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MINI REVIEW

Nanomaterials-based enzymatic biofuel cells for wearable and implantable bioelectronics

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Abstract Enzymatic biofuel cells (EBFCs), which generate electricity through electrochemical reactions between metabolites and O_2/air, are considered a promising alternative power source for wearable and implantable bioelectronics. However, the main challenges facing EBFCs are the poor stability of enzymes and the low electron transfer efficiency between enzymes and electrodes. To enhance the efficiency of EBFCs, researchers have been focusing on the development of novel functional nanomaterials. This mini-review first introduces the working principles and types of EBFCs, highlighting the key roles of nanomaterials, such as enzyme immobilization and stabilization, promotion of electron transfer and catalytic activity. It then summarizes the recent advancements in their application in wearable and implantable devices. Finally, it explores future research direction and the potential of high-performance EBFCs for practical applications.

Keywords enzymatic biofuel cells, functional nanomaterials, self-powered bioelectronics, wearable electronics

1 Introduction

Implantable and wearable electronics play a critical role in modern biomedicine by performing the functions of malfunctioning organs and collecting *in vivo* physiological data for diagnosis, therapy, and prognosis. As such, they are becoming increasingly essential. A reliable, safe, and long-lasting power source is indispensable for these devices. Currently, lithium and alkaline batteries are the dominant power sources for bioelectronics, but they contain hazardous substances and require careful packaging. Additionally, replacing the power source in implanted devices is both costly and potentially painful for patients. Therefore, there is an increasing interest in developing biocompatible power sources that can harvest external energy and convert it into electricity. In particular, energy harvesting from living organisms has attracted considerable attention, leveraging various physical activities such as walking, running, muscle stretching, blood flow, and heart pulsations. Several energy harvesting methods have been developed, including those based on thermoelectric, piezoelectric, and triboelectric effects [1]. However, these methods have limitations due to their high dependence on physical movement or environmental conditions. For example, energy harvesting from physical motions (e.g., walking or running) can be interrupted when the body is stationary, while pyroelectric-based harvesting methods may fail at higher ambient temperatures.

In this context, energy harvesting from internal physiologic activities could offer a more reliable solution, as the physiologic conditions inside a living body are relatively stable. Thus, biofuel cells, which generate electricity through electrochemical reactions between metabolites (e.g., glucose, lactate) and O_2/air, are considered a promising alternative power source for bioelectronics. [2]

A biofuel cell resembles a conventional fuel cell in the basic configuration and working principle, with the major differences lying in the catalysts and working conditions. Biofuel cells use biocatalysts, such as enzymes and living microorganisms, and usually operate under near-neutral conditions (pH = 5–8) and low temperatures (25–37 °C). In contrast, conventional fuel cells rely on inorganic catalysts, primarily noble metal nanomaterials, and often require harsh conditions (extremely acidic or alkaline

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environments and higher temperatures) to ensure high power output. Biofuel cells are generally categorized into two categories: enzymatic biofuel cells (EBFCs) and microbial biofuel cells (MBFCs), based on the type of biocatalysts used. Compared to MBFCs, EBFCs usually exhibit higher power densities, making them suitable for integration into miniature electronics [1,3]. Furthermore, the presence of living microorganisms in MBFCs may raise additional concerns when implanting devices. EBFCs, on the other hand, can be designed using biocompatible materials [4], making them a more promising option for implantable and wearable bioelectronics. Meanwhile, MBFCs are often better suited for larger-scale power generation, such as wastewater treatment [1,5].

This minireview will provide a concise overview of the working principles of EBFCs, followed by discussions of recent advances at both the material and device levels. It will highlight the key functions of various nanomaterials used in EBFC electrodes, including enzyme immobilization and stabilization, electron transfer facilitation, and catalytic reactions. Moreover, it will explore the applications of EBFCs in wearable and implantable devices, including power supply, self-powered sensing, and self-powered molecule release. Finally, it will conclude with perspectives and future outlooks on this emerging field.

2 Working mechanism and types of enzymatic biofuel cells

As previously mentioned, the configuration and working principles of a typical EBFC are basically similar to those of conventional fuel cells, with the main difference being the electrodes used [6]. Typically, an ion-exchange membrane is placed between anode and cathode to prevent crossover reactions, forming double-chamber EBFCs (Fig. 1(a)). However, it is worth noting that by using enzymes with high selectivity, crossover reactions can be avoided even in the absence of an ion-exchange membrane. This allows for the development of membrane-less (also called single-chamber) EBFCs [7]. The removal of the membrane results in a more compact design and enables more efficient charge transfer between the anode and cathode, which is an attractive advantage of EBFCs over traditional fuel cells.

The most widely used fuel in EBFCs is glucose, due to its relatively high concentration in the blood (at the mmol/L level). Lactate, abundant in sweat, is also commonly used, especially for wearable electronics. Other fuels include alcohol [8], sucrose [9], fructose [10], and others. Common anodic enzymes for these fuels include glucose oxidase (GOx), lactate dehydrogenase, glucose dehydrogenase (GDH), fructose dehydrogenase, and lactate oxidase (LOx), among others. In some cases, employing multiple enzymes can facilitate a cascade reaction, resulting in higher power output [11]. The oxidant at the cathode is usually O_2, which is readily available in biofluids and air. Multicopper oxidases are the most attractive enzymes for catalyzing of O_2 into H_2O, as they enable the $4e^-$-reduction of O_2 with almost no overpotential and without producing toxic intermediates [12].

In contrast to traditional fuel cells, which use inorganic metallic nanomaterials that are good conductors for

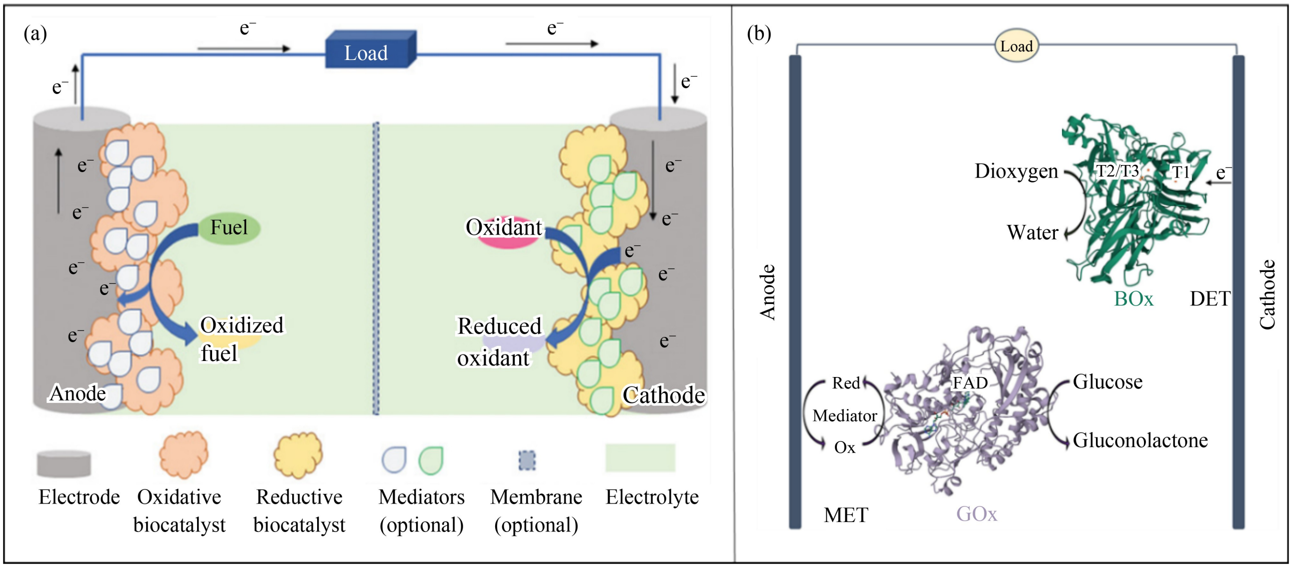

Fig. 1 (a) Schematic illustration of an EBFC (reproduced with permission from Cai et al. [6], copyright 2024, Cell Press); (b) direct (cathode) and mediated (anode) electron transfer between enzymes and electrodes (reproduced with permission from Wu et al. [14], copyright 2021, Wiley-VCH GmbH).

efficient charge transfer between catalysts and current collectors, enzymes have active centers embedded in protein shells. These shells are often far away from the current collectors, making charge transfer between enzymes and electrodes a significant challenge in EBFCs. When the enzyme is properly oriented, with its active center positioned close to the electrode surface, direct electron transfer (DET) can occur via electron tunneling, allowing electrons to transport between the enzyme and the electrode (Fig. 1(b)). In DET, the orientation of enzyme molecules is crucial, and usually, DET can only occur between a monolayer of enzyme molecules and the electrode surface. To overcome the limitations of DET, mediators are employed to enhance electron transfer, which is referred to as mediated electron transfer (MET) (Fig. 1(b)). Mediators are small molecules or polymers, which can undergo reversible redox reactions with redox potential that closely matches that of the enzyme, enabling them to shuttle electrons between the enzyme and the electrode surface. However, introducing mediators could potentially raise concerns related to toxicity and stability [13]. In addition, MET may also result in a drop in cell voltage due to the small potential gap between mediator and enzyme, which is necessary for electron hopping [12].

Due to the short lifespan and poor electron transfer of enzymes, it is challenging to develop a high-performance and stable EBFC with both electrodes immobilized with enzymes. As a solution, hybrid EBFCs have been developed, where only one electrode is immobilized with enzymes while the other uses a regular inorganic catalyst (non-enzymatic).

3 Functions of nanomaterials used for electrodes

As mentioned earlier, the main challenges of EBFCs include the poor stability of enzymes and inefficient electron transfer between enzymes and electrodes. Using nanostructured materials as electrodes or employing nanomaterials in the electrodes can mitigate these problems. Nanomaterials possess a large surface area and unique surface characteristics, allowing for high enzyme loading and better intimate connections, thus facilitating electron transfer. The porous nanostructures enable fast diffusions of mediators and reactants, which improves both electron transfer and catalytic reaction kinetics. In addition, some nanomaterials have good intrinsic catalytic properties or can enhance enzyme activity. Nanomaterials can also create a suitable microenvironment, thus improving the stability of enzymes. Further more, electrode materials that are flexible, compatible with body movement, and stable *in vivo* can be used in EBFCs designed for wearable or implantable electronics.

Given these properties, carbon-based and metallic (e.g., Au, Ag, Pt) nanomaterials, as well as their composites, are good candidates for the electrodes of EBFCs [15]. These materials usually have high electrical conductivity and mechanical robustness, making them suitable for flexible electrodes. Besides, they are generally biocompatible and chemically inert, making them ideal for use in implantable electronics. Moreover, their large surface area, excellent catalytic properties, and ease of surface modifications are crucial for achieving high enzyme loading and facilitating electrochemical reactions. In recent years, emerging nanomaterials such as metal-organic frameworks (MOFs), transition metal dichalcogenides (TMDs), and mxenes [16] have also been utilized to enhance the performance of EBFCs due to their unique features. The following sections will delve into the major functionalities of nanomaterials in the electrodes of EBFCs, highlighting representative materials.

3.1 Immobilizing and stabilizing enzymes

The loading amount and immobilization configuration of enzymes significantly affect the power density and cell voltage of EBFCs, while the stability of enzymes determines the cell lifetime. A large surface area is essential for achieving high loading of enzymes, hence nanomaterials with high specific surface area are purposely designed for enzyme immobilization. The methods for immobilization are categorized into physical and chemical techniques, depending on how the enzyme interacts with the substrate. Physical techniques include adsorption and entrapment, while chemical techniques involve covalent bonding and cross-linking [7].

Carbon nanomaterials are the most commonly used materials for enzyme immobilization, including carbon nanotubes (CNTs) [17,18], 3D-structured graphene or graphene oxide [19–21], mesoporous carbons, and others. The structure and morphology of these carbon nanomaterials have a significant impact on the orientation of immobilized enzymes and the diffusion length of charges, which in turn affects the efficiency of electron transfer [22]. To efficiently utilize the surface area of porous nanomaterials, it is important to control the pore structure and pore size. An effective strategy is MgO-templated growth (Fig. 2(a)). Tsujimura and colleagues [23,24] demonstrated the formation of MgO-templated mesoporous carbon. The size of MgO nanoparticles can be easily tuned (ranging from 2–150 nm), therefore, by using MgO nanoparticles as the sacrificial template, the pore size of mesoporous carbon materials can be controlled to accommodate enzymes of different sizes [23–25]. Other types of nanomaterials have been also explored for efficient enzyme immobilization [26], such as nanoporous Au [27], copper phosphate nanoflowers [28,29], Ni-doped $MoSe_2$ nanoplates [30,31], and metal oxide nanoparticles [32,33]. Enzymes that are physically

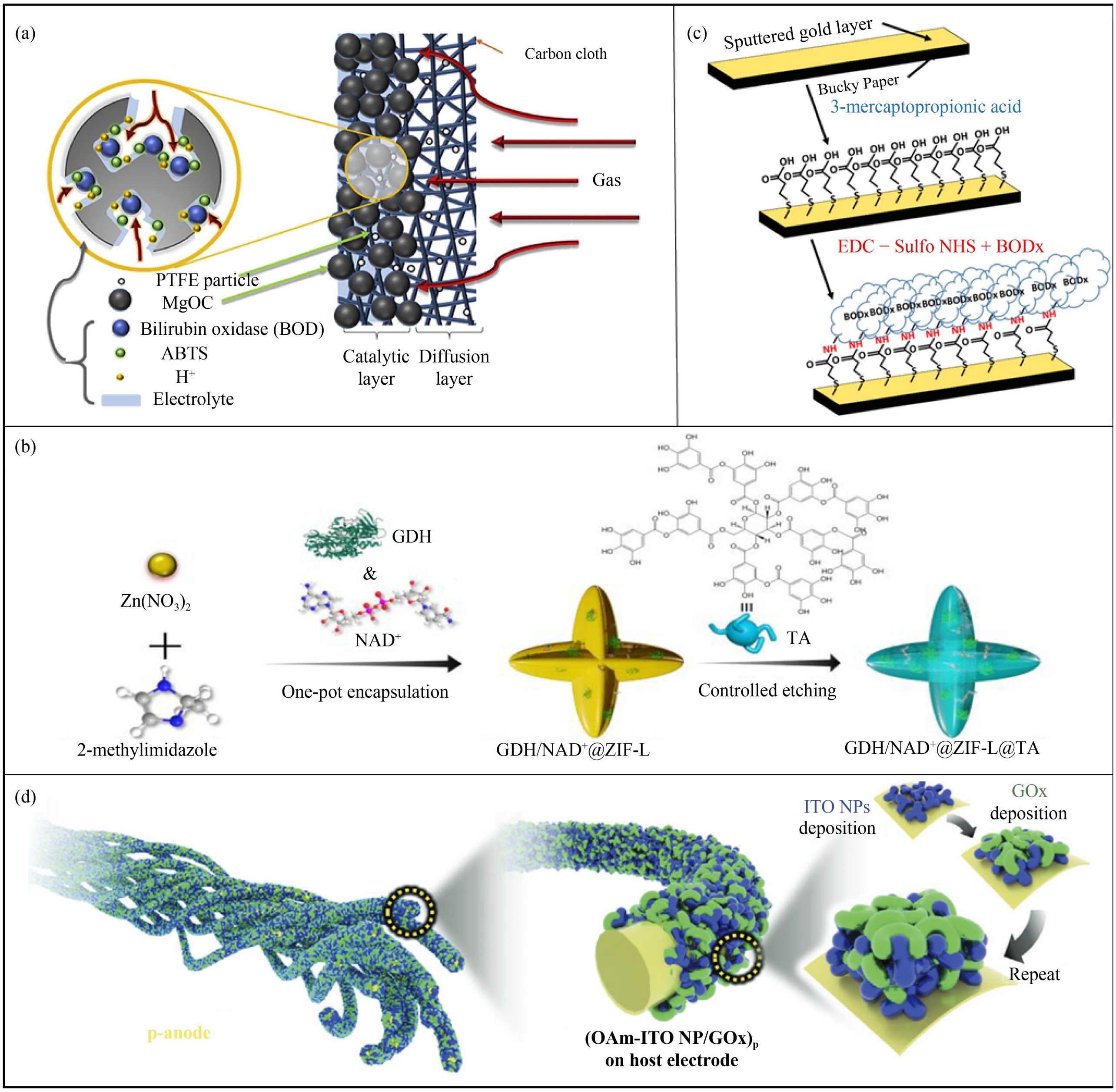

Fig. 2 (a) MgO-templated porous carbon used as an enzyme support (adapted from Shitanda et al. [24] under the terms of CC BY-NC-ND license); (b) synthesis of hierarchical porous GDH/nicotinamide adenine dinucleotide (NAD)@ZIF-L-based microreactor by controlled-etching strategy (reproduced with permission from Yan et al. [39], copyright 2023, Wiley-VCH GmbH); (c) surface modification of Au-coated buckypaper electrode with bilirubin oxidase (BODx) (from *Myrothecium*) (reproduced with permission from Hasan et al. [44], copyright 2018, Nature Publishing Group); (d) scheme of GOx (from *Aspergillus* niger)/ITO nanoblended film on host electrode (reproduced with permission from Kang et al. [50], copyright 2023, Wiley-VCH GmbH).

adsorbed onto nanomaterials can retain their catalytic activity, but they tend to detach from the surface because of weak interactions. Encapsulation of enzymes during the growth of nanomaterials can provide better confinement. Babadi et al. synthesized CNT/3D graphene hybrids and used them for GOx immobilization to overcome the limitations of EBFCs. The CNT nanowires enhanced DET between GCE and GOx (from *Aspergillus niger*), while the porous graphene preserved the three-dimensional structure of GOx, prolonging its enzyme lifetime [34].

Recent studies show that MOFs are promising candidates for the *in-situ* enzyme immobilization [35–38]. MOFs are a class of intrinsically porous nanomaterials which are advantageous for reactant diffusion during electrochemical reactions. The synthesis conditions for some commonly used MOFs are mild, which helps retain the structure of the enzymes during the growth of MOFs. In a very recent study, Yan et al. [39] reported a hierarchical porous MOF for the co-encapsulation of GDH and nicotinamide adenine dinucleotide. The hierarchical porous structure was achieved by tannic acid etching, which not only facilitated reactant transport but also allowed the enzyme to reorient into a more stable configuration with lower surface energy, thus enhancing catalytic performance (Fig. 2(b)). Notably, MOFs can protect encapsulated enzymes from the attack of biomolecules in human blood, greatly enhancing the stability of EBFCs [35]. However, a drawback of MOFs is poor conductivity, therefore conducting carbon nanomaterials (e.g., CNTs) are also incorporated to fabricate nanocomposite electrodes [38].

Besides modifying the morphology or architecture of nanomaterials, chemical modification of nanomaterial surface can provide stronger interactions with enzymes through covalent bonds or non-covalent interactions, as well as better control of enzyme conformation. Surface functionalization serves as a versatile post-treatment approach, ranging from basic oxidative chemical or physical treatments to intricate molecular arrangements [40]. Considerable efforts have been devoted into the surface functionalization of carbon nanomaterials using various interactions such as electrostatic and hydrophobic forces to achieve maximum enzyme loading and rapid electron transfer between the enzyme and the conducting surfaces [41]. Among the various carbon nanomaterials, graphene oxide and reduced graphene oxide are especially notable, as their surfaces are enriched with abundant oxygenated groups, allowing for facile grafting of polymers with reactive functional groups, such as hydroxyl and amine groups [42,43]. These functional groups can be further used to immobilize enzymes through covalent bonding, π–π stacking, or electrostatic attraction.

Carbon nanomaterials or other supporting materials are also commonly decorated with Au nanoparticles, which are the most widely used metallic nanomaterials for enzyme immobilization through surface functionalization [9,44–46] due to their strong bonding capabilities with a wide range of chemicals and well-suited surface chemistry for biomedical applications. For example, due to the unique bonding between Au and –SH groups, 3-mercaptopropionic acid (MPA) molecules can be densely packed on the self-assembled monolayer of Au nanoparticles. The –COOH group from MPA can then be used to covalently immobilize bilirubin oxidase (BODx) (from *Myrothecium*) (Fig. 2(c)) [44]. Furthermore, with a proper choice of chemical linkers, multiple enzyme layers can be constructed using a layer-by-layer assembly technique, which can enhance EBFCs power output and stability [47–49]. It important to note that while covalent immobilization usually result in strong interactions between enzymes and electrodes, it may also cause enzymes to denature. Recently, Kang et al. [50] utilized interfacial interactions to induce assembly between hydrophobic conductive indium tin oxide (ITO) nanoparticles and hydrophilic GOx (from *Aspergillus niger*). By repeatedly depositing GOx/ITO bilayers, they formed a nanoblended GOx/ITO film with multiple layers (Fig. 2(d)), realizing high loading of GOx and efficient electron transfer at the anode.

3.2 Facilitating direct electron transfer (DET)

As previously mentioned, DET is closely related to the distance between the surface of electrode and the active centers of enzymes, which can be effectively shortened by nanostructure engineering. Specifically, nanoporous materials such as mesoporous carbon and nanoporous gold (Au) have been extensively reported to facilitate DET [51]. Even when the enzyme molecules are randomly distributed, nanoporous structures create multidirectional surface interactions with enzymes due to the curvature effect (Fig. 3(a)) [52,53]. As a result, efficient DET is achieved as the pore size is close to enzyme size [54].

Besides nanoporous materials, DET can also be enhanced by orienting immobilization of enzymes in such a way that their active centers are positioned close to the surface of electrode. The aforementioned surface modification of nanomaterials is a commonly used method to achieve oriented immobilization of enzymes. A typical example is electrostatic interaction [52,55]. For example, when two dendritic mesoporous silica nanoparticles (NH_2-DMSNs and OH-DMSNs) with opposite surface charges were used to immobilize P450 BM3, the P450 BM3/NH_2-DMSNs electrode demonstrated enhanced electron transfer efficiency due to the smaller distance between the reductase domain and the electrode surface (Fig. 3(b)) [55].

Interestingly, a novel method that combines the orientation of enzyme with mediation has been reported to achieve efficient electron transfer between a multicopper oxidase and multi-wall CNTs (MWCNTs) [56]. This was achieved by anchoring the CNT surface with a redox mediator that contains aromatic groups for enzyme orientation (Fig. 3(c)). The resulting bioelectrode exhibited a much higher maximum ORR current density compared with those in which enzymes were either mediated or oriented on the MWCNT surface. Furthermore, the incorporation of heteroatoms into the carbon matrix has recently been considered as a promising strategy to modify the electronic properties of carbon. In particular, studies have shown that N-doping can enhance the electron mobility of carbon nanomaterials, thus improving DET between the enzyme active sites and the electrodes [57–59]. Formation of covalent bonding between functionalized carbon materials and enzyme, such as CNFs-COOH and GOx via amid reaction [60], can also facilitate rapid DET.

Moreover, DET can be achieved in composite

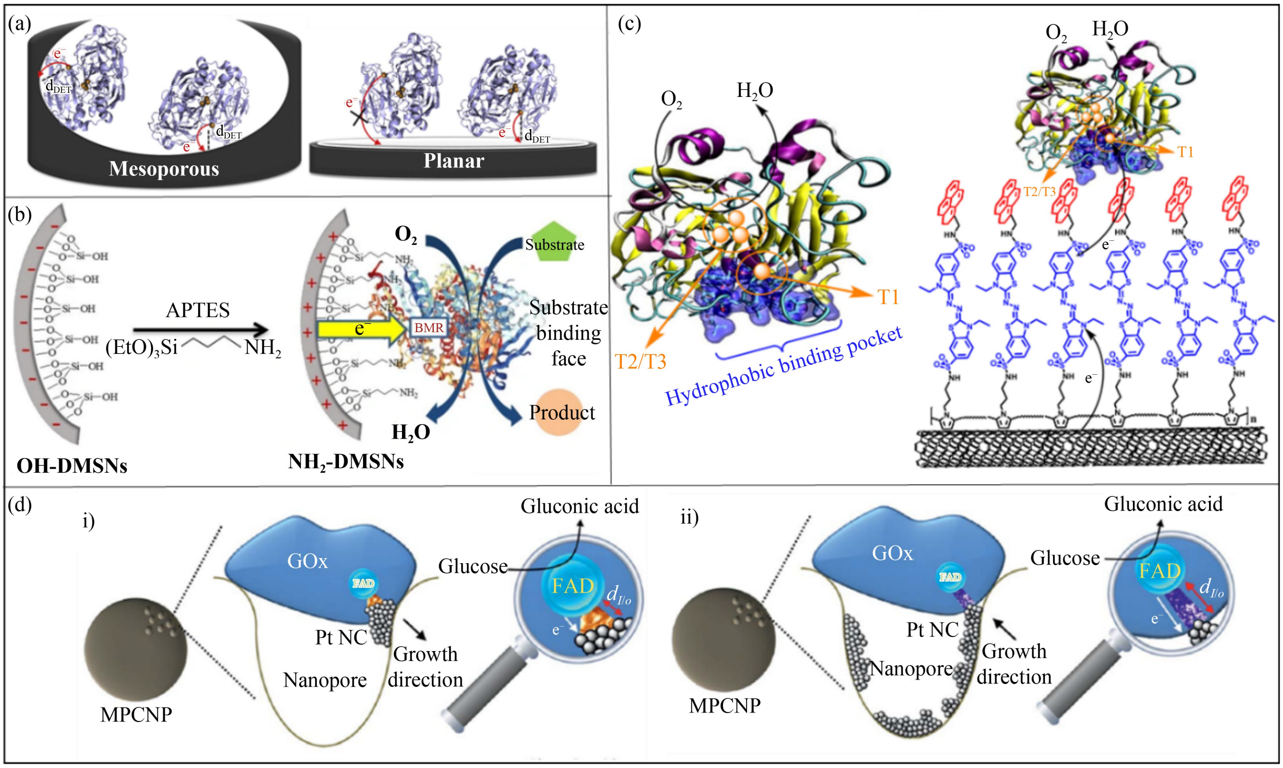

Fig. 3 (a) Immobilization of enzymes inside an elliptical pore and on a planar surface (reproduced with permission from Olloqui-Sariego et al. [53], copyright 2020, Elsevier B.V.); (b) efficient electron transfer between P450 BM3 and NH_2-DMSNs due to the electrostatic effect-induced oriented immobilization (reproduced with permission from Dai et al. [55], copyright 2020, Springer-Verlag GmbH Germany, part of Springer Nature); (c) schemes of Trametes versicolor Lac (from *T. versicolor*) (left), in which the hydrophobic binding pocket acts as the binding site of the enzyme substrate, and the electron transfer from the CNT surface toward Lac (reproduced with permission from Elouarzaki et al. [56], copyright 2018, Springer Nature); (d) DET from GOx (from *Aspergillus niger*) to electrode surface through Pt nanoclusters: i) inside-out enzymatically synthesized electrode, and ii) outside-in electrochemically synthesized electrode (reproduced with permission from Trifonov et al. [63], copyright 2019, The Royal Society of Chemistry).

nanomaterials composed of carbon materials uniformly decorated with fine inorganic nanoparticles. Small-sized noble metal nanoclusters or nanoparticles (usually a few nanometers) [61], such as platinum (Pt) and gold (Au), can function as electron relays or electrical nanoplugs to facilitate electron transfer between the active centers of enzymes and conductive support [62]. For example, Trifonov et al. [63] realized DFT between GOx (from *Aspergillus niger*) and carbon support by implanting Pt nanoclusters in between. They also studied the impact of different synthesis methods of Pt nanoclusters. It was found that the inside-out enzymatically implanting of Pt nanoclusters results in a shorter distance between the FAD cofactor and Pt nanoclusters, leading to more efficient electron transfer compared to the outside-in method (Fig. 3(d)).

In general, the DET-favored enzyme attachment onto electrode can be realized through physical bonding (such as electrostatic, hydrophobic, π–π interactions), chemical bonding (such as amide, imine, maleimide, click chemistry), and host–guest interactions [64]. Appropriate surface modification of nanomaterials is important to regulate these interactions and achieve efficient electron transfer.

3.3 Catalyzing electrochemical reactions

Enzymes are known for their high activity and selectivity in the oxidation of biomolecules and oxygen, but they suffer from poor stability and conductivity. To address these limitations, inorganic nanomaterials have been explored to perform catalytic functions or improve the catalytic performance of enzymes [22,65,66]. Noble metal nanomaterials, known for their excellent catalytic activities in a wide range of electrochemical reactions, have been extensively explored in conventional fuel cells. However, these systems typically require highly acidic or alkaline conditions for noble metal catalysts to exhibit their full potential. However, it would be a challenge to develop highly active noble metal nanocatalysts used for EBFCs as the near neutral conditions are undesired. Pt- and Au-based nanomaterials are commonly used non-enzymatic catalysts for hybrid EBFCs. They can be used to catalyze both cathodic [47,48,67,68] and anodic [44,69] reactions, but they are mostly used for cathodic ORR, whereas anodic Pt- and Au-based catalysts are less reported. There are examples of their application in EBFCs. For instance, a hyaluronate-conjugated Au@Pt (HA-Au@Pt) was synthesized to enhance the ORR performance of EBFCs (Fig. 4(a)) [70], where the hyaluronate improved the biocompatibility and durability of the bimetallic catalyst. In another study, a cathode decorated with Pt-Co nanoparticles exhibited excellent stability and high activity toward ORR. As a result, the assembled EBFC exhibited an unprecedented power density of 3.5 mW/cm^2 in human sweat, which is the highest in untreated human body fluids [67].

Although noble metals possess high intrinsic catalytic activity, the high cost limits their wide application. Therefore, low-cost, noble metal-free carbon nanomaterials have been explored as electrocatalysts for the cathodic reaction of EBFCs. Carbon nanomaterials doped with heteroatoms, such as Fe, Co and N, have demonstrated promising ORR activity and are commonly used as cathodic catalysts for hybrid EBFCs [71–73]. For example, by mimicking the structure of cytochrome c oxidase (CcO), Zhang et al. [74] developed a bionic FeN$_5$ single-atom catalyst, which was used for ORR in a glucose/O$_2$ EBFC (Fig. 4(b)). Interestingly, recently studies have shown that heteroatom-doped carbon nanomaterials can also assist in the oxidation of glucose [75]. In one such study, GOx from *Aspergillus niger* was combined with Fe- and N-doped CNTs (Fe-N/CNTs) and used as the anode for a BFC. In this system, glucose is first oxidized by GOx to generates hydrogen peroxide (H_2O_2), which is then further catalytically oxidized by Fe-N/CNTs [71].

In addition to the commonly reported noble metal- and carbon-based nanomaterials, recent studies have revealed that hydroxyapatite (HAP, $Ca_{10}(PO_4)_6(OH)_2$) nanodots

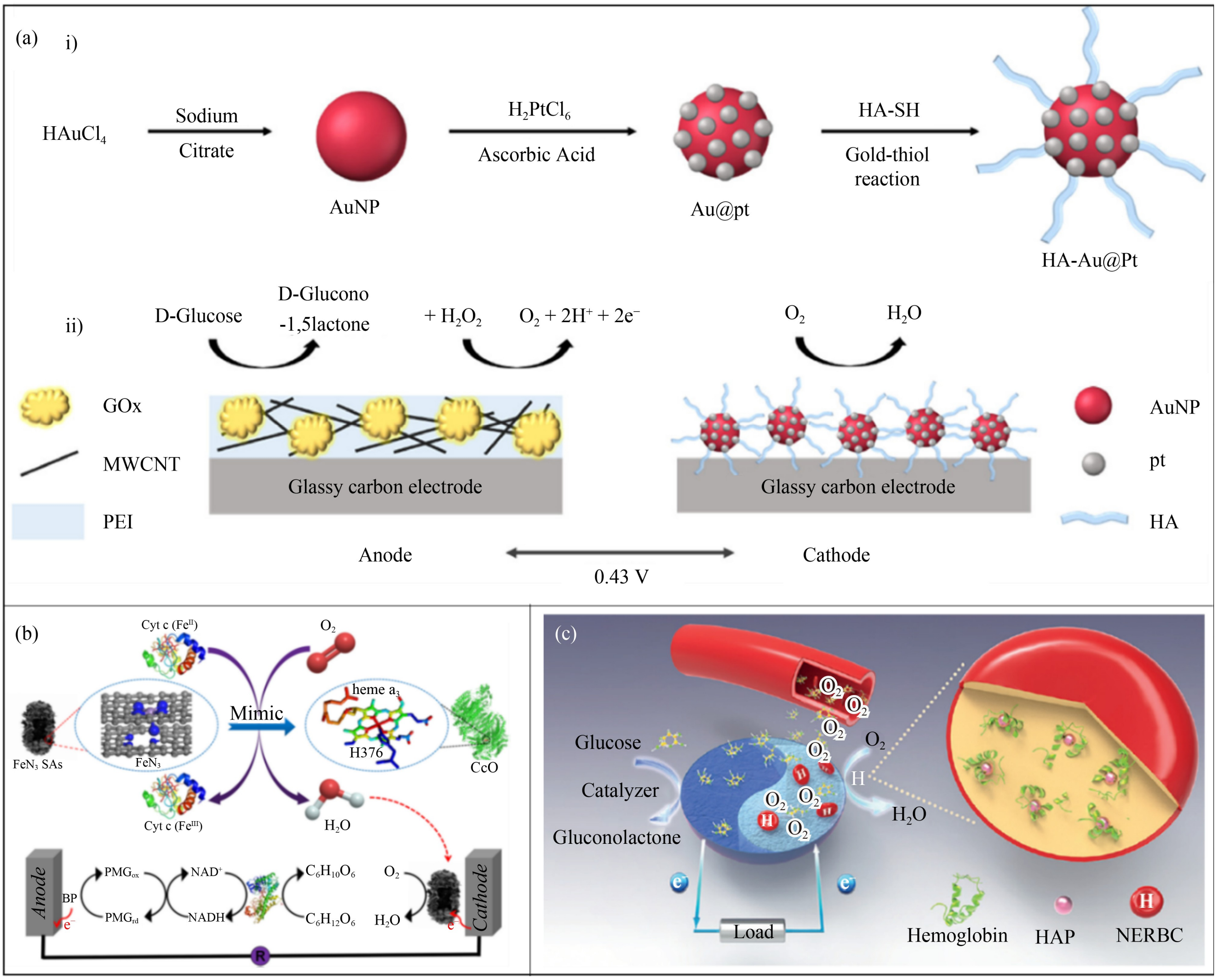

Fig. 4 (a) Scheme illustrating the synthesis process of hyaluronate-Au@Pt nanoparticles and their use as the cathode in a GOx-O$_2$ EBFC (reproduced with permission from Han et al. [70], copyright 2022, American Chemical Society); (b) schematic showing the structure of bionic CcO-like FeN$_5$ single-atom catalyst and its use in glucose-O$_2$ EBFC for cathodic ORR (reproduced with permission from Zhang et al. [74], copyright 2021, Elsevier); (c) EBFC using HAP-embedded RBCs as the cathode biocatalyst (reproduced with permission from Escalona-Villalpando et al. [76], copyright 2019, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

can enhance the catalytic ORR through interaction between –OH groups in HAP and the hemoglobin in red blood cells (RBCs) (Fig. 4(c)) [76]. The performance of a membraneless glucose BFC using HAP-embedded RBCs as the cathode was found to be 1.5 times higher than that using native RBCs, demonstrating the potential application of HAP nanodots in implantable EBFCs.

4 Applications of EBFCs in bioelectronics

4.1 Power sources

The primary function of EBFCs is to supply power to bioelectronic devices. For wearable bioelectronics, flexibility or even stretchability is often essential. Materials commonly used for flexible electrodes include carbon paper [77], carbon cloth [19,78,79], buckypaper [5], cellulose fiber sheet [80], graphene sheet [81], polyimide film [8,82–84], and others. Since a single EBFC usually generates a very low cell voltage at peak power density (several hundred millivolts), flexible EBFC arrays with high power output have been developed for wearable electronics [85]. In addition to flexibility, microfluidic design plays a crucial role in wearable bioelectronics to ensure continuous, high-speed flow [8,78,86–89]. The performance of EBFCs can be significantly affected by solvent evaporation and/or biofuel depletion in the hydrostatic electrolyte. For example, Wang et al. [78] introduced a moisture management fabric (MMF) layer between the carbon cloth-based cathode and anode (Fig. 5(a)), which is composed of polyester and acts as a biofuel transport medium to ensure sufficient chemical reactions. The MMF, with purposely designed cross-sectional geometries, enables rapid absorption and evaporation of water, facilitating high-speed and continuous water flow for a sufficient fuel supply.

To impart stretchability to the electrodes, stretchable polymers are usually required. For example, a stretchable electrode can be created by depositing MWCNTs onto a pre-stretched rubber fiber, followed by depositing an enzyme layer and re-wrapping it with a second layer of MWCNTs (Fig. 5(b)) [90]. The re-wrapping procedure enhances the stability of the biofuel cell, allowing it to stretch up to 100% for 100 cycles without degradation in power density. Wang et al. [91] developed a flexible BFC tubing, denoted as iezTube, which can serve as the first example of a fully stand-alone wearable BFC. This flexible BFC tube was fabricated by integrating a monolayer fluffy plasma (FP)-based microfluidic module, which allows for efficient sampling and utilization of biofuel liquids as well as a stable contact between the biofuel fluids and the wearable BFC for real-time bioenergy generation. An air-breathing module, consisting of a breathable, waterproof, non-woven tape-covered air-breathing module over a centrifuge tube, provides a continuous supply of oxidant (Fig. 5(c)). This system exhibited exceptionally stable and unintermittent power generation, even with insufficiently filled biofuel fluids and typical movement patterns.

In addition to the aforementioned materials and biocatalyst challenges, the performance of EBFCs is also highly dependent on the operation conditions, such as the concentration of oxygen and/or fuels and the pH of electrolyte. Particularly, low O_2 concentration in body fluid is a major limiting factor for the power output of implanted EBFCs. To address this issue, oxygen-rich electrodes [92] and gas diffusion electrodes [93] have been designed to improve the oxygen supply. Nevertheless, the power output of single EBFCs remains generally very low (tens to hundreds of $\mu W\ cm^{-2}$), either due to the intrinsic properties or the surrounding environment, significantly limiting their application to low-power devices.

Moreover, certain implantable electronic devices, such as pacemakers, neurostimulators, and defibrillators, require pulsed energy, making supercapacitors crucial components. To extend the applications of EBFCs, they can be connected to energy storage devices or boost converters [67,94,95]. This strategy has been applied to complex integrated systems powered by EBFCs, such as implantable brain simulators with wireless communication [95], an integrated e-textile microgrid system that combines EBFC with a triboelectric generator for energy harvesting [96], and e-skin capable of multiplexed, wireless sensing (Fig. 5(d)) [67]. The perspiration-powered e-skin shown in Fig. 5(d) consists of a lactate biofuel cell array for electricity generation, connected to a booster convertor for signal potential amplification. This output signal charges a capacitor, powering biosensors and other electronic components. While this strategy ensures steady and high power supply, it also adds extra components to the system. In some cases, such as contact lenses [97], miniature and compact devices are needed, making biofuel cell/supercapacitor hybrids desirable. These hybrids enable the BFC to store and release charges [98].

Such hybrid devices, also known as self-charging biosupercapacitor or supercapacitive BFC, differ from conventional supercapacitors that require external power sources. Lee et al. [99] reported hybrid energy devices that combine supercapacitors with EBFCs, showcasing their outstanding power density as energy storage devices. These hybrid energy devices show self-charging characteristics, maintaining open-circuit voltage and discharging even without fuel supply after charging. The charge-storing components in self-charging biosupercapacitors are based on the supercapacitive features of nanomaterials in EBFCs, which possess good conductivity, mesoporous structures, and large surface area, which are also beneficial attributes for

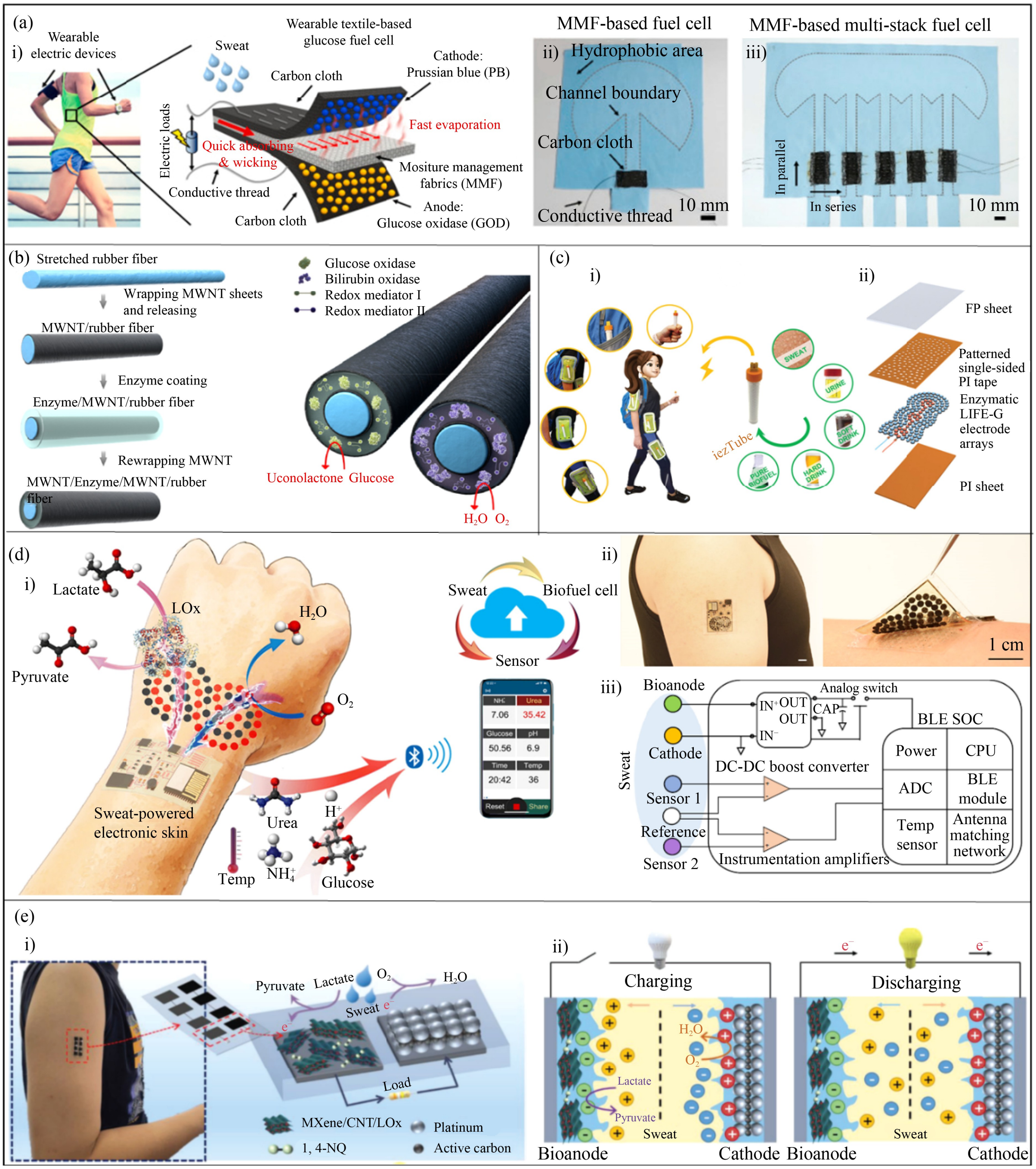

Fig. 5 (a) i) Schematic illustration of the wearable textile-based glucose BFC that incorporates moisture management fabrics (MMF) into sportswear; ii) and iii) photographs showing the fabricated MMF-based single and multi-stack fuel cell, respectively (reproduced with permission from Wang et al. [78], copyright 2020, Elsevier B.V.); (b) schematic illustrations showing the fabrication process and structure of the stretchable fiber-based biofuel cell (reproduced with permission from Sim et al. [90], copyright 2018, American Chemical Society); (c) i) schematic of the i*ez*Tube able to be worn on different body parts and utilizing various easily accessible green biofuel fluids for bio-energy harvesting; ii) schematic of different layers of BFC and microfluidic modules (reproduced with permission from Wang et al. [91], copyright 2022, Wiley-VCH GmbH); (d) i) schematic of an EBFC-powered e-skin capable of multiplexed biosensing and wireless Bluetooth communication with a mobile; ii) photos showing the e-skin on a human arm; iii) schematic diagram showing the components of the e-skin system (reproduced with permission from Yu et al. [67], copyright 2020, American Association for the Advancement of Science); (e) i) schematic illustrations of the skin-mountable capacitive BFC; ii) schematic illustrations of charging and discharging mechanism of the device (reproduced with permission from Guan et al. [101], copyright 2023, Wiley-VCH GmbH).

supercapacitors [92,100]. For example, Guan et al. [101] designed a dual-functional hierarchical anode composed of MXene, single-walled CNTs, and lactate oxidase. The 3D hierarchical structure provides a superior microenvironment for the accommodation of enzymes, enabling energy harvest from sweat while efficiently storing energy via electrical double-layer capacitance (Fig. 5(e)).

Currently, the maximum power density of most EBFCs ranges from tens of μW cm^{-2} to several $\mathrm{mW/cm^2}$, and their performance can last only a few weeks (Table 1). Therefore, there is considerable room for improving the performance of EBFCs as power sources.

4.2 Self-powered devices

Initially, EBFCs were considered suitable power sources for sensors due to their low power output [7]. In 2001, Katz et al. [103] were the first to propose utilizing EBFCs as self-powered biosensors, where they used the output voltage of the EBFC as a transduction signal that correlates with the concentration of the analyte.

4.2.1 Self-powered biosensor

The self-powered sensors most extensively researched for wearable and implantable applications are glucose and lactate biosensors, which mainly rely on the linear correlation between substrate concentration and the electrochemical signals (such as voltage, current, and power density) generated by the EBFCs [36,37,104–110]. In recent years, studies on EBFC-based biosensors have expanded from single EBFC to integrated and wireless sensing platforms capable of multiple functions and easy-to-read outputs. For instance, a wearable self-powered biosensor system was incorporated into diapers to measure glucose levels in the urine of diabetic patients [111]. The EBFC-based biosensor is connected to an energy storage device to power an LED, with the flashing frequency of LED positively correlated with the power generated by the EBFC. This allows for easy evaluation of glucose concentration in the urine of the patient.

As another representative example, Rogers's group designed a battery-free and skin-compatible sensing system that integrated EBFCs, colorimetric reagents, and near-field communication (NFC) technology into a microfluidic platform. The EBFCs are capable of extracting energy from sweat and function as glucose and lactate sensors, while the colorimetric reagents can detect the concentration of chloride, pH, and sweat rate/loss. Additionally, the NFC enables wireless communications between the sensing module and a smartphone (Fig. 6(a)) [83]. Inspired by biofuel cells, Nithianandam et al. developed flexible, miniaturized biosensors with dimensions as small as 50 μm × 50 μm to monitor glutamate synaptically released glutamate in the nervous system (Fig. 6(b)), which has the potential to serve as an effective tool for diagnosis of neurological disorders [112].

Recently, an innovative self-powered biosensor composed of 4 electrodes was reported, where two enzymatic electrodes are connected with two capacitive electrodes (Fig. 6(c)) [10]. The supercapacitor can charge itself using D-fructose as a fuel source, and the accumulated charge can be utilized to detect the concentration of D-fructose. Compared to a standard EBFC ($0.058 \pm 0.004\ \mathrm{mW/(cm^2 \cdot mM)}$), the sensitivity of the supercapacitive BFC shows a significant enhancement of up to 65 times in pulse mode ($3.82 \pm 0.01\ \mathrm{mW/(cm^2 \cdot mM)}$, charging time = 70 min) and approximately 6.5 times in continuous operation ($0.372 \pm 0.011\ \mathrm{mW/(cm^2 \cdot mM)}$).

Table 1 Performance of some recently reported EBFCs

Bioanode	Biocathode	OCV	Max power density	Stability	Ref.
LOx/porous carbon/CC	BODx/porous carbon/CC	0.8 V	4.3 $\mathrm{mW/cm^2}$ under O_2 2.0 $\mathrm{mW/cm^2}$ under air	–	Shitanda et al. [24]
$Ti_3C_2T_x$/MWCNT/Au nanoparticles	$ZnCo_2$@NCNT	–	61.34 μW	–	Sun et al. [46]
Pt/Au wire	BODx/Au/buckypaper	0.735 V	46.31 $\mathrm{\mu W/cm^2}$	–	Hasan et al. [44]
GOx/ITO NPs/Au-MWCNT fibers	Pt/Au-MWCNT fibers	1.0 V	10.4 $\mathrm{mW/cm^2}$	≈ 49% retention after 60 days of continuous operation	Kang et al. [50]
GOx/PEI/MWCNT	Hyaluronate-Au@Pt	0.50 V	15.8 $\mathrm{\mu W/cm^2}$	–	Han et al. [70]
GDH/PMG/BP/ITO	FeN_5 SAs/ITO	0.40 ± 0.01 V	149.2 ± 4.0 $\mathrm{\mu W/cm^2}$	91% retention after 20000 s test	Zhang et al. [74]
Pt/Au alloy/PET membrane	Graphene/GCE	0.42 V	0.32 $\mathrm{mW/cm^2}$	–	Chu et al. [69]
GOx/$Cu_3(PO_4)_2$/ACF	Catalase/$Cu_3(PO_4)_2$/ACF	~0.17 V	50 μW /$\mathrm{cm^2}$	80% retention after one month of operation	Vo et al. [29]
GOx/CC	Hemoglobin/hydroxyapatite/CC	0.636 V	21.11 $\mathrm{mW/cm^2}$	–	Chen et al. [76]
LOx/rGO/CNT/h-Ni	Pt-Co/CNT	~0.6 V	3.5 $\mathrm{mW/cm^2}$ (human sweat)	Stable during a 60-h continuous operation	Yu et al. [67]
(GOx-SFAD-PAM)/cMWCNTs/GCE	BODx/MWCNTs/GCE	0.9 V	1011.21 $\mathrm{\mu W/cm^2}$	94% Pmax retaining after storage for 15 days	Huang et al. [102]
GOx/rGO/CNT/Ni foam	LOx/rGO/CNT/Ni foam	0.89 V	0.9 $\mathrm{mW/cm^2}$	Stable during a 120-h continuous operation.	Li et al. [57]

Notes: LOx: lactate oxidase; CC: carbon cloth; BODx: bilirubin oxidase; GOx: glucose oxidase; GCE: glassy carbon electrode; MWCNT: multi-wall carbon nanotubes; rGO: reduced graphene oxide; ITO: indium tin oxide; SAs: single atoms; ACF: activated carbon fibers.

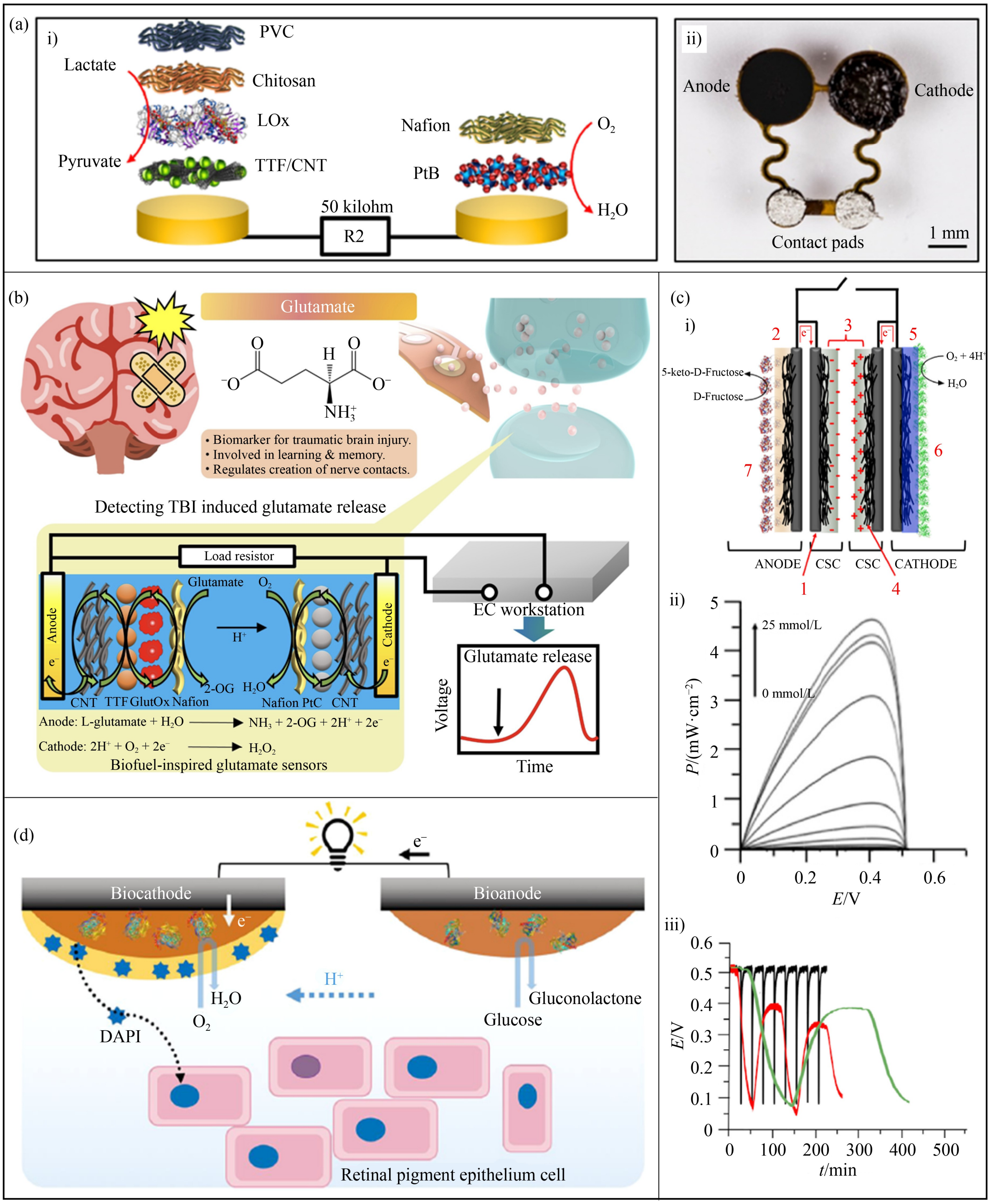

Fig. 6 (a) i) Schematic illustration of the layer makeup of the BFC-based lactate sensor; ii) photograph of the lactate sensor (reproduced with permission from Bandodkar et al. [83], copyright 2019, American Association for the Advancement of Science); (b) schematic illustration of a BFC-based glutamate biosensor (reproduced with permission from Nithianandam et al. [112], copyright 2023, Wiley-VCH GmbH); (c) scheme showing the charging process of an enzyme-based biosupercapacitor (CSC: charge storing components); ii) power output profiles of the enzyme-based biosupercapacitor when working as a self-powered biosensor in a buffer solution containing different concentrations of D-Fructose; iii) charge/discharge curve of the enzyme-based biosupercapacitor (reproduced with permission from Bollella et al. [10], copyright 2020, Elsevier B.V.); (d) scheme showing the self-powered release of DAPI in a cell culture medium (reproduced with permission from Xiao et al. [121], copyright 2020, American Chemical Society).

These various biosensors utilize a sensing principle based on the effect of fuel concentration on output power. Besides, there are other EBFC-based biosensors that are based on principles such as change in enzyme loading amount [59,113], diffusion of fuels to the enzyme [114], and the amount of electron acceptor [115–117], which usually require biorecognition agents for biomolecule detection. For example, according to the principle of controlling anodic enzyme loading, Zhu and colleagues developed a self-powered biosensor aimed at detecting cancer-related mRNAs (miR-21, and miR-141), in which the anode was modified with capture DNAs [59]. In the presence of target mRNAs, they hybridize with the capture DNAs, and the target mRNAs further hybridize with receptor probes conjugated with enzymes. A higher concentration of target RNAs leads to a higher enzyme loading and higher power output. In another example, Wang et al. fabricated an anode by anchoring ssDNA onto SiO_2@gold nanoparticle surface (SiO_2@AuNPs–aptamer) [114]. In the absence of a target protein, steric hindrance prevents glucose from diffusing toward glucose oxidase, resulting in a low open circuit voltage (OCV). Upon adding the target protein, it is recognized by the aptamer, causing the SiO_2@AuNPs–aptamer to detach from the bioanode, allowing glucose to reach the active sites of glucose oxidase, significantly enhancing the OCV. Moreover, controlling the release of electron acceptors such as $[Fe(CN)_6]^{3-}$, is commonly used for designing EBFC-based biosensors [115,118]. For example, Li et al. confined the cathodic electron acceptor $[Fe(CN)_6]^{3-}$ in porous mesoporous silica nanoparticles with a positive charge, capped with biogate DNAs. In the presence of target miRNA, hybridization with the biogate DNAs triggers the controlled release of $[Fe(CN)_6]^{3-}$, leading to a significant rise in OCV.

4.2.2 Self-powered molecule release

In contrast to the intensively studied self-powered biosensing, the self-powered molecule release based on EBFCs is still in its early stages [119,120]. Recently, Xiao et al. [121] eveloped an EBFC for *in situ* release of drugs in cell culture media, demonstrating the potential for self-powered drug release system for implantable devices. The cathode of the EBFC was modified by an additional layer of conductive polymer, into which drug molecules were incorporated via electrostatic interaction. In the presence of glucose and O_2, and under close-circuit conditions, the redox reactions can alter the electrostatic interactions in the polymer-drug layer, causing the drug molecules to be released (Fig. 6(d)).

In an interesting study, Bollella et al. [122] developed an EBFC that functions as a self-powered molecule release system controlled by chemical signals processed through Boolean logic gates. This work highlights the potential of EBFCs in the emerging field of self-powered biocomputing.

5 Summary and perspective

In summary, significant progress has been made in improving the power density and stability of EBFCs by employing nanomaterials to enhance enzyme immobilization/stabilization, improve direct electron transfer efficiency, and facilitate catalytic reactions. In addition to the well-known carbon nanomaterials, noble metal, and metal oxide nanoparticles, emerging nanomaterials such as MOFs, TMDs, and mxenes, have also demonstrated their promising potential in the aforementioned functions. At the device level, EBFCs, as the power sources, have been integrated into complex systems for wearable and implantable electronics. Recently, supercapacitive EBFCs, combining the features of both fuel cells and supercapacitors, have attracted increasing interest for devices that require pulse energy supply. Beyond power supply, EBFCs can also function in self-powered sensing and drug release. Self-powered sensors have been widely explored for detecting various substances, including body metabolites and biomolecules. In contrast, self-powered drug release systems are still in its infancy and require more efforts.

Although the substantial improvements in the performance of EBFCs, several challenges remain that hinder their commercialization. First, the power density and stability are still not fully satisfactory. Strategies like proper surface functionalization of nanomaterials and the sophisticated design of hierarchically porous structures could be effective for immobilization and stabilization of enzymes. Furthermore, machine learning has emerged as a powerful tool for designing new materials and predicting their properties, which is expected to play an important role in the future design of high-performance nanomaterials with enzyme-like catalytic properties. Beyond materials selection, the fabrication method can also affect enzyme immobilization. For example, *in situ* encapsulation of enzymes during the formation of MOFs has shown better power output and stability compared to post-formation encapsulation [37]. Therefore, innovations in the preparation method of enzymatic electrodes also deserve further research.

To address the short lifespan of EBFCs, developing low-cost, replaceable enzymatic catalysts could be potential solution for extending the lifetime of wearable electronics. For instance, incorporating magnetic nanoparticles into electrodes could offer a convenient method for assembling and exchanging enzymatic biocatalysts [123]. For implantable EBFCs, the biocompatibility of nanomaterials must be systematically evaluated, and any potential leakage of nanoparticles, which could cause chronic health issues, should also be carefully considered.

As textile-based EBFCs for wearable electronics gain attention, washable electronics have recently sparked research interest. For example, supercapacitors printed on T-shirts maintain electrochemical activity upon exposure to laundry [124], yet no reports of washable EBFCs have been found. Furthermore, most reported EBFC-based sensors detect only a single metabolite or biomolecule, but multiplexed sensing would be crucial for fabricating more compact, miniature bioelectronics and could improve the accuracy and reliability of health monitoring or disease diagnosis. Up to date, developing multiplexed self-powered sensors still remains a challenge.

In conclusion, EBFCs are expected to play an irreplaceable role in wearable and implantable bioelectronics for healthcare, and the various challenges in this field present numerous opportunities. The application of nanomaterials in EBFCs hold great promise, with efficiency and durability expected to improve significantly through the continuous optimization of their structure, function, and interaction with enzymes. Future research will focus on developing multifunctional nanomaterials, improving environmental adaptability, and enhancing charge transfer efficiency to accelerate the maturation and commercialization of this green energy technology [125].

Competing Interests The authors declare that they have no competing interests.

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