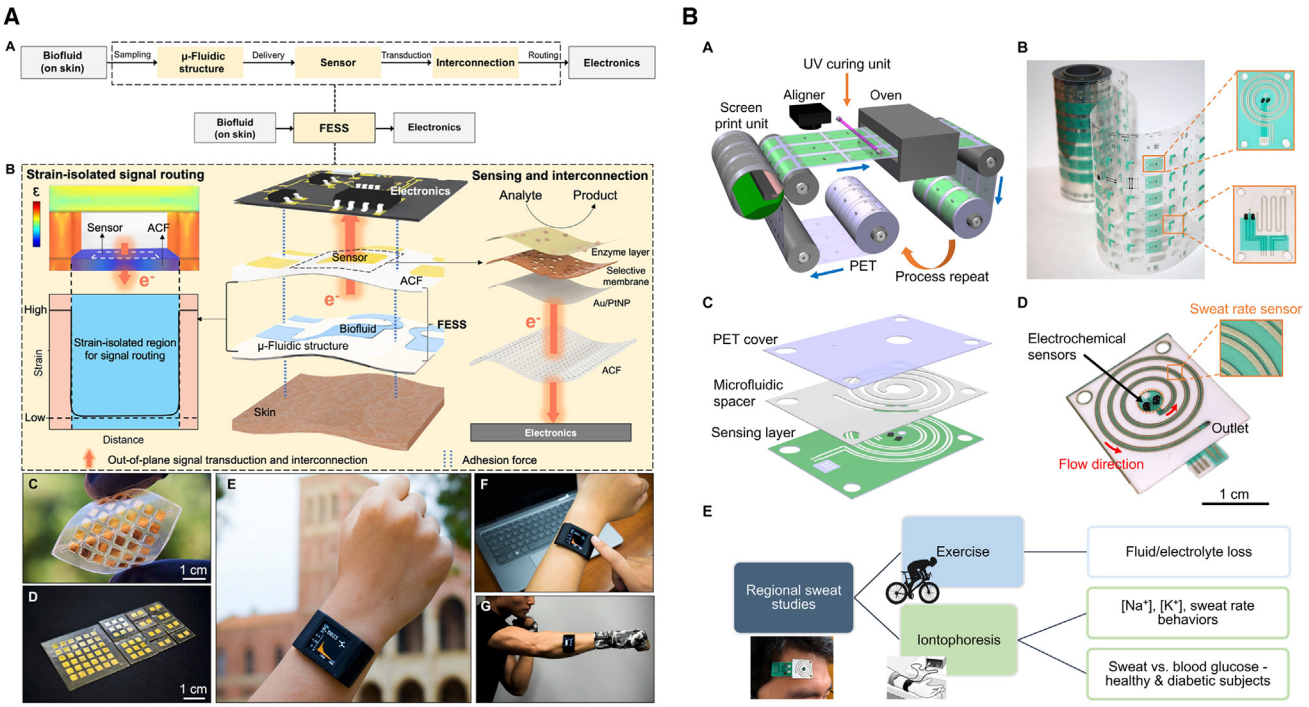

Figure 4. Immobilization of nanozymes by electrodeposition for developing wearable biosensors

(A) Electrodeposition of platinum nanoparticle (Pt NP)-coated Au electrode in a smartwatch for sweat analysis. Reproduced with permission.[39] Copyright 2020, the American Association for the Advancement of Science.

(B) Electrodeposition of PB in a patch for sweat analysis. Reproduced with permission.[40] Copyright 2019, the American Association for the Advancement of Science.

to loaded glucose oxidase (GOx) through covalent binding for glucose detection, which exhibited pronounced tolerance to high temperature and acid-base.[45] However, the covalent bonding method also has notable limitations. The immobilization process is often complex, time-intensive, and requires meticulous handling, which can impede its widespread adoption in the construction of wearable sensors. These challenges highlight the need for balancing fixation stability with operational efficiency when employing covalent bonding techniques in wearable device design.

DETECTION TECHNOLOGY

Wearable biosensing technology represents a non-invasive solution that replaces traditional medical detection methods. Various detection technologies are available, each employing distinct chemical or physical approaches. Broadly, these sensing methods can be categorized into optical and electrochemical techniques.

COLORIMETRIC DETECTION

Colorimetric detection methods have garnered significant attention in the development of simple, cost-effective wearable detection devices. These methods are particularly advantageous because they are visual, easy to perform, and do not require sophisticated instrumentation.[46] By combining simplicity with enzyme-based strategies, colorimetric detection allows for rapid assessment of target concentrations. The intensity or depth of the color directly correlates with the concentration of the target, offering a user-friendly and intuitive approach to biomarker analysis. Colorimetric assays can be designed for qualitative and quantitative analysis. Qualitative colorimetric analysis identifies the presence or absence of a target analyte without determining its specific concentration. In contrast, quantitative colorimetric analysis relies on the construction of a standard curve to determine the precise concentration range of the target.[47]

QUALITATIVE DETECTION

Qualitative detection in colorimetry is primarily based on visual observation of color changes resulting from chemical reactions between the analyte and colorimetric reagents. This approach offers significant advantages, including operational simplicity, cost-effectiveness, portability, and visibility to the naked eye.[48] Wearable biosensors employing this method are fast-responding, simple in construction, easy to carry, and low in cost, allowing direct acquisition of analytical results without the need for any integrated electronic devices.[49,50] For example, Shan et al. developed a colorimetric microneedle patch integrated with Fe ion-gallic acid coordination polymer nanodots on silicone molds, which can provide real-time monitoring of wound changes through observable color shifts.[51]

Despite these advantages, the practical application of qualitative colorimetric methods in wearable biosensors faces several challenges. First, the low concentration of biomarkers in bodily fluids such as sweat often makes subtle color changes difficult to detect with the naked eye. For example, the concentration of glucose in sweat is approximately 1% or less of its concentration in plasma.[52] Second, substrates loaded with nanozymes—such as paper-based sensors—are prone to random diffusion of reagents. For example, using filter paper as a substrate for color detection may result in uneven color development due to the capillary action and the concentration effect of the edges.[53] Third, variations in sample volume can impact the intensity of the colorimetric signal, resulting in inaccurate readings. For example, evaporation of sweat at a rate that exceeds the absorption rate of the substrate reduces the reliability of the detection signal.[54]

To address these challenges, integrating colorimetric detection with microfluidic systems has emerged as a promising solution.[55] Microfluidic chips enable precise *in situ* sample collection and analysis by integrating multiple processes—including sample collection, processing, target recognition, and result detection—into a compact, multifunctional device. For example, microfluidic colorimetric chips leverage the advantages of both colorimetric analysis and microfluidic technology, providing enhanced sensitivity, accuracy, and portability.[56] These systems are particularly well suited for applications requiring real-time, non-invasive monitoring of biomarkers in small volumes of sweat and hold significant potential for the development of advanced wearable biosensors.

QUANTITATIVE DETECTION

In contrast to qualitative testing, where colorimetric signals are observed directly with the naked eye, quantitative colorimetric analysis relies on external equipment, such as spectrophotometers, to obtain precise and accurate measurements.[57] These devices provide stable, sensitive, and standardized detection results, making them invaluable for detailed analyses. However, spectrophotometers and similar equipment are often limited by poor portability, high costs, and operational complexity, which can impede their use in wearable applications. For example, Huang et al. developed a wearable microneedle patch by immobilizing Au@Ag-Pt nanoparticles on Norland optical adhesive polymer, which enables dual-mode detection of tyrosinase via Raman scattering and colorimetric analysis on human skin[58] (Figure 5A). Similarly, Fan et al. synthesized bovine-serum-albumin-templated MnO_2 nanoparticles with dual nanozymatic activities and mixed them with polyacrylamide to develop a hydrogel for rapid and straightforward glucose detection[59] (Figure 5B). Although such approaches demonstrate the feasibility of combining advanced nanomaterials with wearable detection systems, the challenges associated with traditional laboratory equipment underscore the need for more portable solutions.

To achieve immediate, portable, and accurate quantitative detection results, wearable devices are increasingly integrated with smartphones or cameras for image-based analysis.[47] The principle involves capturing images of the colorimetric reaction using a smartphone app, extracting color intensity data in the form of RGB or grayscale values, and correlating these values to analyte concentrations using a pre-established relationship curve. Smartphones not only facilitate real-time image acquisition but also enable on-device analysis through specialized applications, often enhanced by artificial intelligence algorithms. Furthermore, these systems allow for remote data transmission, backup storage, and enhanced portability, significantly reducing the reliance on laboratory equipment such as UV-visible spectrophotometers.[60]

The combination of wearable detection systems with flexible sensors, microprocessors, and communication devices represents a major trend in biosensor development. However, challenges such as variable lighting conditions during image capture can affect the accuracy of smartphone-based colorimetric analysis. To address this, Chen et al. introduced a color bar as a reference standard, effectively eliminating the interference caused by ambient lighting variations[61] (Figure 5C). Advances in nanoscience and engineering have also expanded the diversity of carriers used to present colorimetric signals. These include hydrogels,[62] test strips,[63] and microfluidic chips,[64] each offering unique advantages for wearable applications. For instance, Amourizi et al. constructed a microneedle patch integrated with a multilayer sensor via microfluidic channels.[65] This system, composed of cotton fibers, agarose, and nanozymes (MnFeCN/FeFeCN), enabled the colorimetric detection of oxalate in biological fluids (Figure 5D). Such developments highlight the potential of wearable colorimetric systems to revolutionize non-invasive biomarker detection.

ELECTROCHEMICAL DETECTION

Although colorimetric methods are widely utilized in wearable biosensors, they suffer from several limitations, including susceptibility to interference from background signals and the inability to provide continuous, real-time monitoring. These constraints make colorimetric methods less suitable for modern wearable medical applications. In contrast, electrochemical methods offer numerous advantages, such as high precision, excellent selectivity, rapid response times, and adaptability.[66] The fundamental principle of electrochemical sensors is based on the interaction between the analyte and a sensitive element, resulting in an electrochemical reaction. This reaction generates a signal that is converted into an electrical output, enabling the measurement of analyte concentrations through parameters such as current, potential, impedance, and charge. Due to their ease of integration, high sensitivity, and real-time monitoring capabilities, electrochemical detection methods have emerged as a favored option in the development of nanozyme-based wearable biosensors.[67]

The performance of electrochemical sensors largely depends on the properties of the electrode materials. Enhancing the activity of nanozymes is a key research focus to improve the response performance of nanozyme-based wearable electrochemical sensor. One approach involves developing active nano-biomimetic enzymes to address inherent limitations such as poor conductivity, weak catalytic activity, and low utilization rates. For instance, Zhang et al. fabricated a wearable patch based on Fe-SAE with excellent nanozyme activity, which could detect

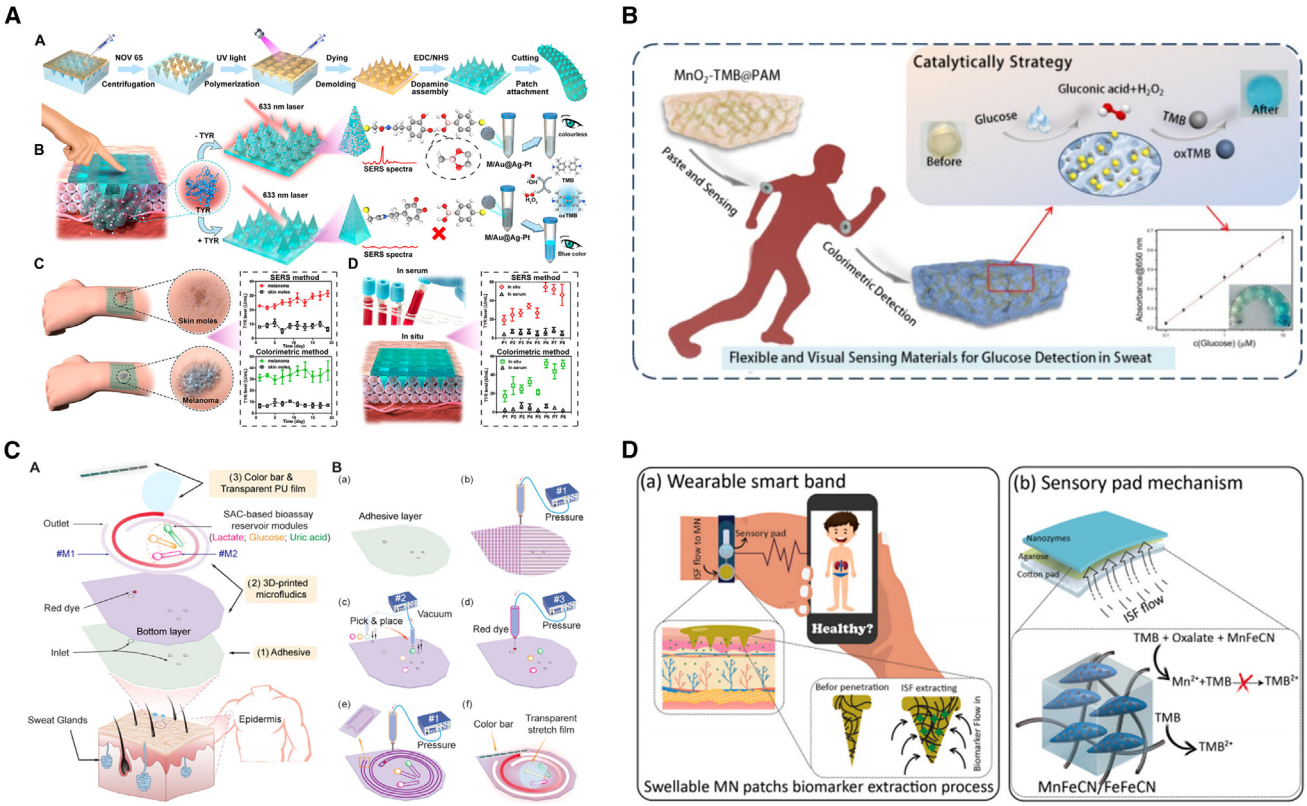

Figure 5. Wearable colorimetric sensors based on nanozymes

(A) Au@Ag-Pt NPs-based microneedle patch for colorimetric and Raman scattering detection of tyrosinase. Reproduced with permission.[58] Copyright 2023, American Chemical Society.

(B) MnO_2 NPs-based patch for colorimetric detection of glucose in sweat. Reproduced with permission.[59] Copyright 2024, Elsevier.

(C) Single-atom nanozyme (SAE)-based wearable monitor for colorimetric detection of sweat biomarkers. Reproduced with permission.[61] Copyright 2024, American Chemical Society.

(D) MnFeCN/FeFeCN-based microneedle patch for colorimetric detection of oxalate. Reproduced with permission.[65] Copyright 2024, Elsevier.

low concentrations of UA[68] (Figure 6A). Another strategy involves modifying the electrode surface with sensitizing materials, such as noble metals,[69] carbon materials,[10] and single-atom catalysts,[70] to enhance electrochemical sensor performance.

Electrochemical methods also enable multiplexed analysis by incorporating multiple circuits to detect multiple biomarkers simultaneously. This capability provides comprehensive information for health monitoring and disease diagnosis, making it a key area of focus in wearable biosensor research.[71] For example, Zhu et al. developed a wearable microneedle for the simultaneous detection of hydrogen peroxide and glucose using a PB/carbon nanotube (CNT) composite[72] (Figure 6B). Similarly, Yu et al. fabricated a wearable patch by modifying a printed screen electrode with g-C_3N_4, which exhibits GOx-like activity. This modification allows for the dual detection of L-dopa and glucose[73] (Figure 6C).

These innovations illustrate the potential of wearable electrochemical sensors for multifaceted biomarker monitoring. Efforts have also been made to miniaturize and integrate electrochemical sensors for high-throughput wearable detection.[74,75] For instance, Hu et al. have developed integrated chip arrays composed of polyethylene terephthalate substrate, cobalt single-atom nanozyme (Co-SAE), and a polyimide layer.[25] The high catalytic activity of Co-SAE enables multichannel *in vitro* and *in vivo* quantification of nitric oxide (Figure 6D). Such advancements highlight the potential of electrochemical sensors to achieve seamless integration into wearable platforms.

Despite their numerous advantages, wearable electrochemical sensors face certain limitations. One challenge is the relatively high background signal, which can hinder the accurate detection of low-concentration biomarkers in bodily fluids. Liu et al. reported to separate the signal molecules from the working electrode to realize zero-background detection of multiple biomarkers (miR-21, alkaline phosphatase, and carcinoembryonic antigen), offering a promising approach to address this problem.[76] Another limitation is the reliance on battery-powered components for generating electrical stimulation, which constrains the devices' potential for cost reduction, simplification, and portability. Fully integrated multi-channel electrochemical sensors have emerged as a highly compelling trend to overcome this obstacle. For instance, Gao et al. reported a fully integrated sensor array capable of simultaneously detecting multiple sweat metabolites without the need for external analysis.[77] Addressing these challenges will require further advancements in materials

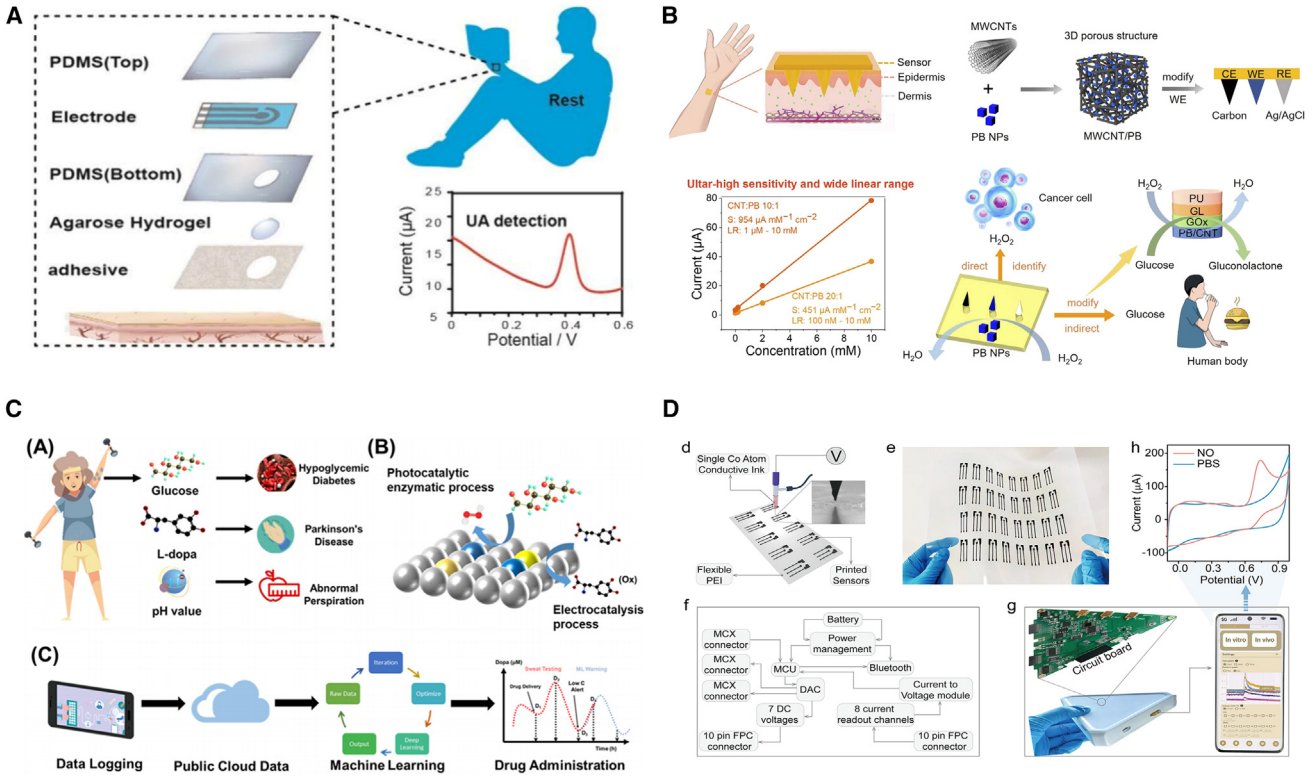

Figure 6. Wearable electrochemical sensors based on nanozymes

(A) Fe-SAE-based hydrogel patch for electrochemical detection of uric acid. Reproduced with permission.[68] Copyright 2023, American Chemical Society.

(B) PB-carbon nanotube composite-based microneedle for electrochemical detection of H_2O_2 and glucose. Reproduced with permission.[72] Copyright 2024, Elsevier.

(C) G-C_3N_4-based chip for electrochemical detection of L-dopa and glucose. Reproduced with permission.[73] Copyright 2022, American Chemical Society.

(D) Co-SAE-based chip array for electrochemical detection of nitric oxide. Reproduced with permission.[25] Copyright 2023, American Chemical Society.

science, power optimization, and device design to fully realize the potential of wearable electrochemical biosensors.

PHOTOELECTROCHEMICAL DETECTION

PEC sensing technology represents an innovative analytical approach that integrates traditional electrochemical detection systems with photoelectrochemical principles. Although PEC sensors share similarities with conventional electrochemical sensors in terms of signal measurement, detection methods, and instrumentation, they distinguish themselves by employing a light source as the excitation signal. This additional light source enables the separation of photo-excited signals from electrochemical detection signals, effectively reducing background noise during detection. Moreover, the electrochemical component facilitates portability, giving PEC sensors a unique combination of high sensitivity, cost-effectiveness, and ease of miniaturization.[78,79] These attributes make PEC technology highly promising for wearable applications.

A critical factor in the performance of PEC sensors is the selection of appropriate photoactive materials, as their structural and functional properties directly impact the sensor's analytical capabilities and application scope. To enhance the photoelectrochemical response of PEC biosensors, researchers are increasingly utilizing nanozymes with high catalytic efficiency.[80,81] These materials can amplify the PEC signal and improve the sensitivity and selectivity of the sensor. In typical nanozyme-based PEC biosensors, the enzymatic reaction translates biological signals into electrical signals via the interaction between a semiconductor material and the biocatalytic reaction chain under illumination. This enables the detection of specific analytes with high precision. For example, Lv et al. synthesized a multifunctional CeO_2/CdS heterostructure that serves as both a photoactive material and a peroxidase mimic.[82] The heterostructure catalyzes CeO_2 to produce hydroxyl radicals (·OH), which *in situ* etch CdS and reduce photocurrents. This mechanism significantly enhances sensitivity for detecting carcinoembryonic antigen, demonstrating the potential of PEC sensors for high-performance biomarker analysis.

Despite its promising advantages, PEC technology faces certain challenges that limit its widespread adoption in wearable biosensors. The production cost of PEC sensors remains relatively high, and the degree of integration with wearable platforms is currently insufficient, posing barriers to their scalability and commercialization. Additionally, PEC sensing relies heavily on light for measurement, making it susceptible to interference from environmental factors such as light intensity and wavelength. Some strategies have been developed to address these

limitations, such as developing self-powered sensing systems[83] and utilizing dual-signal response mode for self-calibration.[84] Continued advancements in materials science are expected to drive down costs and enhance the functionality of PEC sensors.

BIOMEDICAL APPLICATIONS

Glucose detection

Glucose is a critical biomarker for the diagnosis and management of diabetes mellitus. Monitoring glucose levels is essential for evaluating therapeutic efficacy and making necessary adjustments to treatment regimens. Traditional glucose detection primarily relies on a cascade catalytic reaction involving two key steps: (1) GOx catalyzes the decomposition of glucose to produce hydrogen peroxide (H_2O_2); (2) in the presence of horseradish peroxidase (HRP), H_2O_2 reacts with chromogenic substrates (e.g., a mixture of 3,5-dichloro-2-hydroxybenzenesulfonic acid and 4-aminoantipyrine) to produce a red or yellow color.[8,85] Although widely used, traditional methods are typically invasive. In contrast, wearable sensing systems for glucose detection in sweat, interstitial fluid, and other bodily fluids offer non-invasive, portable, and highly sensitive alternatives with minimal skin irritation.[86,87]

Since glucose detection relies on a two-step cascade reaction, research has focused on finding alternatives to GOx. Numerous nanomaterials, such as metallic nanoparticles,[88,89] carbon nanomaterials,[90] and metal oxides,[91] have demonstrated GOx-mimetic activity. These materials have enabled the development of wearable biosensors for portable glucose detection. For example, Li et al. synthesized polyvinyl alcohol (PVA)-modified Au NPs with excellent GOx-like activity.[92] A double-layer microneedle patch by loading PVA-AuNPs on the matrix of methacrylated hyaluronic acid was designed to detect glucose concentrations ranging from 1 to 20 mM in interstitial fluid (Figure 7A). Another approach involves replacing HRP in the cascade reaction with alternative catalysts.[93,94] For instance, Kim et al. developed contact lenses embedded with hyaluronate-modified gold-platinum bimetallic nanozymes (HA-Au@Pt BiNCs) for continuous glucose monitoring.[95] In this system, H_2O_2 generated by GOx is decomposed on the surface of HA-Au@Pt BiNCs, producing a current response that allows highly sensitive glucose detection (Figure 7B). These studies show the potential of nanozyme in wearable detection of glucose.

The development of multifunctional nanozymes capable of single-step glucose detection has emerged as a significant research direction. For example, Fan et al. designed a biomimetic nanozyme, GOx@copper 1,4-benzenedicarboxylate (CuBDC), which integrates the functions of an MOF and a peroxidase-mimetic nanozyme. This multifunctional material preserves GOx activity and enables efficient cascade reactions. A wearable sweat-glucose detection device based on GOx@CuBDC demonstrated a detection range of 40–900 μM and a limit of detection of 20.7 μM, showcasing the potential for highly efficient glucose monitoring[96] (Figure 7C).

In addition to monitoring, integrating glucose sensing with smart insulin delivery systems represents a promising advancement in wearable device technology. Hsu et al. developed a microneedle system comprising a glucose-biosensing microneedle patch and an insulin-delivery microneedle patch.[18] This dual-function system utilizes GOx-conjugated MnO_2/graphene oxide nanozymes (GOx-MnO_2@GO) to measure glucose concentrations. Simultaneously, elevated blood glucose levels trigger the automatic release of insulin, enabling real-time glucose control. This innovative approach could significantly enhance the efficiency of glucose management in diabetic patients (Figure 7D). Wearable glucose sensing technologies continue to evolve, driven by advances in nanozyme design and integrated smart systems. These innovations offer non-invasive, precise, and efficient solutions for glucose monitoring and management, paving the way for improved therapeutic outcomes and quality of life for individuals with diabetes.

UA detection

UA is the final circulating metabolite of purine nucleotides in the body and serves as an important biomarker for diagnosing gout and assessing renal excretory function. The development of artificial uricase to replace conventional urate oxidase has gained considerable interest in recent years. For example, Wang et al. reported a coordination polymer-based dual-site nanozyme composed of Ni metal centers and 3,3′-diaminobenzidine ligands, which demonstrated selectivity in the oxidation of UA.[97] Point-of-care testing for UA increasingly focuses on sweat-based detection using flexible wearable patches. For instance, Li et al. synthesized Co-doped MnO_2 (Co@MnO_2) nanozymes with oxidase-like activity.[98] They found that UA exhibits a distinct quenching effect on Co@MnO_2-catalyzed colorimetric reactions using tetramethylbenzidine (TMB) and $ABTS^{\cdot+}$ systems. Based on this, a wearable microfluidic colorimetric chip was developed for detection of UA in sweat.

Despite these advancements, sweat-based UA detection presents several challenges. First, the concentration of UA in sweat is low (0.02–0.1 mM), and even during heavy sweating, the amount of UA excreted is a minimal fraction of total body excretion, necessitating highly sensitive sensors. Second, UA detection is affected by sweat pH (5.5–8.0), with varying pH conditions potentially biasing the sensing signal. Third, the low secretion rate of resting sweat limits the availability of sufficient samples for reliable detection. To overcome these limitations, researchers are working to develop nanozymes with enhanced catalytic activity while optimizing sweat collection and detection processes. For example, Chen et al. introduced a three-dimensional (3D) printed flexible wearable monitor incorporating self-supporting microfluidic channels and SAE.[61] The self-supporting microfluidic design minimizes sweat evaporation and contamination, enabling precise *in situ* measurements of sweat rates. Meanwhile, the use of SAEs improves the sensitivity of biomarker detection. This combination of 3D printing and advanced nanozyme materials offers a non-invasive approach to monitor sweat rates and biomarker concentrations.

In addition to sweat-based detection, there has been progress in detecting UA in interstitial fluids. For example, Li et al. synthesized polypyrrole nanoparticles with peroxidase-like activity.[99] These nanoparticles facilitate the reaction between H_2O_2 and TMB, producing a color change that correlates with the concentration of H_2O_2 generated by UA oxidation. Using this mechanism, a wearable microneedle colorimetric patch was developed for *in situ* UA detection. This approach demonstrates the

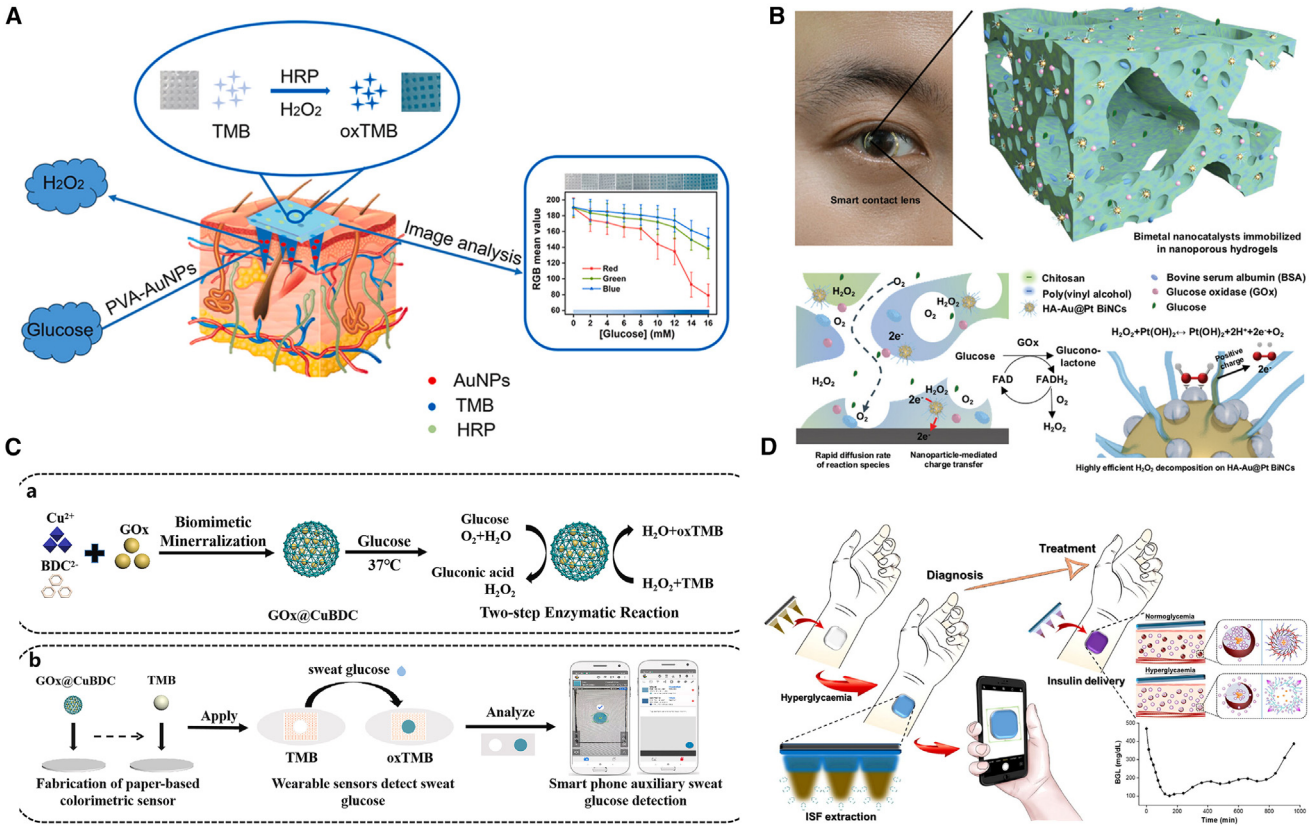

Figure 7. Nanozyme-based wearable sensors for detection of glucose

(A) Gold-nanoparticles-based microneedle patch for detection of glucose in interstitial fluid. Reproduced with permission.[92] Copyright 2024, Elsevier.

(B) Gold-platinum bimetallic nanozymes-based contact lens for detection of glucose. Reproduced with permission.[95] Copyright 2022, Wiley-VCH.

(C) GOx@CuBDC-based wearable sensor for detection of glucose in sweat. Reproduced with permission.[96] Copyright 2024, Elsevier.

(D) glucose oxidase-MnO_2@GO nanozymes-based microneedle patch for detection of glucose. Reproduced with permission.[18] Copyright 2022, Elsevier.

potential for accurate and real-time monitoring of UA in interstitial fluid, further expanding the scope of wearable biosensor. Although sweat-based detection offers non-invasive detection options, interstitial fluid-based approaches provide complementary solutions for more robust UA monitoring. Future research should focus on addressing the challenges of sensitivity, pH dependency, and sample availability while further integrating advanced nanozymes and detection platforms to enhance diagnostic accuracy and reliability.

Lactic acid detection

Lactic acid is the end product of anaerobic glycolysis, and its concentration serves as a critical indicator of tissue hypoxia.[100,101] Traditional methods for lactate detection, such as colorimetry, spectrophotometry, fluorescence, and chromatography, are often time-consuming, require complex procedures, and are associated with high costs.[102] In contrast, wearable sensors offer a non-invasive, highly sensitive, cost-effective, and user-friendly alternative, enabling rapid and accurate biomarker detection. These attributes make wearable sensors a promising platform for lactate monitoring.

Most wearable biosensors for lactate detection utilize either lactate oxidase (LOx)[103] or lactate dehydrogenase[104] as enzymatic recognition elements. Among these, LOx is more commonly employed, particularly for sweat-based detection, due to its robust catalytic activity.[105] However, to reduce the cost of natural enzymes and mitigate their susceptibility to environmental factors such as temperature and pH, nanozymes with high catalytic properties have been explored as substitutes for LOx in the electrooxidation of lactic acid.[24] Another approach involves combining nanozymes with lactate oxidase to enhance detection sensitivity. For instance, Weng et al. developed a nanozyme-enzyme electrochemical biosensor based on CeO_2-MoS_2 nanozyme and LOx. This sensor achieves a high sensitivity of 25.58 $\mu A\ mM^{-1}\ cm^{-2}$ and a limit of detection as low as 0.135 mM.[106] These results highlight the potential of nanozyme-enzyme composites for improving the analytical performance of wearable lactate sensors.

Simultaneous detection of multiple biomarkers, including lactate and glucose, is gaining significant interest due to its potential to provide comprehensive insights into physiological states. Unlike glucose, which is present in much lower concentrations in sweat compared to blood, sweat lactate levels are significantly higher than their plasma counterparts. This distinction underscores the importance of monitoring these two biomarkers simultaneously, as it facilitates early detection of

abnormal physiological changes and enhances athletic performance monitoring. Studies have demonstrated the feasibility of developing dual-analyte biosensors for real-time tracking of these biomarkers.[107,108] For instance, Daboss et al. developed an innovative biosensing platform based on oxidases and core-shell nanozymes PB-nickel hexacyanoferrate.[109] This platform enables simultaneous detection of glucose and lactate, providing a robust tool for managing conditions such as diabetes and hypoxia. These advancements highlight the potential of wearable biosensors for precision health monitoring and performance optimization.

Despite the advantages of wearable biosensors, several challenges remain in lactate analysis. One major challenge is the high concentration of lactate in sweat, which ranges from 4 mM to 25 mM in healthy individuals, compared to 0.5 mM–1.5 mM in plasma.[110] To address this, sensors must be designed with a sufficiently wide linear detection range to accurately measure lactate concentrations in real-world conditions.[111] Additionally, physical motion during activities such as exercise can cause signal fluctuations due to bending, electrode corrosion, and mechanical instability, thereby affecting the accuracy of lactate detection.[112] These challenges highlight the need for further research into high-performance nanozymes and the development of mechanically robust, stable sensors capable of maintaining reliable signal acquisition under dynamic conditions.

H_2O_2 detection

H_2O_2 is a by-product of enzyme-catalyzed reactions and serves as a critical biomarker for assessing oxidative stress, disease states, immune responses, and drug efficacy.[113] A variety of materials, including Pt NPs,[114] graphene-based materials,[115] transition metal chalcogenides,[116] and metal oxides,[117] have been explored for H_2O_2 detection due to their catalytic properties. Wearable sensors for H_2O_2 primarily focus on developing nanomaterials with high peroxidase-mimicking activity, which catalyze the production of ·OH from H_2O_2, enabling colorimetric or electrochemical signal generation.[72]

Since glucose metabolism often produces H_2O_2 as a by-product, H_2O_2 detection is frequently combined with glucose monitoring in wearable devices. For instance, Ma et al. developed wearable sensors for simultaneous detection of H_2O_2 and glucose using screen-printed Berlin green arrays.[118] The sensors demonstrated high sensitivity, with detection sensitivities of 27.25 $\mu A\ mM^{-1}\ cm^{-2}$ for H_2O_2 and 20.22 $\mu A\ mM^{-1}\ cm^{-2}$ for glucose. This approach offers a simple and convenient solution for fabricating wearable sensors capable of dual-analyte monitoring, highlighting their potential for real-time physiological assessments.

A single nanozyme often provides limited electron transfer capabilities, which can be insufficient for wearable detection. To address this, researchers frequently incorporate nanozymes into composite materials to improve catalytic performance and sensitivity. For example, Ying et al. synthesized a composite material comprising sulfur-vacancy-rich molybdenum disulfide (MoS_2-X) and multi-walled CNTs, forming coaxially layered CNTs/MoS_2-X structures.[119] These were further combined with titanium dioxide nanoparticles (TiO_2) to construct a microfluidic platform using PB as a redox probe. The sulfur vacancies and coaxial layering enhanced the electrochemical sensor's sensitivity and performance, demonstrating the importance of material engineering in wearable biosensor development.

Ascorbic acid detection

Ascorbic acid is an essential nutrient vital for numerous physiological processes, and its detection provides critical insights into intake levels and metabolic status. Real-time monitoring of ascorbic acid concentrations offers a non-invasive approach for health tracking, facilitating continuous assessment of an individual's nutritional intake and overall health status. Ascorbic acid is specifically recognized and captured by natural ascorbate oxidase due to the high affinity of its tryptophan (Trp) and histidine (His) residues for ascorbic acid.[120] Several nanozymes have been developed to mimic ascorbate oxidase activity, leveraging these binding interactions for selective detection.[121,122] For instance, Wang et al. reported the preparation of His-and Trp-functionalized Cu-MOF via epitaxial growth and post-synthetic modification.[123] These functionalized MOFs demonstrated high specificity for ascorbic acid oxidation and were incorporated into wearable sensors. The resulting sensors exhibited exceptional sensitivity, achieving 0.18 and 0.48 mA cm^{-2} mM^{-1} in acidic and alkaline sweat, respectively. This demonstrates the potential of wearable biosensors constructed from natural oxidase-inspired nanozymes for the specific detection of ascorbic acid.

Portable detection of ascorbic acid faces several challenges. One significant issue is the rapid oxidation of ascorbic acid under atmospheric conditions, necessitating real-time detection immediately upon secretion to ensure accurate concentration analysis. Additionally, as a reducing agent, ascorbic acid may interfere with the detection of other analytes, posing a challenge for multi-analyte wearable sensors. Strategies to address these challenges include developing ascorbate oxidase-mimicking nanozymes with enhanced specificity, optimizing sensor design, and incorporating rapid response mechanisms to mitigate interference from oxidative degradation and cross-reactivity.

Oxalate detection

Elevated oxalate levels are a hallmark of hyperoxaluria, a condition that can lead to serious health issues such as kidney stones, renal calcium deposits, and, in severe cases, kidney failure.[124] Healthy individuals typically maintain low oxalate levels in body fluids, whereas individuals with progressive kidney disease often experience impaired oxalate elimination. Consequently, oxalate testing is essential for diagnosing and managing hyperoxaluria. Regular monitoring of oxalate levels enables healthcare providers to develop tailored treatment plans, which may include dietary modifications, pharmacological interventions, or symptomatic therapies such as dialysis.

Current oxalate diagnostics largely rely on materials with oxalate-oxidase-mimicking activity, which catalyze the oxidative degradation of oxalate. For instance, MnFeCN/FeFeCN nanozymes have been developed to mimic natural oxalate oxidase and catalyze oxalate degradation effectively.[65] A wrist-worn microneedle device fabricated using this nanozyme demonstrated impressive performance, with a broad linear detection range (3.73–186.5 μM) and a low detection limit of 0.897 μM. This

device shows significant potential for visualizing oxalate levels in interstitial fluid, enabling non-invasive and real-time monitoring. Another approach leverages the reducing nature of oxalate. Oxalate reacts with nanozymes, reducing their catalytic activity and altering their oxidative performance toward substrates. This characteristic provides an alternative mechanism for oxalate detection, broadening the range of diagnostic tools available for hyperoxaluria management.[125,126] However, the development of nanozymes with high selectivity to replace oxalate oxidase for detection of oxalate remains a considerable challenge. The complexity of the constituents in body fluids and the interference of coexisting compounds (e.g., UA, ascorbic acid, and glucose) also hamper the specificity and reliability of the nanozymatic-based oxalate assay.[127,128]

CONCLUSIONS AND OUTLOOK

Wearable biosensors are revolutionizing the healthcare field. Nanozyme-based wearable biosensors, in particular, provide significant advantages in cost-effectiveness, portability, and environmental adaptability, providing strong technical support for health monitoring and personalized medicine.[129] This review focuses on the enzyme-mimicking properties of nanozymes, which render them well suited for the development of wearable biosensors. It discusses the immobilization strategies of nanozymes, the detection technologies of nanozyme-based wearable biosensor, and their biomedical applications. Despite the rapid progress made on this frontier, there are still several research gaps and obstacles that must be overcome to fully harness the capabilities of nanozymes in the development of wearable biosensors.

First, although various strategies have been developed to enhance the catalytic activity of nanozymes, their reported performance often lags behind that of natural enzymes. Since the sensitivity of wearable sensors is heavily dependent on the catalytic efficiency of nanozymes, significant efforts are required to design nanozymes with higher activity levels. The precise control of active centers in nanozymes, coupled with the optimization of their ligand environments, provides an efficient strategy for mimicking the active sites of natural enzymes.[130,131] For instance, the conversion of nanoparticle-based nanozymes into SAEs to expose metal catalytic sites represents an effective approach to significantly enhance their catalytic activity.[132] Additionally, developing multi-enzyme mimetic nanozymes capable of simulating cascade reactions in biological systems could expand their catalytic efficiency and application scope.

Second, achieving catalytic specificity remains a critical challenge for nanozyme-based wearable biosensors. Nanozymes often exhibit cross-reactivity with multiple substrates, reducing selectivity and complicating the detection of specific analytes. Surface modification and functionalization of nanozymes, including altering their morphology, crystalline facets, and surface defects, is an effective way to improve the catalytic selectivity of nanozymes. For instance, modification of Au nanoclusters with dendrimers leads to the loss of their peroxidase-like activity, whereas their catalase-like activity remains intact under physiological conditions.[133] Mimicking the active site architectures and microenvironments of natural enzymes through bionics engineering is another promising strategy to enhance specificity.[134] For instance, nanozymes synthesized by grafting copper-histidine (Cu-His)-coordinated cores onto MOF show higher selectivity than natural catechol oxidase.[135] Advances in artificial intelligence have also made the bottom-up or top-down design of nanozymes more precise, allowing for the development of highly selective nanozymes tailored to target analytes. For instance, machine learning models can be used to predict the types of enzymatic catalytic activities, such as the peroxidase, oxidase, and superoxide dismutase.[136]

Third, studies on the toxicological mechanisms or potential toxicity of nanozymes have not been highly reported, which severely hinders the application of nanozymes in actual clinical detection. Since wearable biosensors come into direct contact with the human body, the integration of nanozymes in wearable biosensors needs to be rationally designed to avoid any potential toxicity. More research is needed to systematically evaluate the toxicity of nanozymes. For *in vivo* toxicity assessment, animal models have been widely used to monitor changes in physiological parameters.[137] For *in vitro* toxicity assessment, computational toxicology tools and nanotoxicity prediction models can provide valuable insights into the potential risks of nanozymes and guide their safe design. For instance, quantitative-structure activity relationship models have been developed to predict cytotoxicity of metal oxide nanoparticles.[138,139] In addition, the read-across method is also an attractive tool for preliminary hazard assessment of nanozyme.[140]

Finally, the practicality, reusability, and long-term durability based on nanozyme-based wearable sensors require further investigation. In practical applications, wearable sensor may suffer from deformation, corrosion of sensing electrodes, and other mechanical or environmental challenges, which can compromise their functionality. Developing wearable sensors with enhanced stretchability and flexibility represents a promising strategy to address this issue.[141] In addition, nanozyme often exhibits insufficient catalytic efficiency and limited concentration availability, leading to performance degradation during repeated use. Continued exploration is still needed to develop nanozymes with improved catalytic stability and repeatability to enhance their reliability and functionality in practical applications.[142] Furthermore, the substrate materials in wearable devices are susceptible to aging over extended periods, potentially causing nanozyme shedding or degradation, thus undermining the device's durability. Therefore, the selection and optimization of substrate materials with superior electrical, mechanical, and chemical properties are critical for ensuring the long-term stability and reliability of wearable sensors.

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AUTHOR CONTRIBUTIONS

Y.Z., Y.Y., and Z.Y. collected the information and wrote the original draft. Y.Z. and Y.Y. revised and edited the manuscript. L.H. and J.W. contributed to the conception and revised the final manuscript for submission.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

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