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## Non-enzymatic sweat-based glucose sensors: progress, difficulties, and prospects

 P. Kirubha,<sup>a</sup> B. S. Sreeja<sup>a</sup> and S. Fouziya Sulthana \*<sup>b</sup>

Effective diabetes therapy requires continuous glucose monitoring (CGM), yet existing blood-based measurement techniques are invasive and pose discomfort during prolonged use. Sweat's non-invasive collection, real-time secretion and compatibility with skin-conforming wearables have made it a promising substitute biofluid. Compared to enzyme-based platforms, non-enzymatic glucose sensors have attracted a lot of attention recently because of their greater stability, extended operating lifetime, and resistance to environmental deterioration. With an emphasis on the electrocatalytic mechanisms, novel materials, flexible substrates, and microfluidic integration techniques that allow precise detection of ultralow glucose concentrations in human sweat, this review provides a thorough overview of developments in non-enzymatic, sweat-based glucose sensing. Sensitivity, selectivity, and wearing compatibility are examined in connection to important material types, including as transition metals, metal oxides/hydroxides, noble metals, carbon nanomaterials, and hybrid composites. Along with commercially available sweat-sensing prototypes, recent advances in wireless communication, flexible electronics, and microfluidic sweat harvesting are discussed. The study critically analyses major barriers to clinical translation, such as sweat-rate variability, interference from electroactive species, sensor fouling, and challenges associated with accurate calibration. Lastly, future perspectives highlight the necessity of large-scale human validation, uniform calibration models, AI-based data processing, and multiparameter sensing. The purpose of this review is to direct the creation of wearable platforms for non-invasive glucose monitoring that are next-generation, dependable, and customized.

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### 1. Introduction

As of 2021, around 537 million people globally have diabetes mellitus; by 2030, that figure is expected to rise to 643 million (International Diabetes Federation, 2021).<sup>1</sup> Diabetes mellitus is a rapidly expanding global health burden. In order to avoid long-term consequences such as neuropathy, cardiovascular disorders, and retinopathy, continuous glucose monitoring (CGM) is crucial.<sup>2</sup> Conventional glucose detection predominantly relies on invasive, blood-based methods, which are often linked to patient discomfort, heightened infection risk, and decreased adherence, particularly among paediatric and geriatric populations.<sup>3</sup> These limitations have driven increasing research interest in the development of non-invasive and minimally invasive techniques for continuous, real-time glucose monitoring.

Sweat has become a very appealing medium among other alternative biofluids, such as saliva, tears, and interstitial fluid, because of its non-invasive collection, copious secretion during activity, and compatibility with wearable technology.<sup>4–6</sup> Sweat is a great option for near-real-time monitoring when combined with suitable calibration algorithms, even though the concentration of sweat glucose is usually lower (10–200  $\mu\text{M}$ ) than blood glucose (3–8  $\text{mM}$ ) according to several studies.<sup>7,8</sup> Additionally, regulated sweat sampling, decreased evaporation, and enhanced sensor–skin interface stability have been made possible by developments in microfluidics and flexible electronics, greatly improving data dependability.<sup>9,10</sup> Conventional glucose biosensors primarily rely on enzymatic components, specifically glucose dehydrogenase (GDH) and glucose oxidase (GOx). Several inherent limitations are associated with enzymatic systems, including enzyme degradation, limited thermal stability, pH sensitivity, and high production costs, despite their high sensitivity and specificity.<sup>11,12</sup> Their long-term application in wearable technology is limited by these restrictions. Because of this, non-enzymatic glucose sensors have been increasingly popular in recent years.<sup>13–15</sup> These sensors rely on the direct electrocatalytic oxidation of glucose on nanostructured

<sup>a</sup> Department of Biomedical Engineering, College of Engineering Guindy, Anna University, Chennai 600025, India

<sup>b</sup> Department of Mechatronics Engineering, College of Engineering and Technology, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu 603203, India. E-mail: [fouziyas@srmist.edu.in](mailto:fouziyas@srmist.edu.in)



materials. Transition metals (Cu, Ni, Co), their corresponding oxides/hydroxides, noble metals (Au, Pt, Pd), conductive polymers (PANI, PEDOT), and carbon-based nanomaterials (CNTs, graphene, rGO, NGO) are just a few of the many catalytic materials that have been designed to improve mechanical flexibility, electron transfer, and surface area for wearable applications.<sup>16–20</sup>

In addition to high selectivity against interfering species such as lactate, uric acid, and ascorbic acid, recent studies have shown remarkable analytical performance with detection limits down to the micromolar level for sweat glucose.<sup>21–23</sup> Additionally, the incorporation of these sensors into wearable patches, wristbands, and epidermal electronics has been made easier by flexible substrates such as PDMS, PET, polyimide, and textiles.<sup>24,25</sup> Sweat-rate variability, individual physiological variations, the instability of some metal-oxide catalysts, and the requirement for trustworthy sweat-blood glucose correlation models are among the major obstacles that still exist despite these developments.<sup>26,27</sup>

Over the past ten years, non-enzymatic sweat glucose sensing has advanced dramatically, mostly because of developments in wearable electronics, microfluidic sweat management, and nanostructured catalysts. Carbon-based composites, stretchable skin-conforming platforms, and metal/metal-oxide electrocatalysts are important advancements that allow real-time, interference-free glucose

monitoring in trace sweat volumes.<sup>28–32</sup> To enable real-time glucose monitoring during physical activity, the authors in ref. 29 developed a stretchable MnO<sub>2</sub>/GO-based patch integrated with microfluidic sweat-routing channels, which exhibited excellent electrocatalytic performance, mechanical flexibility, and resistance to sweat-induced fouling. In a related approach, the authors in ref. 30 demonstrated an AuNP-decorated laser-induced graphene (LIG) epidermal biosensor capable of detecting glucose at parts-per-billion levels, with high flexibility and efficient electron-transfer kinetics, making it suitable for both athletic and clinical monitoring applications. Additionally, bimetallic metal oxide catalysts, such as Cu–Ni and Ni–Co nanostructures, have been reported to exhibit synergistic catalytic effects that significantly enhance sweat glucose oxidation while simultaneously minimizing interference from common analytes, including Na<sup>+</sup>, lactate, and urea.<sup>28,31</sup> Several commercial prototypes of sweat-based glucose sensors have been reported in the literature. A graphene-based epidermal e-skin wearable patch employs low-power electrochemical sensing modules integrated with microfluidic channels to enable wireless, continuous monitoring of sweat glucose levels.<sup>33</sup> In another example, a disposable microfluidic sweat sticker developed at the University of California, San Diego (UCSD) quantifies glucose using less than 3 μL of sweat through the use of capillary burst valves and screen-printed

**Table 1** Non-enzymatic sweat glucose sensors in the literature

Material/system	Detection range	LOD	Sensitivity	Key advantages	Ref.
Cu–Ni bimetallic oxide nanoflakes	1–500 μM	0.3 μM	2400 μA mM <sup>-1</sup> cm <sup>-2</sup>	Stable for 10 days; high selectivity vs. lactate & uric acid	28
Au nanosheets	0.1–300 μM	1.3 μM	10.89 μA mM <sup>-1</sup> cm <sup>-2</sup>	Bendable/stretchable; stable after 200 cycles	29
MXene-based flexible electrodes	0.5–400 μM	0.05 μM	3500 μA mM <sup>-1</sup> cm <sup>-2</sup>	Ultra-fast electron transfer; long-term reliability	32
2Au nanoflowers in carbon cloth	0.008–4 mM	5.18 μM	63.9 μA mM <sup>-1</sup> cm <sup>-2</sup>	High selectivity, wide linear interval, and fast response recovery characteristics	36
BP-gCN heterostructure	—	—	1.1 μA mM <sup>-1</sup> cm <sup>-2</sup>	Stability testing showed 84% peak current retention over 50 cycles.	37
Thermal-transfer printed flexible electrodes	0.01 mM to 1.0 mM	0.003 mM	—	Exhibits good stability	38
GLAD-fabricated NiO nanostructures	0.5 μM–9 mM	7 nM	4400 μA mM <sup>-1</sup> cm <sup>-2</sup>	Showed desirable selectivity with negligible response to common interferents (uric acid, dopamine, serotonin, ascorbic acid) and was not poisoned by high sodium chloride amounts	39
Pt/Ti <sub>3</sub> C <sub>2</sub> MXene electrode	0.003–1.5 mM	29.15 μmol L <sup>-1</sup>	100.85 μA mM <sup>-1</sup> cm <sup>-2</sup>	Demonstrates wearable integration	40
GDYO/AuNPs electrode	4.11 μM	—	168 μA mM <sup>-1</sup> cm <sup>-2</sup>	Exhibits superior selectivity with the coexistence of four common substances in human sweat and maintains glucose detection capabilities under neutral or slightly acidic conditions	41
AuNP-functionalized AMWCNTs on flexible SPEs	50–600 μM	3.2 μM	—	It maintains functionality after 500 bending repetitions at 180° and shows exceptional stability and repeatability	21
Flower-like Au nanostructures on graphene oxide	160 μM to 5 mM	123 μM	474 617 μA mM <sup>-1</sup> cm <sup>-2</sup>	Good selectivity against lactic acid, uric acid, NaCl, dopamine, ascorbic acid, and inorganic salts	42
Co <sub>1.22-x</sub> Ni <sub>x</sub> O <sub>4</sub> /f-MWCNTs	0.001–8.0 mM	20 μM	1190.9 and 1312.1 μA mM <sup>-1</sup> cm <sup>-2</sup>	Shows good long-term stability and excellent selectivity	43
Ni–Co MOF/Ag/rGO/PU fiber	0 μM–0.66 mM	—	425.9 μA mM <sup>-1</sup> cm <sup>-2</sup>	Extremely high stretching and bending stability, high selectivity, and long-time storage stability	44



electrodes, offering a low-cost, skin-safe, and rapid analysis time of under two minutes.<sup>34</sup> Additionally, a flexible Ni/NiO thin-film smart patch has been commercialized to provide real-time glucose analytics for health and athletic performance monitoring, featuring low power consumption, long-term operational stability, and Bluetooth connectivity.<sup>35</sup>

Table 1 lists the essential components, sensitivity, stability, LOD, and detection range of non-enzymatic sweat glucose sensors over a decade.

Thus, to direct future innovation, a thorough grasp of materials, fabrication techniques, electrochemical tactics, and wearable integration approaches is crucial.

With a focus on material selection, sensor design, performance parameters, and practical issues, this paper offers a thorough overview of current developments in non-enzymatic, sweat-based glucose sensing. It also identifies potential lines of inquiry for developing non-invasive glucose monitoring systems that are precise, reliable, and clinically significant. Major scientific databases, such as Web of Science, Scopus, PubMed, and Google Scholar, provided the material used in this review. The terms “non-enzymatic glucose sensor”, “sweat glucose”, “wearable glucose monitoring”, and “electrochemical sweat sensor” were utilized. Only peer-reviewed papers on non-enzymatic glucose detection in sweat or wearable platforms that were published between 2010 and 2025 were included. Studies using blood-only monitoring or enzymatic glucose sensors were not included unless they were essential for comparison. Key factors such as sensitivity, detection limit, linear range, selectivity toward common sweat interferents, operational stability, compatibility with near-neutral pH settings, and suitability for wearable applications are used in this evaluation to assess sensor performance.

## 2. Sweat as a biofluid for glucose monitoring

Sweat's simplicity of collection, constant secretion, and compatibility with wearable sensing devices have made it one of the most promising non-invasive biofluids for real-time glucose monitoring.<sup>45</sup> Sweat from human eccrine sweat glands, which are found all over the body, contains a variety of indicators, such as glucose, lactate, sodium, potassium, chloride, urea, amino acids, and metabolites linked to stress.<sup>46,47</sup> Even though sweat's glucose concentration (usually 10–200  $\mu\text{M}$ ) is much lower than that of blood (3–8 mM), a number of studies have shown that sweat glucose correlates with blood glucose trends, making it a useful medium for non-invasive glucose estimation when the right calibration models are used.<sup>48,49</sup> Although the exact mechanisms are still being studied, transdermal diffusion across the epidermal layers and active secretions from eccrine glands are the primary ways that glucose is transported from blood to sweat.<sup>50</sup> Nevertheless, there are a number of difficulties with sweat-based sensing, such as low

analyte concentration, fluctuating sweat rate, evaporation loss, and contamination from skin surface residues.<sup>46</sup>

Microfluidic channels, hydrogel interfaces, and flexible substrates are used in contemporary wearable technology to get around these restrictions, allowing for stable sampling, less evaporation, and enhanced sensor–skin contact.<sup>51,52</sup> Additionally, ambient factors, food, exercise intensity, and level of hydration can all affect the composition of sweat.<sup>53</sup> Because of this, the creation of trustworthy non-enzymatic sweat glucose sensors depends not only on sophisticated electrode materials, but also on integrated fluid-handling systems and flexible calibration techniques. Despite these challenges, tremendous advancements in thin-film materials and sweat-collection microfluidics have fueled the creation of next-generation sweat-based glucose monitors intended for continuous, painless, wearable medical diagnostics. Table 2 gives the amount of glucose concentration pertinent to wearable non-enzymatic glucose sensing.

Sweat glucose tracks blood glucose trends, according to a number of research; however, it's crucial to distinguish between trend correlation and absolute concentration prediction. Because of physiological transport hurdles and dilution effects, sweat glucose levels frequently track changes in blood glucose levels but do not offer quantitatively similar readings. Furthermore, due to diffusion through interstitial fluid and production by eccrine glands, there is usually a temporal lag between changes in blood glucose and corresponding fluctuations in sweat glucose. Individual physiology, sweat rate, and measurement conditions all affect reported lag times. Because sweat composition is impacted by a variety of parameters, including hydration state, physical activity, food, metabolic rate, and environmental circumstances, interpretation is further complicated by significant inter- and intra-subject variability. As a result, creating universal calibration models is challenging. While genuine calibration-free monitoring is still a research topic, the majority of wearable systems currently in use rely on customized calibration techniques, ranging from one-time calibration to frequent recalibration. Therefore, compared to accurate quantitative assessment of blood glucose concentration, contemporary sweat glucose sensors are typically more reliable for trend tracking and event detection—such as spotting hyperglycemic or hypoglycemic excursions. To achieve clinically reliable non-invasive glucose monitoring, more developments in sensor precision, physiological modelling, and multimodal sensing techniques are needed.

**Table 2** Glucose concentration pertinent to wearable non-enzymatic glucose sensing

Human biofluid	Glucose concentration
Blood	3–8 mM
Tears	0.05–0.5 mM
Saliva	0.008–0.2 mM
Sweat	10–200 $\mu\text{M}$



### 3. Working mechanism of non-enzymatic glucose sensing

Non-enzymatic glucose sensing relies on the direct electrocatalytic oxidation of glucose at the surface of functional electrode materials, eliminating the need for biological recognition elements. In such systems, transition-metal-based catalysts facilitate electron transfer through redox reactions, enabling stable and continuous glucose detection under physiological conditions.

#### 3.1 Principle of electrocatalytic glucose oxidation

Unlike enzymatic sensors, which depend on biological catalysts, non-enzymatic glucose sensing is based on the direct electrocatalytic oxidation of glucose at an active electrode surface. Through surface redox reactions of catalytically active metal or metal-oxide sites, glucose oxidation occurs in alkaline environments. The general response is typically stated as:



In many transition-metal-based glucose sensors, reversible redox couples like Ni(OH)<sub>2</sub>/NiOOH (Ni<sup>2+</sup>/Ni<sup>3+</sup>) and Cu<sup>2+</sup>/Cu<sup>3+</sup> are essential to electrocatalysis. The lower-valent metal hydroxide is electrochemically converted to a high-valent oxyhydroxide (such as NiOOH or CuOOH) during anodic polarization in alkaline media, which serves as the actual active species for glucose oxidation. Through a surface-mediated process involving hydroxyl groups, this oxyhydroxide layer oxidizes adsorbed glucose to gluconolactone while concurrently reducing the metal center back to its initial state, completing a catalytic redox cycle. Catalytic activity is maintained by continuous electrochemical regeneration of the active species during subsequent potential cycling, which also produces electrons that are gathered at the electrode as an anodic current proportional to glucose concentration.<sup>12,54,103,105</sup>

To improve glucose adsorption and reaction kinetics in alkaline settings, base-metal and metal-oxide electrodes make use of multivalent redox chemistry, extensive surface hydroxylation, and a high density of accessible active sites. On the other hand, glucose oxidation is mostly catalysed by noble metals like Au, Pt, and Pd *via* direct adsorption and dehydrogenation routes involving surface-adsorbed hydroxyl molecules. Although these materials usually function at lower overpotentials, long-term stability may be limited by surface poisoning caused by firmly bonded intermediates.<sup>15,104</sup>

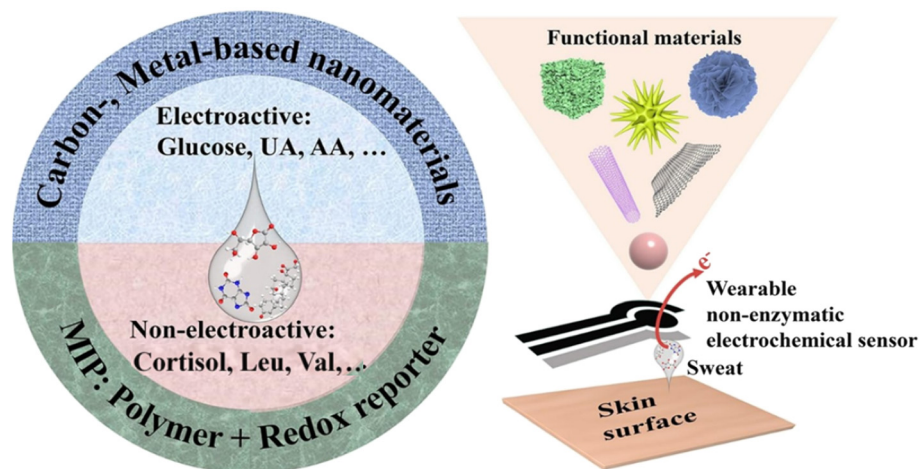
The conductivity of the supporting material and the electrode surface architecture, which includes defect density, exposed crystal facets, and porosity, has a significant impact on the electrocatalytic performance of non-enzymatic glucose sensors. The operating potential and overall sensitivity are influenced by these structural characteristics, which also control mass-transport behavior, charge-transfer efficiency,

and glucose adsorption strength. When compared to enzyme-based sensors, non-enzymatic electrodes often have longer operational lives and better chemical and thermal stability. However, these benefits are frequently accompanied by problems including surface fouling, interference from coexisting electroactive species, and restricted selectivity, which call for sensible surface engineering and material design for dependable sensing performance.<sup>12,103</sup> Wearable sweat sensors function in physiological settings that are almost neutral, despite the fact that the electrocatalytic oxidation of glucose is typically characterized in extremely alkaline media. Because human sweat usually has a pH between 4.5 and 7, reaction kinetics can be much slower than those seen in alkaline electrolytes. However, electrochemical production of hydroxide ions during anodic polarization may cause local interfacial alkalization at the electrode surface, resulting in a microenvironment that promotes glucose oxidation even in the absence of an alkaline bulk solution. Sweat's complex makeup, which includes proteins, metabolites, and salts, can also affect catalytic activity and adsorption behavior. For wearable applications, materials that can effectively oxidize glucose without the need for external alkaline support are therefore very desirable. For practical sweat-based glucose monitoring, noble metals, defect-engineered metal oxides, and hybrid nanocomposites have shown encouraging performance under near-neutral circumstances.

#### 3.2 Electrochemical detection techniques

The electrochemical detection performance of wearable non-enzymatic glucose sensors is greatly influenced by the selection of active electrode materials, detection methods, and electrode arrangement. The various materials utilized in electrochemical wearable sweat glucose sensors are schematically presented in Fig. 1. The choice of electrode material directly affects sensitivity, working potential, limit of detection (LOD), selectivity, and mechanical compatibility with flexible substrates.<sup>55,56</sup> Ni, Cu, Co, and Mn are the frequent transition metals and metal oxides because of their redox-active centers, which enable efficient electrocatalytic glucose oxidation when structured into nanoscale morphologies such as nanosheets, nanowires, or hollow structures. Although many metal oxides have low intrinsic electrical conductivity, they are selected for their chemical stability under sweat-like conditions and are often coupled with conductive substrates to enhance charge transfer.<sup>54,57</sup> Because of their better conductivity and lower oxidation overpotentials, which enable direct glucose oxidation through dehydrogenation routes, noble metals like Pt, Pd, and Au are utilized as independent catalysts or in modest loadings to enhance base-metal systems while lowering material costs.<sup>15</sup> The fast development of wearable electrochemical sensing technologies has been highlighted by recent developments that show how hierarchical nanostructured catalysts can be integrated with flexible platforms to reach ultralow detection





**Fig. 1** Sweat components and related materials utilized in wearable electrochemical glucose sensors that are non-enzymatic. Transition-metal oxides, noble metal catalysts, carbon-based supports, and hybrid composites are important sensing components. Reproduced from ref. 94 distributed under the terms and conditions of the Creative Commons Attribution-NonCommercial 3.0 Unported Licence. <http://creativecommons.org/licenses/by-nc/4.0/>.

limits and stable operation under mechanical deformation.<sup>106–108</sup>

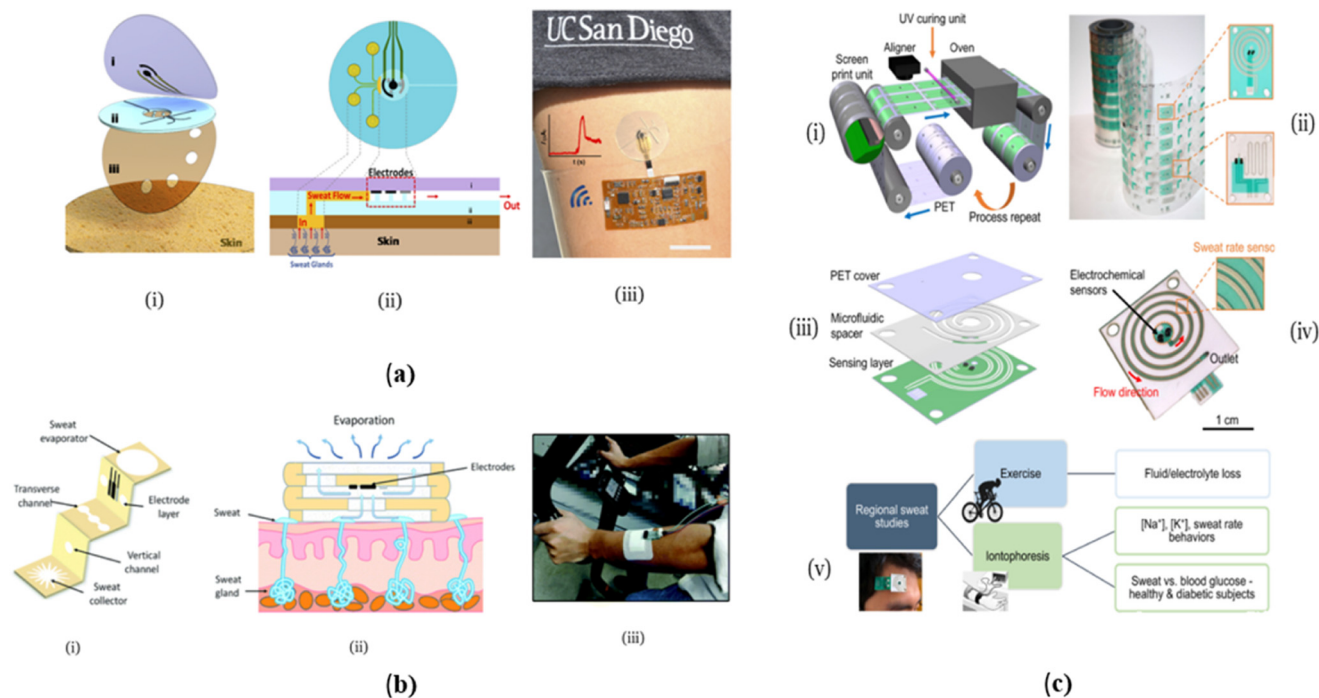
Because of their high electroactive surface area, enhanced electron-transport capability, and mechanical flexibility, carbon-based materials and conductive polymers such as graphene, reduced graphene oxide (rGO), nitrogen-doped graphene oxide (NGO), carbon nanotubes (CNTs), and polyaniline (PANI) greatly improve wearable sensor platforms. In particular, by adding more defect sites and altering surface chemistry, heteroatom-doped graphene materials improve metal-support interactions and facilitate faster electron transfer kinetics.<sup>58,59</sup> Hybrid composite systems, which combine metal or metal-oxide catalysts with carbonaceous or polymeric supports, are widely employed to achieve the best possible balance between catalytic activity, conductivity, and mechanical robustness. Synergistic approaches like alloying, heterojunction creation, and defect engineering are frequently employed to reduce overpotential, enhance anti-fouling behavior, and increase sensor performance in real sweat settings.<sup>57,60</sup> Multifunctional hybrid systems that combine catalytic nanomaterials with stretchy substrates and microfluidic sweat management layers have been further proven in recent reports.<sup>106,107</sup>

This allows for dependable real-time monitoring under dynamic physiological settings. Electrochemical detection techniques are essential for both practical glucose measurement and sensor characterisation. Cyclic voltammetry (CV) is commonly used to study redox behavior, catalytic activity, oxidation and reduction peaks, and surface modification effects. Another advantage of CV measurements is the ability to determine the optimal working potential for subsequent amperometric detection.<sup>61</sup> Because of its great sensitivity, fast reaction time, and straightforward signal processing, amperometry is the most widely used technique for continuous glucose monitoring in wearable devices. It typically involves delivering a constant potential and

recording current as a function of time. In amperometric sensing, the measured current is calibrated to directly correlate with the glucose concentration of the target biofluid.<sup>62</sup> A common method for confirming successful electrode alteration and evaluating the effectiveness of anti-fouling coatings is electrochemical impedance spectroscopy (EIS). It provides complementary information about interfacial characteristics such as diffusion behavior, double-layer capacitance, and charge-transfer resistance.<sup>63</sup> In order to increase accuracy and account for motion artifacts and sweat variability, modern wearable platforms also use multiplexed sensing architectures and sophisticated signal-processing algorithms.<sup>108</sup> Examples of integrated three-electrode configurations and electrochemical detection techniques, including cyclic voltammetry, amperometry, and electrochemical impedance spectroscopy for glucose sensing in microfluidic wearable electrochemical sensor systems for sweat analysis, are shown in Fig. 2.

Accurate electrochemical sensing in wearable devices also requires a suitable electrode layout with working, counter, and reference electrodes. The material composition and nanostructure of the working electrode, which serves as the active sensing interface where glucose oxidation occurs, largely determine the sensitivity, LOD, and selectivity.<sup>60</sup> The counter electrode, which completes the electrical circuit and must have sufficient conductivity and surface area to prevent polarization effects during continuous operation, is often made of platinum or flexible carbon-based inks in wearable versions. A stable potential reference is provided by the reference electrode, which is usually based on Ag/AgCl chemistry. Wearable and sweat-based sensors frequently use quasi- or pseudo-reference electrodes, although careful design is required to minimize potential drift under sweat conditions high in chloride.<sup>27</sup> Generally speaking, wearable electrochemical sensor design must also consider biocompatibility, mechanical flexibility and stretchability,





**Fig. 2** Examples of integrated three-electrode setups and electrochemical detection methods, such as cyclic voltammetry, amperometry, and electrochemical impedance spectroscopy for glucose sensing in microfluidic wearable electrochemical sensor devices for sweat analysis. (a) Microfluidic device design: (i) representation of layered configuration; (ii) microfluidic device; (iii) microfluidic device integrated with wireless conformal electronics on skin. Reproduced from ref. 48 with permission from the ACS Publications, 2017. (b) Schematic of the 3D paper-based microfluidic electrochemical integrated device: (i) layered structure of the device; (ii) schematic diagram of the 3D-PMED applied on the human skin; (iii) on-body measurement of glucose in sweat. Reproduced from ref. 64 with permission from the Royal Society of Chemistry, 2019. (c) Schematic of sweat sensing patches: (i) screen printing of wearable patch; (ii) optical image of sensing electrode patterns; (iii) layered view; (iv) assembled biosensing patch; (v) patch as wearable. Reproduced from ref. 65 with permission from the AAAS, 2019.

resistance to protein adsorption and chloride interference, and long-term electrical stability under bending and sweating conditions.<sup>9,60</sup> In order to preserve signal stability during extended on-body operation, recent research additionally highlight encapsulation techniques, skin-conformal structures, and integrated wireless modules.<sup>106–108</sup>

## 4. Materials used in non-enzymatic sweat-based sensors

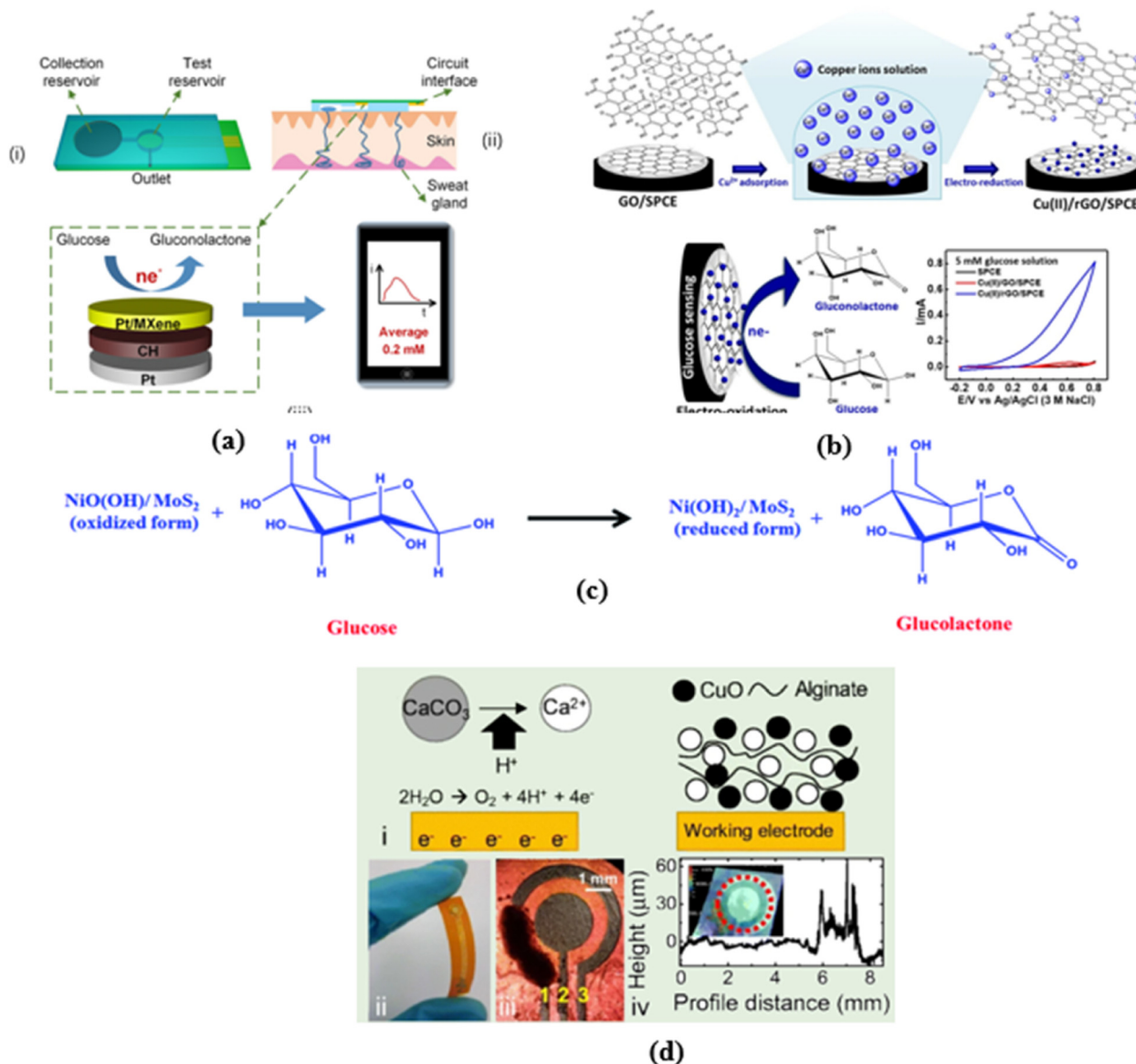
### 4.1 Metal oxides/hydroxides

Because of their active redox centres that enable direct glucose oxidation, transition and noble metal hydroxides and oxides often in nanostructured forms act as the main electrocatalysts in non-enzymatic glucose sensors. There are two primary mechanisms that have been suggested: the incipient hydrous oxide/adatom mediator (IHOAM) pathway, which involves surface-generated metal hydroxide or oxide species mediating electron transfer and lowering the oxidation overpotential, and the chemisorption pathway, which involves glucose adsorption and dehydrogenation at metal active sites. Metal oxides have difficulties despite their promise for catalysis, including surface poisoning, interference by sweat metabolites (lactate, uric acid, and ascorbic acid), and stability issues when operating repeatedly

or in different pH environments.<sup>66</sup> Because of their reversible redox couples (e.g.,  $\text{Ni}^{2+}/\text{Ni}^{3+}$ ,  $\text{Cu}^{2+}/\text{Cu}^{3+}$ ,  $\text{Mn}^{3+}/\text{Mn}^{2+}$ ), which offer plenty of catalytic sites for glucose oxidation, especially under alkaline conditions, metal oxides like NiO, CuO,  $\text{MnO}_2$ , and  $\text{Co}_3\text{O}_4$  are frequently used in wearable non-enzymatic glucose sensors. A crucial tactic to improve sensor performance is morphological engineering, which includes nanorods, porous architectures, and facet-controlled crystals. In complex biofluids, surface changes such as heteroatom doping, high-surface-area porous or hollow structures, and conductive composite creation enhance electron transport, active site density, and selectivity.

Because of a high density of exposed  $\text{Ni}^{2+}/\text{Ni}^{3+}$  redox sites, NiO nanorods on 2D supports (Fig. 3a) show higher catalytic currents. Because of their porous shape, which promotes glucose passage and reduces interference,  $\text{MnO}_2$  nanorods (Fig. 3b) exhibit enhanced electron transfer and selectivity. In contrast, electrodes based on nanoparticles exhibit narrower linear ranges and lower currents, highlighting the significance of nanostructural control. These illustrations show how sensor metrics, like lower limits of detection (LOD) and greater linear dynamic ranges, are strongly correlated with structural design, making them appropriate for continuous monitoring in sweat-based wearable platforms. However, further optimization through composite formation





**Fig. 3** Metal oxides used in non-enzymatic sweat based sensors (a): (i) flexible non-enzymatic continuous glucose detection sensor; (ii) cross sectional view; (iii) oxidation reaction with glucose on Pt/Mxene. Reproduced from ref. 32 with permission from the ACS Publications, 2023. (b) Fabrication of a non-enzymatic glucose sensor based on Cu(II)/rGO. Reproduced from ref. 68 with permission from the Springer Nature, 2021. (c) Electrocatalytic oxidation mechanism of glucose at NiO/MOS<sub>2</sub>/GCE. Reproduced from ref. 60 with permission from the Springer Nature, 2016 (d) Electrodeposition with CuO nanopowder: (i) scheme of the electrodeposition mechanism; (ii) flexible chip formed after electrodeposition; (iii) working, counter and reference electrodes; (iv) film thickness. Reproduced from ref. 69 with permission from the Springer Nature, 2020.

or selective surface functionalization is still necessary to achieve accurate and repeatable glucose measurements in practical applications, as metal oxide electrodes are susceptible to interference from co-existing sweat metabolites and environmental factors.<sup>67</sup>

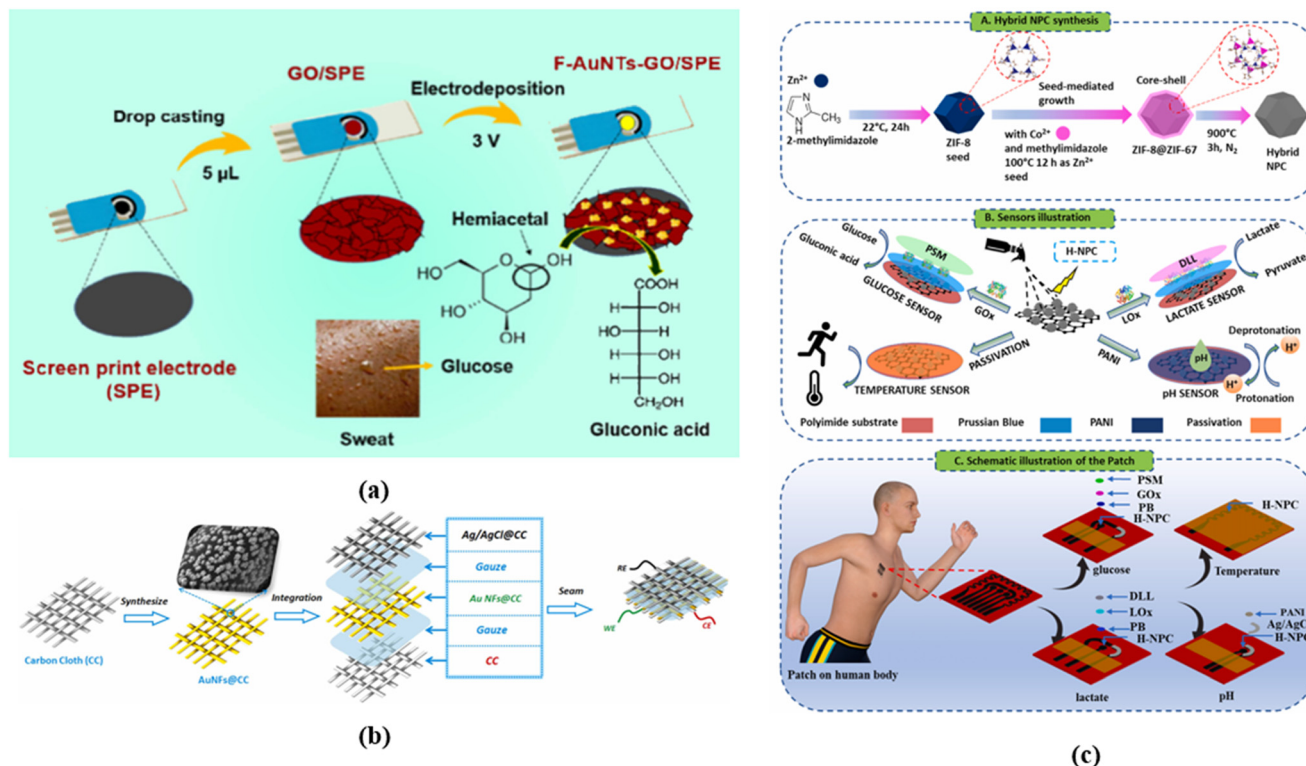
#### 4.2 Carbon-based nanomaterials

In wearable sweat sensors, carbon scaffolds serve as both conductive substrates and structural platforms that regulate mass transport, catalyst dispersion, electron-transfer paths, and mechanical flexibility. Representative topologies that

address various trade-offs between manufacturing simplicity, mechanical robustness, and electrochemical performance are shown in Fig. 4, ranging from planar printable electrodes to textile substrates and tailored porous carbons.<sup>70,71</sup>

A graphene oxide (GO) layer applied to a screen-printed electrode (SPE) in Fig. 4a offers a significant electroactive surface area and an abundance of oxygen-containing functional groups that improve hydrophilicity and encourage consistent anchoring of metallic nanostructures. While maintaining compatibility with scalable printing methods, this hybrid design enhances charge transfer and lowers the working potential needed for non-enzymatic glucose





**Fig. 4** Carbon based materials in sweat based sensors. (a) Illustration of flower like nanostructures and graphene oxide on the graphite sheet screen printed electrode. Reproduced from ref. 42 with permission from the ACS Publications, 2022. (b) Illustration of the flexible sensitive device based on AuNF@CC. Reproduced from ref. 36 with permission from the Elsevier, 2023. (c) Proposed biosensor: (A) hybridized nanoporous carbon synthesis procedure; (B) sensor illustration; (C) schematic illustration of the patch. Reproduced from ref. 71 with permission from the Elsevier, 2023.

oxidation.<sup>70,72</sup> In contrast to planar electrodes in Fig. 4b, carbon cloth (CC) was used as a three-dimensional textile current collector, providing better mechanical durability, flexibility, and breathability. Catalytic nanostructure decoration creates a porous conductive network that boosts active site density and promotes effective sweat diffusion, allowing for steady sensor performance under bending or stretching circumstances typical of on-body operation.<sup>71,73</sup>

Engineered porous carbon compounds, such as nitrogen-doped porous carbons made from metal-organic framework precursors, are shown in Fig. 4c. These materials have a high specific surface area, a lot of defect sites, and good electrical conductivity. These features enable effective charge transport and high catalyst loading on flexible substrates while preserving mechanical compliance.<sup>72,74</sup>

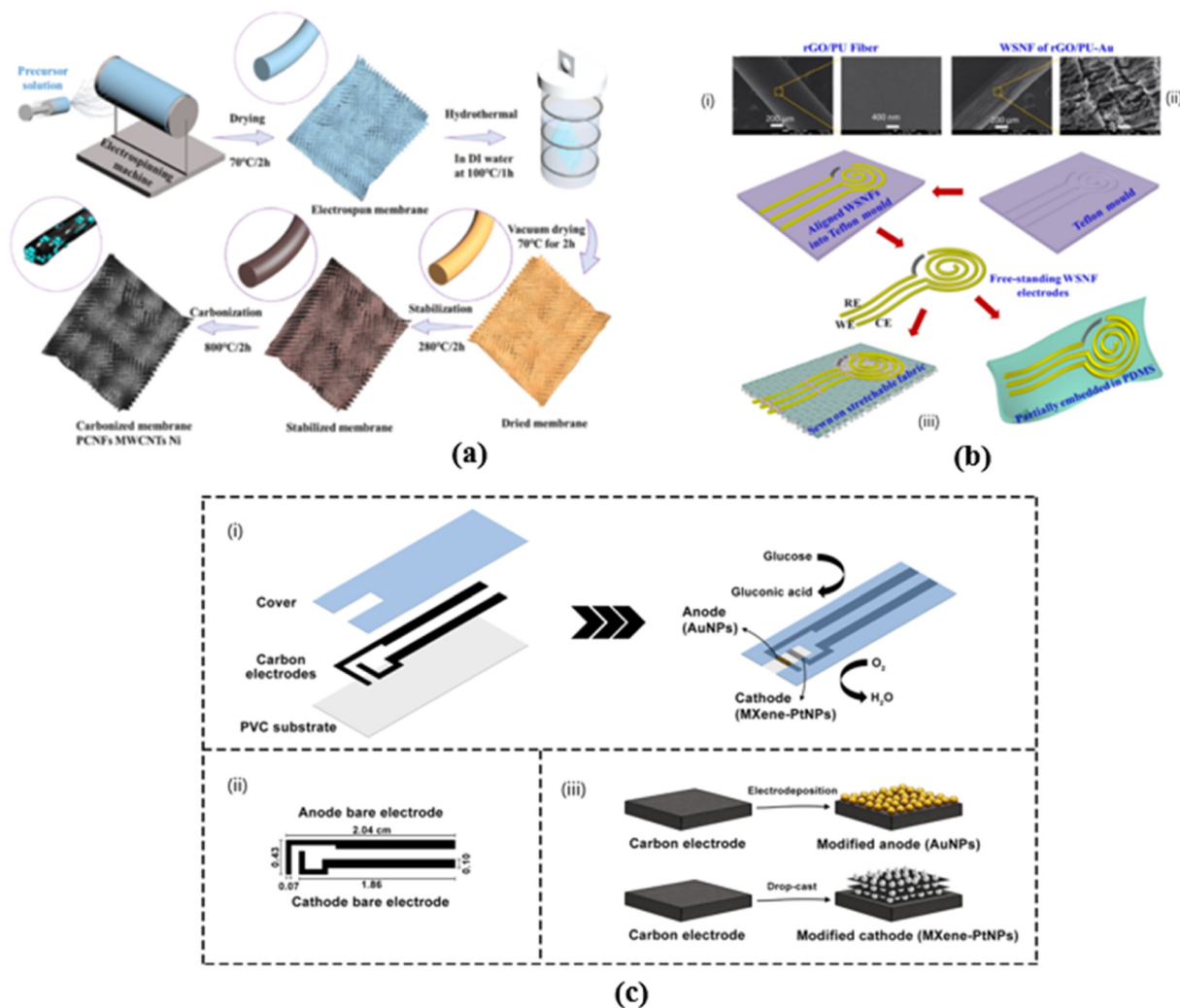
All things considered, the architectures depicted in Fig. 4 indicate a transition from platforms for quick prototyping to mechanically durable fabrics and highly tailored porous carbons. Carbon materials always function mainly as structural and conductive scaffolds, and the required electrocatalytic activity is provided by hybridization with metal or metal-oxide catalysts. These carbon-based hybrid systems are ideal for continuous, non-enzymatic sweat glucose monitoring in wearable devices because they usually function at lower potentials with improved sensitivity and flexibility.<sup>70–74</sup>

### 4.3 Hybrid/composite materials

Because several components serve complimentary purposes, hybrid material systems are especially useful for non-enzymatic wearable glucose monitoring. While embedded metal or metal-oxide nanostructures serve as the main electrocatalytic sites for glucose oxidation, a conductive and mechanically compliant matrix (such as carbon nanomaterials, polymers, or MXenes) offers effective charge transport, flexibility, and resistance to fouling. Three typical hybrid design approaches that address different on-body sensing requirements are shown in Fig. 5.

A porous carbon nanofiber membrane containing Ni nanoparticles and multi-walled carbon nanotubes (MWCNTs) is shown in Fig. 5a. This membrane is produced *via* electrospinning, hydrothermal treatment, stabilization, and high-temperature carbonization. Sweat diffusion and quick electron transport are made possible by the interconnected nanofiber network, which creates a freestanding, binder-free scaffold with a large electroactive surface area and open porosity. This architecture is appropriate for flexible textile electrodes because the embedded Ni and MWCNTs offer a large number of catalytic sites and the carbon framework guarantees structural stability and electrical continuity. A stretchable fiber-based electrode made of reduced graphene oxide/polyurethane (rGO/PU) fibers shaped into wavy





**Fig. 5** Hybrid/composite materials in sweat based sensors. (a) Fabrication process and morphology of the composite. Reproduced from ref. 74 with permission from the Elsevier, 2025. (b) Characteristics of the sweat glucose sensor: (i) field emission scanning electron microscopy images of the rGO/PU nanocomposite fiber; (ii) FE-SEM images of rGO/PU/AU; (iii) fabrication process of the free standing stretchable nanohybrid electrode. Reproduced from ref. 75 with permission from the ACS Publications, 2019. (c) Illustration, components and fabrication process of the glucose biofuel cell: (i) assembly of the flexible strip sensor; (ii) dimension of electrodes; (iii) electrodeposition of AuNPs on the anode and drop casting of MXene-PtNPs hybrid onto the cathode. Reproduced from ref. 76 with permission from the Elsevier, 2026.

serpentine nanofibers and adorned with Au nanoparticles is shown in Fig. 5b. The Au nanoparticles improve catalytic activity, the rGO/PU core adds conductivity and elasticity, and the serpentine design allows for mechanical deformation by dispersing strain along the waveform. Free-standing electrodes that retain electrochemical performance with repetitive stretching are made possible by such designs, which is crucial for wearable applications that are subjected to body motion. A planar hybrid device with asymmetric catalytic modification made of screen-printed carbon electrodes on a flexible PVC substrate is depicted in Fig. 5c. While an MXene–Pt nanoparticle composite is placed on the cathode to aid in oxygen reduction, Au nanoparticles are coated on the anode to encourage glucose oxidation. This arrangement creates a fuel-cell-style sensing device that can provide a signal on its own. While Pt nanoparticles lower the

overpotential for oxygen reduction, allowing operation at low applied bias, the MXene component offers excellent conductivity and hydrophilicity for effective catalyst dispersion.

Together, these examples show how hybrid architectures can be modified to satisfy various mechanical and electrochemical requirements: planar asymmetric electrodes for low-power or self-powered operation, stretchable serpentine fibres for strain tolerance, and porous nanofiber scaffolds for high catalyst loading and permeability. The simultaneous accomplishment of the mechanical durability and sensitivity needed to detect low glucose concentrations in sweat is made possible by such synergistic designs.<sup>72</sup> Additional benefits of non-enzymatic wearable sensors based on hybrid materials include quick response times, enhanced operational stability when compared to enzyme-based



systems, compatibility with flexible substrates, and dynamic ranges that may be adjusted by materials engineering. However, there are still a number of obstacles to overcome, including establishing accurate calibration between sweat and blood glucose levels, minimizing interference from other electroactive species, maintaining long-term stability on skin, and achieving detection limits in the low-micromolar range typical of sweat glucose. Selective protective membranes, on-device calibration techniques, and multi-layer hybrid architectures suited for real-world conditions are some of the current attempts to address these problems.<sup>73</sup>

## 5. Sweat-based wearable platforms

From basic flexible patches, sweat-based wearable biosensing devices have developed into highly integrated platforms that can continuously monitor physiological indicators in real time. The viability of non-invasive sweat analysis was demonstrated early on, and more recent advancements focus on the multifunctional integration of flexible substrates, effective sweat management, and wireless electronics into small epidermal devices that are appropriate for everyday use and tracking athletic performance.<sup>77,78</sup> The transition from proof-of-concept sensors to wearable systems with therapeutic relevance is reflected in this trajectory.

### 5.1 Stretchable and adaptable substrates

In order to guarantee conformal skin contact, mechanical durability, and user comfort, stretchable and flexible substrates are essential. Because of their softness, elasticity, and biocompatibility, materials like polydimethylsiloxane (PDMS), thermoplastic polyurethane (TPU), polyethylene terephthalate (PET), and textiles are frequently used. Because of its exceptional flexibility, optical transparency, and capacity to construct microfluidic structures, PDMS has a particularly significant impact as a foundational material for epidermal devices. Strong skin conformability reduces motion-induced artifacts and makes sweat collection dependable.<sup>79–81</sup> Nevertheless, PDMS by itself has drawbacks, such as poor mechanical strength and restricted scalability. As a result, wearable sensor production on a wide scale has drawn interest in TPU and PET films. While PET offers mechanical robustness, dimensional stability, and compatibility with roll-to-roll production processes, TPU offers higher elasticity and tear resistance.<sup>82</sup> Another development is the direct integration of sensors into clothing without sacrificing comfort or breathability thanks to textile-based substrates. Functional textiles incorporating conductive fibers, carbon-based inks, or screen-printed electrodes (SPEs) allow distributed sensing across large skin areas and support long-term wearability.<sup>83,84</sup> For both enzymatic and non-enzymatic electrochemical detection, SPEs printed on PDMS, PET, or fabric substrates offer affordable and repeatable platforms.

Many reported sensors rely on alkaline conditions, which are different from physiological sweat settings, despite

tremendous progress. Signal instability, sweat component interference, and individual variability continue to be significant obstacles to practical deployment. Future studies should concentrate on long-term stability, neutral-pH operation, and calibration techniques for practical wearable applications.

### 5.2 Microfluidic transport and collection of sweat

Because uncontrolled accumulation or evaporation can result in false results, efficient sweat treatment is crucial for dependable sensor performance. Early wearable sensors frequently experienced contamination and uneven sample delivery. Sweat collection, routing, and storage were made possible by the incorporation of microfluidic designs, which represented a significant advancement. Passive transport techniques like capillary action, wicking *via* porous materials, or hydrogel-assisted pumping are commonly used in microfluidic systems made with screen printing, laser patterning, or soft lithography. These methods provide constant fluid flow to the sensor contact without requiring external power.<sup>85,86</sup> In order to ensure a continual supply of analytes like glucose, lactate, electrolytes, and metabolites for real-time monitoring, hydrophilic microchannels facilitate quick absorption and steady sweat transfer.<sup>87</sup> More advanced designs include time-resolved sampling capabilities, micro reservoirs, and multiplexed channels, which allow for the simultaneous detection of several biomarkers and temporary storage for later analysis. Another significant advancement is hybrid colorimetric–electrochemical platforms, which combine the great sensitivity of electrochemical sensing with color changes that are easily understood. These dual-mode systems improve diagnostic accessibility and dependability, especially for non-specialist users.<sup>88</sup> However, as microfluidic complexity increases, manufacturing difficulties and individual differences in sweat flow may arise, underscoring the necessity for optimal designs.

### 5.3 Combining wireless communication with flexible electronics

The integration of electronics for signal processing, data transmission, and user interaction is the last crucial element of sweat-based wearable platforms. To enable ongoing remote monitoring, modern devices use wireless communication technologies including Bluetooth low energy (BLE), near-field communication (NFC), radio-frequency modules, and Internet-of-Things connectivity.<sup>89–91</sup> Sensor patches incorporate NFC antennae, stretchable interconnects, flexible printed circuit boards, and ultrathin power sources to sustain functioning under repetitive mechanical deformation.<sup>92</sup> Real-time visualization, tailored feedback, and integration with telemedicine platforms or sports performance dashboards are all offered by smartphone-based readout systems.<sup>93,94</sup> Because they reduce device thickness, do away with heavy batteries, and enhance long-term wearing comfort, NFC-powered or battery-free devices are especially appealing.



Smart patches, textile-integrated sensors, and soft electronic skins that can simultaneously detect several indicators, including glucose, hydration state, pH, electrolytes, and stress-related hormones, are examples of recent innovations. A major advance toward thorough, non-invasive physiological monitoring in practical contexts is represented by these multipurpose devices.<sup>95,96</sup>

Collectively, the convergence of soft materials, microfluidic engineering, and wireless electronics has transformed sweat-based biosensors into sophisticated wearable platforms. While substantial progress has been achieved, challenges such as inter-individual variability in sweat composition, long-term sensor stability, and correlation with blood biomarkers must still be addressed before widespread clinical adoption. Continued advances in materials science, device engineering, and system integration are expected to further enhance the reliability and practical utility of wearable biochemical monitoring technologies.

## 6. Challenges and limitations in non-enzymatic sweat glucose sensing

Despite quick progress, a number of scientific, technical, and translational obstacles still prevent non-enzymatic sweat glucose sensing from being widely used.

### 6.1 The physiological association between blood sugar and sweat

Sweat and blood glucose have a weak and complicated interaction, which is a key constraint. Sweat glucose concentrations are orders of magnitude lower than blood glucose levels, usually falling between 10 and 200  $\mu\text{M}$ .<sup>21</sup> Furthermore, time delays and non-linear correlations result from the passive diffusion and active glandular mechanisms that carry glucose from blood to sweat. This link is further complicated by individual variations in metabolism, skin permeability, sweat gland density, and hydration.<sup>101</sup> As a result, it is still challenging to develop a universal conversion model between sweat and blood glucose, which restricts the clinical interpretability of sweat-based measurements.

### 6.2 Individual variability and sensor calibration

Strong calibration techniques that are customized to each person's physiology are necessary for accurate quantification. The majority of wearable devices rely on customized calibration procedures and regular recalibration because sweat composition changes greatly between people and even within the same person over time.<sup>102</sup> To increase accuracy, multi-parameter correction techniques that take temperature, electrolyte content, pH, and sweat rate into account have been suggested. Large-scale commercialization and regular clinical use are hampered by these constraints, which also make the system more complicated and less convenient for users.

### 6.3 Coexisting electroactive species' interference

Lactate, uric acid, creatinine, ascorbic acid, urea, and other ions are among the many electroactive substances found in sweat that can oxidize at potentials similar to those of glucose.<sup>97</sup> Selectivity may be compromised and erroneous signals may be produced by such overlapping electrochemical reactions. To reduce interference, techniques like ion-selective coatings, permselective membranes, and metal-oxide heterostructures have been used. Although somewhat useful, these layers may hinder analyte diffusion and lower sensor sensitivity, resulting in a trade-off between response time and selectivity.

### 6.4 Variability in the sweat rate and sampling difficulties

External temperature, physical activity, the amount of hydration, and personal physiology all have a significant impact on sweat production.<sup>98</sup> Inconsistent sampling volumes may result from variations in the sweat rate, which might change analyte concentration through dilution or accumulation effects. The development of microfluidic technologies has improved measurement reliability by controlling sweat collection, transport, and evaporation.<sup>99</sup> However, the complexity of the device, the cost of production, and the power requirements all rise when such components are included.

### 6.5 Long-term stability and surface fouling

One significant barrier to continuous wearable sensing is biofouling. Proteins, lipids, salts, and environmental pollutants found in sweat can adsorb onto electrode surfaces, obstructing catalytic sites and raising charge-transfer resistance.<sup>100</sup> Extended exposure can also cause metal-oxide catalysts to passivate or undergo structural deterioration in non-enzymatic systems. As a result, many devices struggle to maintain consistent performance after 24 hours of operation, and signal drift and decreased sensitivity are frequently reported.<sup>92</sup>

### 6.6 The requirement for extensive clinical validation

Lastly, the majority of sweat glucose sensors that have been reported have been tested in small groups in carefully monitored lab settings. There are currently insufficient thorough clinical investigations with a variety of populations, long-term monitoring, and real-world settings. Transforming laboratory prototypes into approved medical devices requires the establishment of standardized testing procedures, regulatory routes, and clinically meaningful performance indicators.

## 7. Conclusion

Over the past decade, substantial progress has been achieved in the development of non-enzymatic sweat glucose sensors, driven by advances in flexible substrate technologies, integrated microfluidic systems, and highly active catalytic



materials. These developments show how wearable electrochemical systems have the potential to provide continuous, noninvasive glucose monitoring with better stability and durability than their enzyme-based competitors. Enhancing electrocatalytic performance, reducing detection limits, and boosting resistance to environmental degradation have all been made possible by non-enzymatic materials, including carbon-based nanostructures, noble metals, and transition-metal oxides and hydroxides. These materials enable effective handling of low-volume sweat, selective glucose oxidation, and real-time signal stability when paired with flexible printed electrodes and microfluidic sweat-sampling layers.

Future wearable glucose monitoring devices will need to incorporate wireless data transfer, AI-based signal processing, multiparameter sensing, on-patch calibration techniques, and seamless electronics integration. Long-term biocompatibility, reducing interference, and obtaining precise sweat-to-blood correlation are still crucial objectives. Non-enzymatic sweat glucose sensors have the potential to develop into useful, customized health-monitoring systems for patients, athletes, and the general public with further advancements in materials engineering and microfluidic design.

## Author contributions

Kirubha P.: conceptualization, literature collection, data curation, writing – original draft preparation, figure preparation, and overall manuscript organization. Sreeja B. S.: validation, critical review of scientific content, editing, and supervision. S. Fouziya Sulthana: validation, critical review of scientific content, editing, and supervision. The authors have read and approved the final manuscript.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Data availability

All data supporting the findings of this study are available within the article and its referenced literature.

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