Biosensors and Bioelectronics: X 19 (2024) 100500

Contents lists available at ScienceDirect

Biosensors and Bioelectronics: X

journal homepage: www.journals.elsevier.com/biosensors-and-bioelectronics-x

Wearable technology for one health: Charting the course of dermal biosensing

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ARTICLE INFO

Keywords:
Wearable molecular sensors
Epidermal sensors
Subdermal sensors
Sweat
Skin interstitial fluid (ISF)
Biomarkers
One health
Clinical applications

ABSTRACT

Over the last decade, a significant paradigm shift has been observed towards leveraging less invasive biological fluids—such as skin interstitial fluid (ISF), sweat, tears, and saliva—for health monitoring. This evolution seeks to transcend traditional, invasive blood-based methods, offering a more accessible approach to health monitoring for non-specialized personnel. Skin ISF, with its profound resemblance to blood, emerges as a pivotal medium for the real-time, minimally invasive tracking of a broad spectrum of biomarkers, thus becoming an invaluable asset for correlating with blood-based data. Our exploration delves deeply into the development of wearable molecular biosensors, spotlighting dermal sensors for their pivotal roles across both clinical and everyday health monitoring scenarios and underscoring their contributions to the holistic One Health initiative. In bringing forward the myriad challenges that permeate this field, we also project future directions, notably the potential of skin ISF as a promising candidate for continuous health tracking.

Moreover, this paper aims to catalyse further exploration and innovation by presenting a curated selection of seminal technological advancements. Amidst the saturated landscape of analytical literature on translational challenges, our approach distinctly seeks to highlight recent developments. In attracting a wider spectrum of research groups to this versatile domain, we endeavour to broaden the collective understanding of its trajectory and potential, mapping the evolution of wearable biosensor technology. This strategy not only illuminates the transformative impact of wearable biosensors in reshaping health diagnostics and personalized medicine but also fosters increased participation and progress within the field. Distinct from recent manuscripts in this domain, our review serves as a distillation of key concepts, elucidating pivotal papers that mark the latest advancements in wearable sensors. Through presenting a curated collection of landmark studies and offering our perspectives on the challenges and forward paths, this paper seeks to guide new entrants in the area. We delineate a division between wearable epidermal and subdermal sensors—focusing on the latter as the future frontier—thereby establishing a unique discourse within the ongoing narrative on wearable sensing technologies.

1. Introduction

Wearable sensors have significantly transformed the landscape of health engagement and monitoring over the past two decades, evolving from basic physical activity trackers to sophisticated devices capable of molecular sensing through less invasive biological fluids such as skin interstitial fluid (ISF), sweat, tears, and saliva. This transition aims to democratize health monitoring, making it accessible even to non-specialized personnel while capitalizing on minimal invasiveness and real-time data provision. The unique composition of skin ISF, closely mirroring that of blood, offers unparalleled advantages for the continuous and minimally invasive monitoring of a wide range of biomarkers,

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https://doi.org/10.1016/j.biosx.2024.100500
Received 2 April 2024; Received in revised form 8 May 2024; Accepted 19 May 2024
Available online 23 May 2024

thus potentially setting new standards in health diagnostics and personalized medicine.

The journey of wearable biosensors, highlighted by significant contributions from industry pioneers like Abbott, Dexcom, Fitbit, Apple, and BioIntelliSense, has been marked by relentless innovation towards enhancing the convenience and efficacy of health monitoring. This includes real-time analysis of vital health indicators such as glucose levels (Huang et al., 2024), heart rate (Ates et al., 2024), oxygen saturation (Kazanskiy et al., 2024), electrocardiogram readings (Franklin et al., 2023), calorie expenditure (Slade et al., 2021), body temperature (Su et al., 2020), blood pressure (Konstantinidis et al., 2022), and oxygen levels (Dcosta et al., 2023) directly from the user's skin. Further advancements have been spurred by companies like Senseonics, Medtronic, Insulet Corporation, GlySens Incorporated, and LifeScan, which have broadened the horizons of diabetes care and beyond, through innovative glucose monitoring systems and integrated diabetes management solutions (Jafri et al., 2020). Emerging technologies are expanding the scope of monitoring capabilities to encompass a wider array of biomarkers, including electrolytes, metabolites, and oxygen levels, thanks to efforts from companies like Eccrine Systems (Heikenfeld 2016), Kenzen, Gatorade, Profusa, and Lief Therapeutics (Davis et al., 2024). These advancements not only enhance our understanding of the body's physiological state but are also steering the shift towards more personalized healthcare, enabling proactive health management and the realization of the one health initiative. Despite these technological leaps, commercially available wearable biosensors face several challenges, such as limitations in detecting a broad spectrum of analytes, high costs, accuracy of analyte measurement in the skin, biofouling effects, and the need for extensive field trials before large scale commercialization. Evaluating the academic landscape of wearable biosensors for real-time transdermal biomarker analysis uncovers a field ripe with potential and characterized by innovations in accuracy and precision, owing to advancements in sensor technology and data analysis (Kim et al., 2019). These devices are pivotal for patient monitoring, personalized medicine, and fitness tracking. Yet, they encounter significant hurdles, such as limitations in durability, wearer comfort, long-term stability, high production costs, and the absence of high throughput manufacturing processes. Addressing these challenges through innovation and research is vital for enhancing sensor longevity, affordability, and production scalability (Tu et al., 2020). Moreover, ethical and privacy considerations are paramount in the development and application of wearable biosensors. Issues surrounding data security, informed consent, and potential biases in algorithmic decision-making demand rigorous scrutiny. Ensuring the protection of sensitive health data, while navigating the ethical landscape, is critical for maintaining patient trust and complying with regulatory standards (Ginsburg et al., 2024; Nahavandi et al., 2022).

The field stands on the cusp of breakthroughs in real-time, continuous monitoring (Poudineh 2024), with emerging technologies and materials, such as innovative textiles (Adeel et al., 2022), offering new possibilities. Novel applications that extend beyond traditional metabolite monitoring, such as the detection of larger biomarkers indicative of neurodegenerative diseases, underscore the potential for wearable biosensors to transform healthcare (Rao et al., 2024). Interdisciplinary collaborations, merging insights from bioengineering, materials science, and clinical practice, will be instrumental in overcoming current limitations and unlocking the full potential of wearable biosensors in transdermal biomarker analysis (Brasier et al. 2024a, 2024b). Furthermore, the integration of advanced data analytics and artificial intelligence (AI) tools remains a pivotal area for enhancement, promising to unlock deeper insights from the vast data collected, thereby augmenting the effectiveness and utility of wearable biosensors (Nahavandi et al., 2022). A detailed discussion of the challenges and future prospects will be given towards the end of the manuscript.

Our paper navigates through the microanatomy of the skin, which is essential for effective sensor integration, alongside the design, fabrication, and operational mechanisms involved wearable epidermal (sweat-based) and subdermal (ISF-based) electrochemical sensors. We extend this analysis to showcase their broad applications in human, veterinary, and plant health, emphasizing the interdisciplinary impact of these innovations. Highlighting the challenges faced in sensor development and implementation, we present a curated selection of seminal technological advancements, aiming to spark further exploration and innovation within the field. By featuring a curated collection of technological breakthroughs, our work not only navigates through recent developments but also highlights potential directions for wearable sensing technologies in healthcare monitoring, suggesting the promising future of subdermal wearable patches. Through this, we offer a novel narrative in the wearable biosensor domain, encouraging a broader understanding and advancement of personalized medicine and the One Health approach.

2. The microanatomy of the skin

The skin, being the largest organ in the body, serves as an excellent sample matrix for an array of biomarkers relevant to both well-being and clinical assessments. In our exploration of skin-based biomarkers and diverse sampling methods, the following section delves into the intricate structure of the skin (Fig. 1A). By delineating the distinct layers, we aim to highlight potential avenues for tapping into this structure to obtain valuable analytical insights. As shown in Fig. 1A, the skin comprising three distinct layers (epidermis, dermis, and subcutaneous tissue), plays a crucial role in wearable sensing applications. The outermost layer, the epidermis, has five distinct layers, with the *stratum basale* being the deepest and biologically active. The dermis imparts mechanical strength, while the subcutaneous tissue accommodates skin appendages. Understanding the microanatomy of the skin enriches our grasp of wearable sensor capabilities (Kolarsick et al., 2011). Transitioning from the foundational knowledge on skin microanatomy, the discussion advances to the origin of biomarkers within the skin layers, crucial for the development and accuracy of wearable sensors. The two-compartment model and the ectodermal origin theory represent key frameworks in understanding biomarker distribution.

3. Presence of biomarkers in skin compartment

The two-compartment model describes the distribution of biomarkers between the vascular system (including blood) and the ISF in the skin (Fig. 1B). According to this model, there is a dynamic equilibrium between the molecules found in the blood and those in the dermal ISF. This equilibrium is maintained through the process of diffusion across the vascular endothelium, the thin layer of cells that lines the interior surface of blood vessels. The model is particularly useful for understanding how biomarkers related to various physiological or pathological states can be detected in the dermal ISF, making it accessible for wearable biosensors. The model emphasizes that the skin can reflect the body's internal biochemistry, making it possible to monitor health conditions, metabolic states, or the effects of medication through non-invasive means (La Count et al., 2019).

The ectodermal origin theory suggests that certain tissues and organs in the body share a common developmental origin from the ectoderm, the outermost layer of the embryo (Fig. 1C). This includes both the skin and the nervous system, which comprises the brain and spinal cord. According to this theory, because the skin and the nervous system are derived from the same embryonic layer, they may share certain biochemical markers and pathways. This connection is particularly significant in the context of neurodegenerative diseases, where biomarkers typically associated with brain pathology can also be found in the skin. For example, proteins or genetic markers linked to conditions like Alzheimer's or Parkinson's disease may be detectable in skin cells. This shared origin provides a unique opportunity for non-invasive monitoring of neurological health through skin-based biosensors,

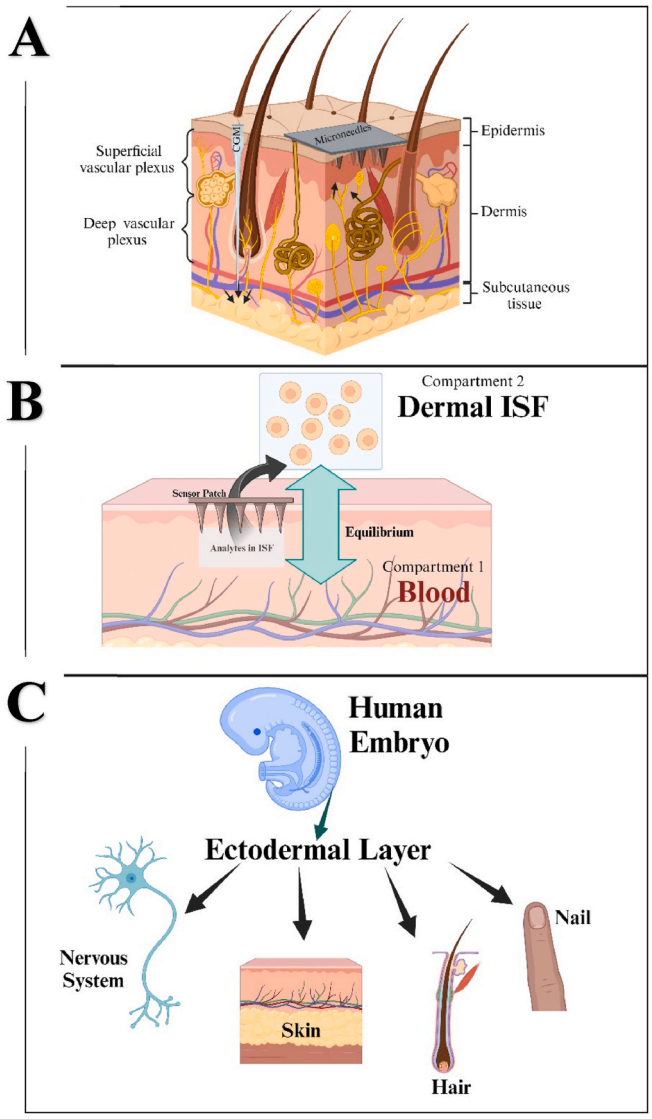

Fig. 1. (A) An illustrative diagram showing the three primary layers of the skin – epidermis, dermis, and subcutaneous tissue – highlighting the different vasculatures based on the depth. Two continuous monitoring devices, a continuous glucose monitor (CGM) and a microneedle array, are depicted, indicating their penetration point into the skin layers. (B) An illustrative diagram depicting the 2-compartment model where an equilibrium of analytes exists between the blood compartment and dermal ISF; (C) The ectodermal stage gives rise to nervous system, skin, hair and nail.

offering a window into the central nervous system's status without the need for more invasive diagnostic methods (Jameson et al., 2023).

The two-compartment model and ectodermal origin theory, present a multidimensional understanding of biomarker origins, which is essential for the design of effective wearable sensing devices, enabling precise health monitoring and disease diagnosis (Castanedo-Cazares and Rodriguez-Leyva 2015; Rodríguez-Leyva et al., 2014). The integration of these theories underpins the scientific basis for developing sensors that can accurately and non-invasively monitor a broad spectrum of health conditions, from metabolic states to neurodegenerative diseases, through analysis of the skin.

4. Matrices for analyte monitoring

Sweat and ISF are two bodily fluids increasingly targeted for wearable sensing due to their potential for non-invasive biomarker analysis. Both matrices offer unique advantages and challenges for the development and implementation of wearable biosensors, serving as windows into the body's physiological and metabolic state. However, when considering the future direction of wearable sensing, ISF presents several compelling advantages over sweat.

On one hand, sweat-based sensing offers a non-invasive and easily accessible method for monitoring health, leveraging sweat's availability on the skin's surface. It is informative, containing electrolytes, metabolites, and small biomolecules that can reflect various health statuses like hydration and electrolyte balance. However, it faces challenges such as variable secretion rates influenced by external factors, a limited biomarker range that may not encompass the breadth found in blood or ISF, and a high risk of contamination from external substances (Gao et al., 2023). On the other hand, ISF-based sensing provides a closer approximation to blood as seen from the two-compartment model, offering access to a richer array of biomarkers relevant to health status, including glucose, hormones, and larger proteins. It benefits from stable collection conditions, with ISF levels and composition being less influenced by external factors and presents a reduced risk of contamination due to the minimally invasive methods required for ISF collection. These methods, however, introduce their own set of challenges, including the barrier to continuous, user-friendly monitoring and the increased technical complexity and costs of ISF sensing devices (Wu et al., 2024). From a practical implementation perspective, sensing methods that work on extraction of ISF are limited by the negative pressure of this matrix and extremely low extraction volumes, which leads to hinderances in sensing analytes from extracted ISF. However, this limitation does not apply to solid microneedle (MNs), which carry out sensing in the skin compartment.

The future of wearable sensing is increasingly moving towards ISF-based sensing, considering its direct relevance to the body's internal physiological state and its broader biomarker spectrum. ISF-based sensing stands as a more comprehensive and accurate tool for health monitoring and disease diagnosis (Brinkman et al., 2023). The minimally invasive nature of ISF extraction, while a challenge, is being addressed by advancements in MN technology and skin-interfacing sensors, making ISF-based sensing more accessible and user-friendly. The stability and reduced contamination risk associated with ISF collection further support the development of reliable, long-term wearable biosensors. Despite existing challenges, the potential of ISF-based sensing to provide deeper insights into an individual's health status marks a significant step forward in personalized medicine and continuous health monitoring. Table 1 summarises the levels of clinically relevant molecules found in plasma, dermal ISF, and sweat. It can be seen that dermal ISF and plasma possess a good correlation, which implies the scope that ISF holds in the wearable sensing field.

5. Fabrication methods, underpinning sensing mechanisms and techniques in subdermal wearable sensing

Due to the inherent advantages associated with ISF based sensing, a significant spotlight has been given in this manuscript to discussions on subdermal sensors. A universal requirement across fabrication techniques is high resolution, consistently below 20 μm (Hirt et al., 2017). This precision is crucial for crafting sharp MN tips (in this manuscript, the terms 'subdermal patches' and 'MNs' are used interchangeably as they refer to the same structures that are used to sample the ISF from the skin compartment) to ensure painless skin penetration, minimal damage, and mitigating immune responses. Various factors govern effective skin penetration including aspect ratio, geometry, spacing, and layout of the MN patch. Studies highlight the significance of these parameters, revealing that MNs with a 400 μm base diameter exhibit higher penetration rates (60%) compared to those with a 200 μm diameter. Additionally, a MN array with 2400 μm spacing, though requiring greater penetration force, demonstrated a 20% increase in skin penetration compared to arrays with 800 μm spacing (Kochhar et al., 2013). Sharper

Table 1
Comparison of analytes of clinical relevance found in plasma, skin ISF, and sweat.

	Na^+	K^+	Lactate	Glucose	Cortisol	Cytokines	Antibodies
Mol. wt. (Da)	23	39	90	180	362	>10,000	>1,00,000
Plasma	135–145 mM	3.5–5 mM	0.5–10 mM	4.1–6.9 mM	>100 nM	pM to nM	0.4–16 mg/mL
Skin ISF	~ plasma	~ plasma	~ plasma	~ plasma	~ plasma	80% of plasma	15–25% of plasma
Sweat	>10 mM	~5–15 mM	~5–10 mM	~1% of plasma	~ plasma	<0.1% of plasma	Diluted

MN tips have been shown to reduce the necessary penetration force in other studies (Ahn 2020). The 'bed of nails effect', which reflects on the challenge of ensuring minimal discomfort while achieving effective skin penetration is a major factor relating to the fabrication of MN containing wearable subdermal patches (Turner et al., 2021). This principle illustrates how force, when distributed over multiple tiny points, can painlessly breach the skin's surface without reaching the more sensitive dermal layers. However, the practical application of this concept requires careful consideration of MN geometry. Studies have also shown that the penetration depth is linearly correlated with MN length and inversely correlated with MN density. Importantly, the bed-of-nails effect begins to have a negative impact on penetration at interspacing values smaller than 150 μm (Loizidou et al., 2016). This suggests a critical balance in MN design: while distributing the force across multiple points minimizes pain and skin damage, overly dense arrays can hinder effective penetration, underscoring the need for optimized MN spacing and length to utilize this effect beneficially in wearable sensors. This also affects fluid dynamics, facilitating efficient biomarker diffusion to the sensor, which is crucial for responsive and reliable monitoring. Beyond geometry and spacing, material properties such as mechanical fracture toughness and Young's modulus, determining MN stiffness, are critical considerations for safety and functionality. Ensuring materials biocompatibility and accounting for the elasticity of the skin are also important whilst designing MNs (Teymourian et al., 2021).

Fabrication of Subdermal Wearable Sensors: Subdermal patches were initially developed for transdermal drug delivery and have catalysed

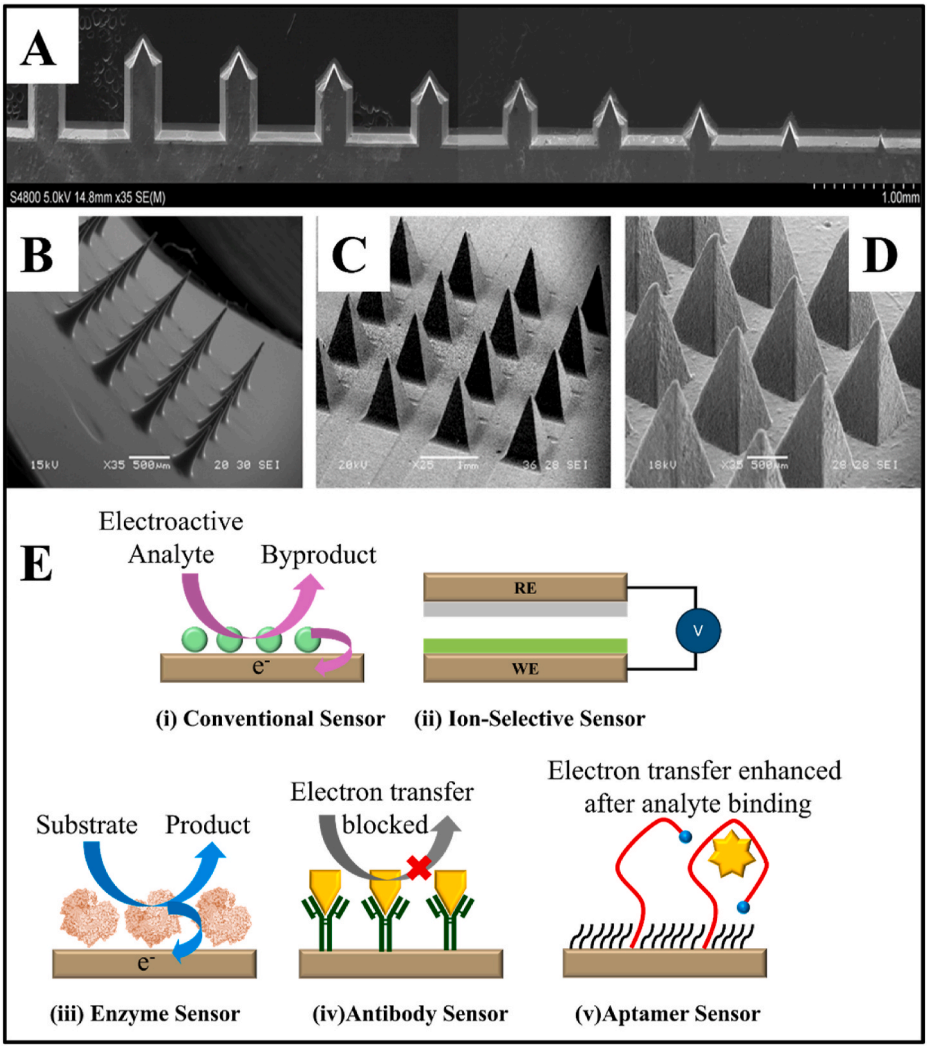

Fig. 2. Illustration of different microneedle arrays made out of different materials and employing different fabrication methods. **(A)** silicone microneedle manufactured using photolithography and wet etching methods. **(B)** Shows epoxy SU8 100 based MN arrays. These structures were fabricated in a clean room using photolithography and quartz wafers. **(C)** Shows MN arrays fabricated on an aluminium block using electric discharge milling. **(D)** Shows polycarbonate MN arrays fabricated using injection molding. **(E)** Schematic of underpinning sensing mechanisms showing **(i)** conventional, **(ii)** ion-selective, **(iii)** enzyme, **(iv)** antibody, and **(v)** aptamer sensor.

advancements in subdermal wearable sensors (Gerstel and Place 1976). Subdermal wearable patches are constructed from materials like silicon, stainless steel, ceramics, and polymers using various fabrication techniques (Teymourian et al., 2021; Vora et al., 2023). The choice of materials is crucial as it impacts durability, functionality, and biocompatibility of the subdermal patch. Silicon is favoured for crafting sharp, durable patches, though its fabrication process is complex, and may fracture upon insertion into the skin. These can be designed as solid, hollow, or coated subdermal patches. Metals, such as stainless steel and titanium, offer longevity and overcome the fragility of silicon but require careful post-processing and might trigger allergies. Ceramics are used for their chemical stability and compressive strength, albeit with limited tensile durability and are suitable to fabricate both solid and hollow patches. Polymers stand out for their excellent biocompatibility, low toxicity, and affordability, despite concerns about their structural strength. Yet, advancements have demonstrated their potential in creating diverse patches including solid, hollow, coated, and dissolvable configurations (Aldawood et al., 2021; Waghule et al., 2019). It is crucial to briefly examine the fabrication techniques that have been pivotal in realizing the potential of these materials in practical applications (Fig. 2). Photolithography is a mature technology that has played a pivotal role in silicon-based subdermal patch fabrication (Howells et al., 2022). This method involves coating silicon wafers with photoresist, followed by UV exposure and etching to create MNs with diverse size, height, and geometry (Fig. 2A and B). While providing high reproducibility and resolution, photolithography entails complex, multistep, and costly procedures, with the producible maximum height dictated by the thickness of the silicon wafer (Eş et al., 2023). Micromachining is a top-down technique that precisely removes material to achieve the desired geometry (Wu et al., 2022). This method, which is executed by a CNC machine, offers flexibility in design, high yield, scalability, and the capability to produce both hollow and solid MN containing patches. Despite its advantages, micromachining requires skilled operators and involves equipment and drill bit costs (Fig. 2C) (Chen et al., 2018). Micromolding is a widely embraced technique, which is simple, scalable, and cost-effective for fabricating subdermal wearable devices (Sharma et al., 2017; Vulpe et al., 2024a) (Fig. 2D). Utilizing molten or liquid materials poured into premade micromolds, it is particularly suitable for materials like metals and polymeric resins. However, micromolding has can be used for fabricating on solid MN containing patches only and offers lower resolution compared to alternative methods (Tarbox et al., 2018). Drawing lithography is a low-cost method, which involves drawing melted polymer directly onto a planar substrate to form 3D MN structures. While overcoming certain dimensional limitations, material choices are restricted. Magnetorheological drawing lithography (MRDL), a modification, employs an external magnetic field to enhance sharpness and length in resulting MNs (Chen et al., 2018). 3D printing encompassing techniques like stereolithography (SLA), fused filament fabrication, digital light processing, and scan, spin, and selectively photocuring (3SP), primarily utilizes polymer-based photocurable resins or filaments (Detamornrat et al., 2022). While versatile in terms of producing varied patch geometries, most 3D printing methods face constraints related to limited true resolution (>50 μm). Two-photon polymerization (TPP) SLA stands out with its higher resolution (10 nm) structures, albeit with associated challenges such as low throughput and high costs (Abdullah et al., 2022; Faraji Rad et al., 2021).

Underpinning Sensing mechanism: Wearable molecular sensors predominantly employ electrochemical sensing mechanisms, with occasional instances of optical signal transduction leading to the development of optical sensors. Despite this, most wearable sensors leverage electrochemical transduction approaches, benefiting from miniaturization, high speed, cost-effectiveness, low power consumption, scalability in fabrication, and seamless integration with MN ISF sensing platforms (Teymourian et al., 2020). Electrochemical (bio)sensors seamlessly merge the sensitivity of electrochemical transduction methods with the selectivity of (bio)recognition elements (Ronkainen et al., 2010). In these sensors, the recognition event, marked by the specific analyte-receptor interaction, translates into a measurable electrical signal by the electrode transducer. The intensity of this signal is directly proportional to the concentration of the target analyte. Diverse recognition chemistries and transduction modes are employed in the development of MN electrochemical sensors, tailored to the targeted analyte (Sharma et al., 2017). The following sections provide a concise overview of varied electrochemical (bio)sensors, shedding light on the receptor and transduction modes they utilize.

Conventional wearable sensing electrodes, devoid of a recognition element, represent the simplest configurations (Fig. 2E (i)). These sensors use the bare surface of the working electrode to detect electroactive analytes, employing scanning-potential voltametric measurements like square wave voltammetry (SWV) and differential pulse voltammetry (DPV). Unmodified carbon paste subdermal sensors, for instance, continually monitor fentanyl opioid molecules. Strategies to enhance selectivity and sensitivity involve surface confinement of various nanomaterials onto working electrodes (Mishra et al., 2020). Ion-selective electrodes (ISEs) translate primary ion activities into an electrical potential difference measured potentiometrically (Fig. 2E (ii)). Wearable subdermal potentiometric sensors, often relying on solid contact ISEs, offering advantages such as simplicity, speed, low cost, and minimal power requirements (Sharma et al., 2011). Particularly suitable for long-term *in-vivo* monitoring operations, these sensors demonstrate compatibility with modern micro/nanofabrication techniques and have been successfully integrated into subdermal platforms for monitoring potassium ion concentrations in the skin compartment (Parrilla et al., 2019). Sensors with ion-selective electrodes (ISEs) are advantageous for their simplicity, low power requirements, and compatibility with micro/nanofabrication techniques. However, they may face limitations in selectivity and sensitivity, particularly in complex biological environments. Enzymes, renowned for their selective behaviour, catalyse the conversion of metabolite biomarkers in amperometric (Saha et al., 2022), voltametric (Arjun and Sandhyarani 2021), or potentiometric modes (Mano et al., 2018). There are several instances of MN-based biosensors that have employed oxidase enzymes for in-vivo monitoring of various biomarkers, including glucose (Sanati et al., 2022), alcohol (Tehrani et al., 2022a), glutamate (Friedel et al., 2023), lactate (Bollella et al., 2019), and theophylline (Sharma et al., 2017) (Fig. 2E (iii)). Despite the efficacy of enzymes in biosensor design, challenges include limited long-term operational stability due to biofouling effects and a restricted scope of detectable analytes in the skin (Clark and Ray 2023). Enzyme-based electrodes offer excellent selectivity and specificity, making them ideal for detecting specific biomarkers. However, they may suffer from limited long-term stability due to biofouling effects and may have a restricted scope of detectable analytes. Affinity sensors, encompassing immunosensors and aptamers, leverage selective binding for specific analytes. While immunosensors, particularly antibody-based, have found applications in MN platforms, they face challenges related to slow kinetics, poor stability, and complicated regeneration procedures (Fig. 2E (iv)). Aptamers, which are artificial nucleic acid ligands, provide an alternative with the potential for continuous, in-vivo monitoring (Li et al., 2023; Parlak 2021). They offer a promising avenue for integration with MN arrays, facilitating high-frequency monitoring of various biomarkers (Friedel et al., 2023) (Fig. 2E (v)). Affinity sensors, such as immunosensors and aptamers, excel in selective binding for specific analytes, offering high sensitivity and specificity. Nevertheless, immunosensors may encounter challenges related to slow kinetics and complicated regeneration procedures, while aptamers may have limitations in terms of availability and optimization. Overall, each type of wearable sensor configuration presents a trade-off between advantages and limitations, necessitating careful consideration based on the specific application requirements.

***Electrochemical Techniques in Wearable Biosensors*:** In wearable biosensors, various electrochemical techniques play crucial roles in

detecting analytes with or without molecular recognition elements. Amperometry, for instance, is employed in enzyme-based sensors to detect analytes through enzymatic reactions, such as glucose oxidase for glucose detection or lactate oxidase for lactate detection (Vulpe et al., 2024b). Chronoamperometry (CA) and chronopotentiometry (CP), on one hand are applied in enzyme-based sensors to study the kinetics of enzymatic reactions by monitoring current or potential changes over time (Tang et al., 2022). Voltammetry, on the other hand, is utilized in sensors with bare surface electrodes to detect electroactive species without specific recognition elements, suitable for non-specific detection or redox-active molecules like ferrocene (Lee et al., 2021). Modified electrodes in voltammetry incorporate specific recognition elements, such as antibodies or aptamers, to enhance selectivity, enabling the detection of target analytes through redox reactions (Lin et al.). Potentiometry, involving ISEs, measures ion concentrations in body fluids like potassium, sodium, or chloride ions (Cao et al., 2024). Meanwhile, impedance spectroscopy analyses changes in impedance due to biomolecular interactions at electrode interfaces, providing insights into biomolecule behaviour and kinetics. Electrochemical impedance spectroscopy (EIS) characterizes the electrical properties of electrode interfaces and monitors changes in impedance due to biomolecular interactions, facilitating label-free detection of biomolecular binding events and offering quantitative information about biomolecular interactions (Greyling et al., 2024).

Wearable platforms are designed to sense either a single analyte or, in some cases, multiple analytes in sweat (epidermal) or skin ISF (subdermal extraction or in situ monitoring) using a combination of sensing mechanisms and techniques (Zhang et al., 2022b). A comprehensive understanding of diverse electrochemical (bio)sensors and their adaptation to subdermal and epidermal wearable sensing platforms is imperative for advancing the field of wearable sensing technology. Each sensor type presents unique advantages and challenges, with the choice depending on the specific requirements of the targeted analyte and the desired application scenario.

Substrates (Base materials) in electrochemical sensing: In the realm of electrochemical sensing, a diverse array of base materials have been employed as electrochemically active substrates, each offering unique properties and advantages. Ceramics, known for their durability and thermal stability, have been utilized as robust substrates for electrochemical sensors, particularly in high-temperature applications (Steinberg et al., 2016). However, ceramics offer limited opportunities for construction of wearable biosensor electrodes (other than in subdermal patch-based sensing) due to limited tensile durability and low conductivities. Additionally, ceramics find more use in fabrication of MN structures only and cannot be used as sensing elements in the case of subdermal wearable patches. Cloth and paper substrates, provide flexibility and comfort, making them suitable for wearable sensors, especially in applications requiring conformal integration with the human body. Although these materials are 'go to' options for epidermal sensors, the use of paper-based sensing elements does not hold much promise in subdermal sensing (Adeel et al., 2022; Dincer et al., 2022; Güder et al., 2016). Metals like Au, Pt, and Ag are frequently chosen as substrates due to their excellent electrical conductivity and chemical stability, crucial for achieving sensitive and reliable electrochemical measurements (Güder et al., 2016; Yi and Xianyu 2022). These metals are versatile and have been used as sensing elements both in epidermal and subdermal sensing. Plastics and polymers mixed with conducting materials offer versatility, allowing for easy fabrication of sensor devices through techniques like 3D printing or soft lithography, and they also provide excellent biocompatibility, making them suitable for both epidermal and subdermal applications (Gao et al., 2019b; Kalkal et al., 2021; Ryan et al., 2022). Organic materials, including carbon-based materials like graphene, carbon nanotubes (CNT), and MXenes offer unique electronic properties, large surface areas, and tuneable surface chemistries, enabling enhanced sensitivity and selectivity in electrochemical sensing (Ankitha et al., 2023; Erdem et al., 2022; Singh et al., 2017) Although these materials provide enhanced conductivities, superior electrochemically active surface areas, and varied options for bioreceptor binding, the applications of these materials are limited by their need to be printed on to the surface of both epidermal and subdermal sensors. These diverse base materials provide a foundation for the development of electrochemical sensors tailored to specific applications, ranging from environmental monitoring to healthcare diagnostics.

This manuscript will provide a comprehensive review of recent advancements in epidermal and subdermal sensing technologies, with a focus on both human and veterinary applications, as well as their potential uses in plant physiology. Despite the inherent constraints associated with epidermal wearable sensors, notable progress in this domain suggests promising pathways for their integration and application in subdermal sensing technologies. This collection aims to highlight innovative approaches and findings that may bridge the gap between surface-level and subdermal sensing modalities, offering insights into their future development and application.

Wearable Sensors for Well-being Monitoring: In the pursuit of comprehensive health monitoring, epidermal sensors have been explored as tools for tracking a diverse spectrum of well-being markers (Section A, Table 2). This includes metabolic molecules (such as glucose (Cass and Sharma 2017; Sharma et al., 2018; Sharma et al., 2016), cholesterol (Gao et al., 2019a), and alcohol (Tehrani et al., 2022a)), essential metals (copper and zinc), neurotransmitters (dopamine and serotonin), and inflammation indicators (interleukin-6 (IL6)), all extracted from sweat. Noteworthy advancements in real-time epidermal monitoring encompass a glove-based biosensor with capabilities to detect vitamin C, ethanol, zinc, sweat chloride, and pH. Similarly, reports of wearable smart bands integrating a glucose-sensing strip with continuous vital sign monitoring underscore significant contributions (Fig. 3A). Fig. 3B illustrates an example of a touch based epidermal wearable sensor for the detection of ketones and glucose. The adoption of innovative materials like highly integrated sensing paper (HIS) and super hydrophobic sensing surfaces further characterizes the evolving landscape of wearable sensors, with intricate designs establishing robust sensing platforms for prolonged and accurate biomarker detection.

The breadth of well-being markers that wearable epidermal sensors can track is impressive, offering a comprehensive view of an individual's health status. From metabolic molecules to inflammation indicators, the ability to extract these biomarkers from sweat presents a non-invasive and continuous monitoring solution. There have been a large number of innovations that have been reported to generate, collect, and sense metabolites in sweat. However, challenges such as inter-subject variations in sweating patterns and the need for standardization in sensor performance metrics remain significant hurdles. Moreover, while advancements in sensor design and material integration enable prolonged and accurate biomarker detection, issues related to sensor calibration, drift, and long-term stability require further attention.

Wearable Epidermal Sensors and Metabolite Detection: The detection of metabolites in sweat has been a focal point, leveraging the use of various nanomaterials. Studies by Yang et al. showcase the application of conductive nickel-based metal-organic frameworks (MOFs) for the successful detection of vitamin C and uric acid (Yang et al., 2022). Additionally, the integration of fibrous textile-based threads by Terse-Thakoor et al. demonstrates the potential for miniaturization and wearability while monitoring sodium, ammonium ions, lactate, and acidity (Terse-Thakoor et al., 2020). Other notable investigations by Zheng et al. and Lei et al. explore cloth-based wearable sensors and MXene-based wearable platforms, respectively, demonstrating the detection of glucose and lactate alongside pH monitoring (Lei et al., 2019; Zheng et al., 2021). Passive sweating at the fingertips, as explored by Sempionatto et al., offers a non-invasive approach to glucose sensing, presenting a promising alternative to blood-based measurements (Sempionatto et al., 2021b). Challenges, such as inter-subject variations in passive sweating and low sweat volume generation, underscore the need for ongoing advancements in this domain. Incorporating additional

Table 2
Recent developments in epidermal, subdermal, and dermal sensing for veterinary applications and plants.

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
Section A: Sweat based epidermal electrochemical sensors for monitoring individual well being									
1	1. Zn^{2+} 2. Ethanol 3. pH 4. Cl^{-}5. Vitamin C	1. ASV 2. CA 3. OCV 4. OCV 5. CA	1. Au/Bi 2. Au/Au nanodendrites/PB/NiHCF 3. Au/PANI 4. Au/(Ag/AgCl) 5. Au/EDOT	2. AlOx 5. AscOx	1. 0–2000 μg/L 2. 0–6.5 mM 3. 4-7 4. 25–200 mM 5. 0–300 μM	Information not given	Bariya et al. (2020)	15/7/20	Glove based sensor for the detection of Zn, Ethanol, pH and Cl- and Vitamin C sensor is based on finger-based cot.
2	Glucose	CA	C/PB	GOx	0–3 mM	Information not given	Hong et al. (2018)	10/10/18	This sensor employs glucose measurement combined with heart rate, SpO2, and activity monitor to give the user information regarding glucose levels during physcial exercise. It is a wearable device worn on the wrist.
3	1. Glucose 2. Ascorbic Acid 3. Na^{+}	1. CA 2. DPV 3. OCP	1. Silk fabric–derived intrinsically Silk NCT 2. Silk NCT 3. Silk NCT/PEDOT:PSS	1. GOx	1. 25–300 μM 2. 20–300 μM 3. 5–100 mM	1. 5 μM 2. 1 μM 3. 1 mM	(He et al.)	17/9/19	The sensor is based on a flexible PET substrate, which can be worn on the arm of a subject.
4	1. Glucose 2. Lactate	1. CA 2. CA	1. HIS/$Ti_3C_2T_x$/MB/Chitosan 2. HIS/$Ti_3C_2T_x$/MB/Chitosan	1. GOx 2. LOx	1. 0–1.25 mM 2. 0–20.3 mM	1. 17.05 μM 2. 3.73 μM	Li et al. (2021a)	19/11/20	This sensor is a highly integrated sensing paper (HIS), which used Mxene as the immobilization platform for the enzymes. Also, the authors have modeled diffusion pathways for efficient sweat collection.
5	1. Glucose 2. Na^{+} 3. K^{+} 4. pH	1. CA 2. OCP 3. OCP 4. OCP	1. CSSY-EF)/PANI/Pt/Chitosan/CNT 2. CSSY-EF/PEDOT-PSS/sodium tetraphenyl boron 3. CSSY-EF/PEDOT-PSS/sodium tetraphenylborate 4. CSSY-EF/PANI	1. GOx	1. 0–250 μM 2. 10–160 mM 3. 2–32 mM 4. 4-7	Information not given	Wang et al. (2022)	2/3/22	This sensor is based on an engineered core- sheath yarn, which is modified using CNTs to create a superhydrophobic substrate. The total volume of sweat required in this case is 0.5 μL.
6	1. NH_4^{+} 2. Na^{+} 3. pH 4. Lactate	1. OCP 2. OCP 3. OCP 4. CA	1. CBCT/non actin- 2-nitrophenyl octyl ether-polyvinyl chloride 2. CBCT/sodium ionophore X-polyvinyl butyral-sodium tetra-kis [3,5-bis(trifluromethyl) phenyl] borate- bis(2-ethylhexyl) sebacate 3. CBCT/PANI 4. CBCT/PB	4. LOx	1. 0.1–100 mM 2. 1–1000 mM 3. 4-9 4. 2–100 mM	Information not given	Terse-Thakoor et al. (2020)	28/7/20	This sensor is a band aid based sensor with individual threads attached to the band aid patch for sensing.
7	Glucose	CA	Cloth/MWCNT-PB	GOx	0.05–1 mM	4.95 μM	Zheng et al. (2021)	19/5/21	This is a cloth based sensor, integrated to a wearable platform having pogo pins to connect to a potentiostat
8	1. Glucose 2. Lactate	1. CA 2. CA	1. CFM/CNT-$Ti_3C_2T_x$/PB 2. CFM/CNT-$Ti_3C_2T_x$/PB	1. GOx 2. LOx	1. 10 μM-1.5 mM 2. 0 mM–22 mM	1. 0.33 μM 2. 0.67 μM	Lei et al. (2019)	8/4/19	This sensor represents an example of a wearable

(*continued on next page*)

Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
	3. pH	3. OCP	3. CFM/CNT-PANI						electrochemical sensor for the detection of glucose, lactate, and pH using a wearable device and also using Mxenes as a detection platform for this purpose.
9	Glucose	CA	PET/PB-carbon	GOx	0.01–1.11 mM	Information not given	Sempionatto et al. (2021b)	28/5/21	This sensor was a fingertip sweat based glucose sensing from passive sweat. The sweat collection film was a PVA film that was attached to the top of the glucose sensing material.
10	1. Glucose 2. Ketone	CA	1. PET/PB-carbon 2. SPCE/AuNPs/TBO-CNT	1. GOx 2. HBD	1.0. 01–1.11 mM 2. 0.1–2 mM	1. Information not given 2. 14.43 μM	Moon et al. (2022)	23/12/22	This is an extension of the work in (8).
11	1. Cortisol 2. Dehydroepiandrosterone (DHEA)	EIS	Polyamide/Gold/DTSSP	1. Cortisol IgG antibody 2. DHEA IgG antibody	1. 0.1–500 ng/mL 2. 0.1–500 ng/mL	1. 0.1 ng/mL 2. 0.1 ng/mL	Upasham et al. (2020)	14/2/21	This paper represents an example where a wearable sensing platform was used for monitoring cortisol and DHEA concentration in sweat using impedance spectroscopy. It is an extension of the work by Upasham et al. (doi.org/10.1039/C9AN01968E)
12	Cortisol	CA	LIG/carboxylate rich pyrrole derivative grafting	Cortisol antibody, peroxidase enzyme	0.43–50.2 ng/mL	0.08 ng/mL	Torrente-Rodríguez et al. (2020)	26/2/20	This work involves the use of a LIG based substrate for the immobilization of cortisol antibody, wherein a competition between sweat cortisol and HRP labeled cortisol leads to a cathodic current inversely proportional to cortisol in biofluids.
13	Cortisol	I–V curve	PAN/PEDOT	Cortisol Aptamer	1 pM-10 μM	10.0 pM	An et al. (2022)	28/1/22	This sensor is an FET based sensor wherein cortisol aptamer is used for the detection of cortisol from sweat
14	Cortisol	DPV	Polyurethane/MOF-CNT	Biotin-Aptamer	0–100 ng/mL	0.032 ng/mL	Su et al. (2023)	2/5/23	This sensor is an MOF based aptasensor for the detection of cortisol where the MOF possesses peroxidase activity, which is suppressed due to the formation of aptamer cortisol complex.
15	Cortisol	Amperometry	Gold substrate	Cortisol Aptamer	1 pM-1 μM	0.2 pM	Singh et al. (2023)	29/1/23	This wearable electrochemical aptasensor is based on a pseudoknot based aptamer

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
									which results in a signal ON response on binding with cortisol.
16	1. Estradiol 2. pH	1. DPV 2. OCP	1. PET/Au/Mxene 2. PET/Au/PANI	1. (a)SH-ssDNA (b) MB-ssDNA (c) Aptamer	1. 0–100 pM 2.5–9	1. 0.14 pM	Ye et al. (2023)	28/9/23	This sensor uses a competitive sensing strategy wherein binding of oestradiol to SH-ssDNA the sensing surface leads to dissociation of MB-ssDNA, which then binds to Aptamer ssDNA leading to signal ON.
Section B: Sweat based epidermal optical sensors for monitoring individual well being									
17	Glucose	Absorbance	Microchamber with check valve	GOx-peroxidase-*o*-dianisidine	0.1–0.5 mM	0.03 mM	Xiao et al. (2019)	3/12/19	This sensor represents a wearable optical sensor which results in a change of color due to the presence of dianisidine, GOx, and peroxidase.
18	1. Glucose 2. Lactate 3. pH 4. Chloride 5. Sweat Volume	Fluorescence	1. Paperdisc/flourescein 2. Paperdisc/flourescein-Fe complex 3. Paperdisc/quinine 4. Paperdisc/quinine	1. GOx, HRP	1. 10–250 μM 2. 1–12.5 mM 3. 4.1–6.6 4. 10–100 mM 5. 15–65 μL	1. 7 μM 2. 0.4 mM 3. −4. 5 mM 5. 8 μL	Ardalan et al. (2020)	16/8/20	This report involves a multiplexed sensor, wherein changes to fluorescence emission of fluorescing molecules are used for sensing of metabolites
19	1. pH 2. Chloride 3. Glucose	Colorimetric	Na_2CO_3 treated cotton thread	3. GOx	1. 5–7.5 2. 0–150 mM 3. 0–2 mM	2. 10 mM 3. 10 μM	Zhao et al. (2021)	30/12/20	This sensor is a colorimetric sensor for the detection of metabolites
20	1. Copper 2. Glucose 3. Chloride 4. pH	1. Absorbance 2. Fluorescence 3. Absorbance 4. Absorbance	Methacrylate-urethane methacrylate (MA-UDMA) and acrylate-isobornyl acrylate (Acrylate-IBA) based microcuvette supplied by microchannels and microvalves 1. Cuprizone reagent dried inside cuvette 2. Glucose assay kit dried into cuvette (GOx and HRP was vacuum dried) 3. Silver Chloranilate and pHEME methanol solution dried into the cuvette 4. bromocresol purple, bromocresol green, and bromothymol blue vacuum dried into cuvette	2. GOx, HRP	1. 0.25–3 ppm 2. 6.25–160 μM 3. 1 mM 4. 4.5–7.5	1. 0.25 ppm 2. 6.25 μM 3. 1 mM 4. 4.6	Yang et al. (2023)	21/8/23	This sensor represents an example of a miniaturised cuvette system wherein analyte reactions lead to change in color or fluorescence
21	1. Chloride 2. Calcium 3. Glucose 4. pH	1. Colorimetric	Hand operated pumps were used for optimum collection of sweat	standard colorimetric assays were used (GOx, HRP)	Physiologically relevant ranges	Physiologically relevant ranges	Mishra et al. (2022)	28/10/22	This report focused on the collection of sweat using a hand operated pump
Section C: Sweat based epidermal sensors for markers of health care									
22	Inflammatory Bowel Syndrome 1. Interleukin-1β (IL-1β) 2. C-reactive protein (CRP)	EIS	Modified SPE	1. IL-1β Antibody 2. CRP Antibody	1. 0.2–200 pg/mL 2. 0–10 ng/mL	1. 0.2 pg/mL 2. 1 pg/mL	Jagannath et al. (2020)	28/7/20	This sensors uses EIS to measure the levels of IL-1β and CRP in live patients for

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
									the early diagnosis of Inflammatory Bowel Syndrome
23	Inflammation 1. Interferon Inducible Protein (IP-10) 2. tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) 3. CRP	EIS	Pharmcheck patch modified with ZnO/thiol crosslinker	Antibody	1. 1–512 pg/mL 2. 1–512 pg/mL 3. 0.2–204 pg/mL	1. 1 pg/mL 2. 1 pg/mL 3. 0.2 ng/mL	Jagannath et al. (2022)	3/3/22	This system represents a wearable impedance based sensing platform for the detection of inflammation
24	Atopic Dermatitis Interleukin-31	EIS	Nanoporous polyamide substrate with serpentine gold electrodes/thiol linker	IL-31 antibody	50–750 pg/mL	50 pg/mL	Upasham et al. (2022)	1/8/22	This system represents a wearable system for the detection of IL-31 coupled with a machine learning algorithm for the detection of Atopic dermatitis
25	Atherosclerosis 1. Cholestrol 2. Transferrin 3. K^+	1. DPV 2. CA 3. OCP	1. PET-SPE/MWCNT-CQD/β-CD 2. PET-SPE/polypyrrole 3. PET-SPE/valinomycin, ion exchanger, plasticizer, and plastic matrix	No bioreceptors used	1. 10^{-10}-10^{-4} M (buffer); 1.8–101.8 μM (real sweat) 2. 0–0.001 g/L 3. 4.5–500 mM	1. 0.42 nM (Buffer) 2. 6.65 ng/mL 3. 1 μM	Wei et al. (2023)	24/10/23	This report details the fabrication of a wearable sensor surface, which does not use bioreceptors and instead uses biomimetic materials for the detection of cholestrol, transferrin, and K^+
26	Cardiovascular Disease 1. Na^+ 2. Ascorbic acid 3. Human neuropeptide Y (NPY)	1. OCP 2. CA 3. EIS	1. PET/(CCP)/CQD/Na + ionophore X 2. PET/CCP/CQD 3. PET/CCP/CQD/Au	2. Ascorbic acid oxidase (AAOx) 3. NPY antibody	1. 0.1–500 mM 2. 1–400 μM 3. 1 fM-100 pM (buffer); 1 fM-1 pM (real sweat)	1. 10.9 μM 2. 12 nM 3. 1.1 fM (buffer)	Wei et al. (2022)	20/9/22	This report details the fabrication of a portable sensor for the detection of biomarkers that index cardiovascular health
27	Kidney Disorder 1. Creatinine 2. Urea 3. pH	Colorimetric	μ reservoir	1. Urease 2. Creatininase	1. 0–250 mM 2. 0–0.5 mM 3. 5-7	Information not given	Zhang et al. (2019)	12/3/19	This paper deals with the creation of a sensor for the detection of kidney disorder biomarkers like creatinine, urea, and pH in sweat, which was collected using a facile method where in the subject had a warm shower.
Section D: Sweat based epidermal sensors for monitoring therapeutic and illicit drugs									
28	Levodopa	CA	SPCE	Tyrosinase	5–30 μM	300 nM	Moon et al. (2021)	17/8/21	This work is based on the detection of Levodopa from fingertip passive sweat after the subjects have consumed L-dopa pill
29	Levodopa	CA	Printed gold electrode/GO-ZIF8	Tyrosinase	1–95 μM	0.45 μM	Xiao et al. (2022)	16/2/22	This paper is based on a wearable patch which uses GO and MOF as the immobilization matrix for Tyrosinase enzyme
30	1. Uric Acid 2. Paracetamol 3. Paroxetine 4. Ethinylestradiol	DPV	1. IF/carbon ink/Carbon Black 2. MF/carbon ink/Printex 6L carbon 3. RF/carbon ink/Printex 6L carbon	No bioreceptors used	1. 1–43 μM (artificial sweat)	1. 1.37 μM 2. 0.247 μM 3. 0.493 μM 4. 0.935 μM	Raymundo-Pereira et al. (2022)	4/2/22	This report details the fabrication of a glove based sensor for the detection of drugs from artificial sweat.

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
			4. Glove little finger/pretreated carbon ink		2. 1–10 μM (artificial sweat) 3. 1–10 μM (artificial sweat) 4. 1–10 μM (artificial sweat)				
31	1. Dipyridamole (DIPY) 2. Acetamenophen 3. Caffeine	DPV	BDDE	No bioreceptors used	1. 0–10 μM 2. 0–10 μM 3. 0–10 μM	1. 50 nM 2. 50 nM 3. 50 nM	Lin et al. (2020a)	24/1/20	This report details the creation of a BDDE based electrode for the optimization of potential window for the determination of DIPY, acetamenophen, caffeine
32	Acetaminophen	DPV	(BDDE)	No bioreceptors used	1–100 μM	1 μM	Lin et al. (2020b)	27/7/20	This report details the creation of a BDDE based electrode that is resistant to biofouling for the optimization of potential window for the determination of acetamenophen
33	1. Cathinones 2. pH	1. DPV 2. OCP	1. Au 2. Au/PANI	Aptamer	1. 0.001–5 μM 2. 4-8	1. 0.57 nM	Zhang et al. (2022a)	7/6/22	This paper reports on the use of aptamers for the detection of multiple illicit drugs with great specificity
Section E: Sweat based smart patches and self- powered epidermal sensors									
34	1. Heart Rate and Blood Pressure 2. Glucose (ISF) 3. Lactate 4. Caffeine 5. Alcohol	1. Time of flight between echoes from anterior and posterior walls 2. CA 3. CA 4. DPV 5. CA	1. Piezoelectric lead zirconate 2. PB 3. PB 4. MWCNT 5. PB	2. GOx 3. LOx 5. AlOx	2. 0–0.1 M 3. 0–30 mM 4. 0–32 mM 5. 0–210 μM	Information not given	Sempionatto et al. (2021a)	15/2/21	This paper detailed the construction of a multiplexed sensor, which measured for the first time HR, BP using a PZT, glucose from ISF (Iontophoresis), lactate, alcohol, and caffeine using the delivery of pilocarpine, which is a sweat inducing drug. All of these parameters were monitored simultaneously when the subjects were subject to activities which varied these metabolites.
35	Glucose	Amperometry	PB	GOx	Physioloigcal Ranges	Information not given	Bolat et al. (2022)	11/1/22	This report details on the combination of the polycarpine based sweat generation with PDMS based sweat direction towards a glucose sensing surface. This patch is used for the wearable detection of sweat glucose.

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
36	1. Glucose (ISF) 2. Alchohol (Sweat)	1. Amperometry 2. Amperometry	1. PB ink 2. PB ink	1. GOx 2. AlOx	1. 0–160 μM 2. 0–40 mM	Information not given	Kim et al. (2018)	2/10/18	This report precedes the work in 34.
37	Vitamin C	Amperometry	Metalized Carbon (Rhodium)	AAOx	100–1000 μM	Information not given	Sempionatto et al. (2020)	26/6/20	This report details a Vitamin C sensor, which can detect Vitamin C from Iontophoretically derived swea after the subject consumes Vitamin C tablet.
38	1. Tyrosine 2. pH	1. DPV 2. OCP	1. Carbon/Tannic Acid-Ag-CNT-PANI 2. Carbon/PANI	No bioreceptors used	1. 10–200 μM 2. 3.98–8.09	1. 3.3 μM	Xu et al. (2023)	28/4/23	This detection of tyrosine in this sensor is achieved by pilocarpine induced iontophoretic generation of sweat. Additionally this sensor is also capable of measurement of sweat pH. Additionally, the composite used in this work posses antibacterial properties, which makes it ideal for wearable applications.
39	1. Na^+ 2. pH 3. Lactate 4. Glucose This whole unit is operated by a standalone battery because of which this comes in the self powered sensing category	1. OCP 2. OCP 3. Potentiometric 4. Potentiometric	1. Carbon/polyvinyl butyral 2. C/PANI 3. C/NQ 4. C/NQ	3. LOx 4. GOx	1. 0.1–100 mM 2. 3-8 3. 0–15 mM 4. 0–0.5 mM	Information not given	Yin et al. (2022)	6/10/22	This report details the fabrication of a standalone wearable sensor, which is powered by a Ag_2O–Zn battery. The sensors on this device are all potentiometric in nature. This sensor is also characterized by a PEDOT: PSS display unit, which is capable of giving instantaneous levels of the analyte because of the change in color due to changes in its redox state.
40	1. Lactate 2. Ascorbic Acid 3. pH This sensor is operated by the storage of powered derived from a LOx-BOx biofuel cell. This power is stored in a Zn–AgCl battery for ensuring long time operation.	1. Self powered sensing (Potentiometric) 2. Self Powered Sensing (Potentiometric) 3. Potentiometric	1. C/NQ/LOx (Anode)-Ag_2O (Cathode) 2. C/tetrathiafulvalene (TTF)-tetracyanoquinodimethane/ Ascorbic Acid (anode)- Ag_2O (Cathode) 3. Ion selective membranates	1. Lox	Physioloigcal Ranges	Information not given	Yin et al. (2023)	11/12/22	This sensor represents a scenario where sweat is used to generate power, which is stored by wearable batteries. The sweat collected for this power generation is also fed to sensors, which measure the concentration of analyses in the potentiometric mode. This example shows an independent sensor, which does not need to be powered by an external power source.

Section F: ISF based subdermal electrochemical sensors for monitoring individual well being

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
41	Lactate	Amperometry	Carbon Ink	LOx	1–20 mM	Information not given	Freeman et al. (2023)	28.3.23	This MN based sensor reports on the use of a 3rd generation (direct electron transfer) based lactate oxidase for the detection of lactate from ISF
42	Lactate	Amperometry	Au MN/Au-MWCNT/pMB	LOx	10–200 μM	2.4 μM	Bollella et al. (2019)	26.10.23	This sensor reports on the use of a second generation based LOx sensor for the detection of ISF from ISF.
43	1. Glucose 2. Lactate 3. Alcohol	Amperometry	1. MN/o-PD	1. GOx 2. LOx 3. AOx	Physiological Range	Information not given	Tehrani et al. (2022a)	9.5.22	This MN based sensor reports on the use of a multiplexed MN based sensor for the detection of glucose, lactate, and alcohol form ISF.
44	Sodium	I–V characteristics	Au/ion selective membrane	No bioreceptors used	10–160 mM	2.78 μM	Zheng et al. (2022b)	16.12.21	This sensor is a FET based biosensor for the detection of sodium from ISF.
Section G: ISF based subdermal electrochemical sensors for monitoring markers of healthcare									
45	β-Lactam	Potentiometric	MN/Gold/IrO_2	β-Lactamase	0–5 mM	6.8 μM	Gowers et al. (2019)	26.4.19	This paper reports the use of a pH based potentiometric sensor involving the hydrolysis of the analyte by its specific enzyme for the detection of the analyte from human ISF.
46	β-Lactam	Potentiometric	MN/Gold/IrO_2	β-Lactamase	0–1 mg/L	0.17 mg/L	Rawson et al. (2019)	30.10.19	This report is the first human based evaluation of the use of MNs for drug monitoring in healthy volunteers.
47	1. Phenylalanine 2. Vancomycin 3. Cortisol	SWV	Au	1. Phenylalanine 2. Cortisol 3. Vancomycin	1. 0–250 μM 2. 0–500 μM 3. 0–5 μM	Information not given	Friedel et al. (2023)	14.6.23	This report is the one of the first human based evaluations of the use of MNs immobilized with aptamers for the detection of drug in human ISF.
48	1. Cefazolin 2. Nicotine	SERS	Cellulose Paper/Au/Agarose	No bioreceptors used	1. 10^{-2} -10^{2} 2. 10-2 -102	1. 0.01 ppb 2. 0.01 ppb	Hsieh et al. (2023)	10.3.23	This manuscript reports the development of a PEGDA/MeHA MN for the extraction of ISF followed by the SERS based detection of Cefazoin and Nicotine from ISF.
Section H: ISF based subdermal theranostic patches									
49	Diabetes management. This patch consists of mesoporous MN based reverse iontophoretic glucose sensor and insulin delivery 1. Glucose sensing 2. Insulin Delivery	1. Amperometry 2. Iontophoretic delivery	1. MN base/Planar Gold/PB 2. PGMA and PEG	1. GOx 2. Insulin	1. 0–20 mM 2. 4 mg/mL (current based, 0.5 mA); 5.8 mg (over 180 min free diffusion)	Information not given	Li et al. (2021c)	3.6.21	This work represents one of the first reports of the use of a simultaneous measurement and sensing system for diabetes management.

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Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
50	Diabetes management inspired by masticatory system of animals 1. MN for ISF exudation (MN puncher@hybrid electrode (MNPHE)) 2. Planar gold electrode for sensing of glucose, Na^+, and K^+ ions 3. Peristaltic pump based insulin delivery (MN puncher@delivery patch) (MNPDP)	1. Pressing of MN for ISF exudation using pump activated pressing 2. Amperometry for sensing glucose, Na+, and K^+ 3. Pump activated MN pressing and delivery of MN stored insulin.	2. PET/rGO-CNT/PtNP (glucose, Na^+, and K^+)Na^+- Sodium ionophore 3. Valinomycin (Potassium ionophore)	2. GOx 3. Insulin	2. 0.4-4- mM (glucose), 5–160 mM (Na^+), 1–32 mM (K^+)	2. 0.4 mM (glucose)	(Yang et al.)	8.2.22	This system presents an example of an animal masticatory system inspired MN needle based glucose sensing and insulin delivery system.
Section I: Wearable Sensors for Veterinary applications									
51	pH	Amperometry	Dopamine conjugated hyaluronic acid embedded with PEDOT:PSS	No bioreceptor used	3.5–8	Information not provided	Odinotski et al. (2022)	27.9.22	Fabrication of a swellable hydrogel based MN sensor for the sensing of ISF pH in small live animals. The swellable nature of this MN makes it capable of drawing more volume of ISF. This work was carried out in mice models
52	CGM Glucose dependent insulin and glucagon delivery	Delivery dependent on CGM readings	Dopamine conjugated hyaluronic acid embedded with PEDOT:PSS	Insulin and glucagon are delivered	4.8 mg insulin and 1.6 mg of glucagon delivered using MN	Information not provided	(Yang et al.)	30.9.22	This report details the creation of a glucose dependent insulin and glucagon delivery for the management of hyper and hypoglycaemia in animals
Section J: Wearable Sensors for plant health monitoring									
53	Growth Monitoring	Bioimpedance spectroscopy	Vapor Printing of p-doped poly (3,4-propylenedioxythiophene)	No bioreceptor used	Information not provided	Information not provided	(Kim et al.)	15.3.19	This sensor, which involves vapor deposited patterns on surfaces of leaves is capable of measuring life cycle of plant
54	1. Volatile organic compounds 2. Temperature 3. Humidity	1. Resistive 2. Resistive (Integrated with humidity) 3. Resistive	1. Solgel layer of methyltrimethoxysilane and tetramethyl ortho silicate/Gold coated Au@Ag NW + MWCNT/ flourothiophenol 2. Au@Ag NW 3. Nafion	No bioreceptor used	1. 100–500 ppm (Acetone); 100–500 ppm (Hexanal)	Information not provided	(Lee et al.)	12.4.23	This report details the fabrication of a multiplexed sensor for the monitoring of leaf metabolites.
55	1.Salicylic acid 2. Ethylene (phytohormones)	1.DPV 2. CV	1. CuMOF 2. Cu complex + CNT	No bioreceptor used	1. 0.1 μM–1000 μM 2. 0.1–115 ppm	1. 0.644 μM 2. 0.6089 ppm	Hossain and Tabassum (2023)	17.6.23	This sensor is capable of measuring phytohormones of plants
56	Glucose in plants	Amperometry	1. Carbon PB	GOx	20–80 μM	9.4 μM	(Perdomo et al., 2023)	8.3.23	This sensor offers the option of measuring light and heat based stress in plants by measuring the glucose levels in plant leaves. Iontophoretic approaches are used for sampling and the sensing surface is attached to the

(*continued on next page*)

Table 2 (*continued*)

No	Analyte	Signal Detection	Material	Bioreceptor	Dynamic Range	LOD	Ref	Date	Other Information
									leaf surface using barium ferrite magnets.
57	Humidity in plants	Resistive sensing	LIG/GO	No bioreceptor used	0–100%	Information not provided	Lan et al. (2020)	30.6.20	This report details the fabrication of a simple sensing surface involving commercially viable LIG surface for the measurement of humidity in leaves.
58	NO_3^-/NH_4^+	OCP	Laser Induced graphene/Ion selective membranes	No bioreceptor used	10^{-5}-10^{-1} M	28.2 ± 25.0 μM (NH_4^+), 20.6 ± 14.8 μM (NO_3^-)	Garland et al. (2018)	14.9.18	This sensor is capable of measuring soil based nitrate and ammonium ions and is based on laser induced graphene
Section K: MNs for plant-based metabolite and pesticide sensing									
59	Glucose in plants	CA	PDMS MN/Silk Fibroin/Pt wire	GOx	30–180 mM	Information not provided	Zheng et al. (2022a)	7.9.22	This MN based sensor is used to monitor glucose in different growth levels of plants
60	Pesticide Residue (Thiram and thiabendazole)	SERS	Au NP/sodium hyaluronate/ polyvinyl alcohol	No bioreceptors were used	10^{-7} to 10^{-4} M (Thiram),10^{-8} to 10^{-5} M (thiabendazole)	10^{-7} M (Thiram) 10^{-8} M (thiabendazole)	Yi et al. (2023)	19.1.23	The MN based sensors here are used to collect pesticide residues from the surface of leaves and these residues are detected using Surface enhanced Raman spectroscopy.

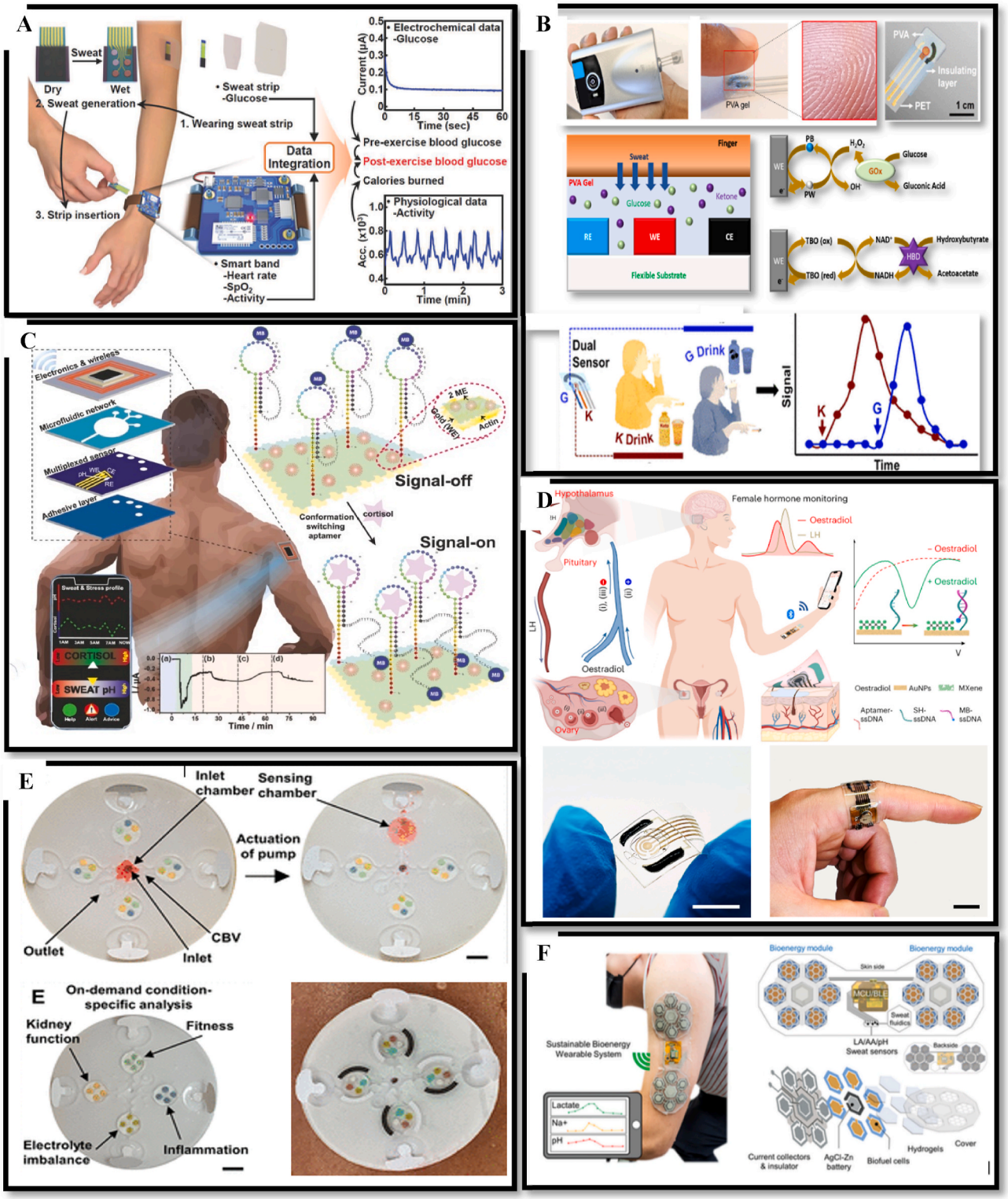

Fig. 3. (A) A wearable sensing strip combining reported by Hong et al. for sensing of glucose from sweat combined with continuous monitoring of vital signs like heart rate, blood oxygen levels, and physical activity. (Reproduced with permission from Wiley Materials) (Hong et al., 2018). (B) A fingertip passive sweat based sensing platform for the sensing of glucose and ketone bodies reported by Sempionatto et al. (Reprinted (adapted) with permission from (Sempionatto et al. 2020, 2021b). Copyright American Chemical Society). (C) Pesudoknot aptasensors developed by Singh et al. for the sweat based detection of cortisol during physical exercise (Reprinted from (Singh et al., 2023) with permission from Elsevier). (D) A wearable sweat based aptasensor developed by Ye et al. for the real time determination of oestradiol from sweat (Reproduced with permission from Springer Nature) (Ye et al., 2023). (E) A wearable colorimetric sweat based sensor for the simultaneous detection of kidney function, electrolyte imbalance, inflammation, and fitness developed by Mishra et al. (Reprinted (adapted) with permission from (Mishra et al., 2022), Copyright American Chemical Society). (E) Wearable lactate powered biofuel cell for powering sweat pH, ascorbic acid, and lactate sensing reported by Yin et al. (Reproduced with permission from Wiley Materials) (Yin et al., 2023).

functionality, Moon et al. successfully integrated a ketone sensor, while microfluidic channelling of sweat provided alternative avenues for glucose detection, as exemplified by Xiao et al. (Moon et al. 2022; Xiao et al. 2022).

While much of the research on sweat-based detection has revolved around glucose, lactate, and ionic analytes, Upasham et al. introduced a novel application—SLOCK, a sensor designed for circadian clock measurement (Upasham et al., 2021). This sensor aims to map an individual's chronobiology by measuring cortisol and DHEA levels in sweat. Utilizing antibody-based sensor surfaces, EIS was employed to measure cortisol (ranging from 0.1 to 500 ng/mL) and dehydroepiandrosterone (DHEA) (ranging from 2 to 131 ng/mL) in sweat. Torrente-Rodriguez presented a graphene-based cortisol sensor created via laser engraving for monitoring diurnal cortisol changes and stress responses. The sensor, utilizing anti-cortisol monoclonal antibodies, successfully detected cortisol in sweat within the range of 5 ng/mL after a 1-min incubation. A positive correlation between sweat and serum cortisol was established for the first time, showcasing the sensor's potential in stress-level monitoring during aerobic exercise (Torrente-Rodríguez et al., 2020).

Several studies explored cortisol detection using aptamers, benefiting from their high specificity, stability, and cost-effectiveness compared to antibodies. An example by Eun An et al. involved a flexible and wearable platform with a cortisol aptamer immobilized on electrospun polyacrylonitrile nanofibers vapor deposited with PEDOT. Operating as a liquid ion-gated field-effect transistor on a PET substrate, this sensor achieved high selectivity, detecting cortisol at 10 pM and 1 nM in a few minutes (An et al., 2022). Su et al. modified a CNT-infused polyurethane film with a Ni-based MOF to capture aptamers with peroxidase activity, resulting in a switch OFF-type sensor for cortisol detection in the range of 0.1–100 ng/mL (Su et al., 2023). Singh et al. developed a pseudoknot-based cortisol aptamer for real-time sweat--based detection in the range of 1 pM to 1 μM, demonstrating its efficacy in induced stress conditions (Singh et al., 2023) (Fig. 3C). Lastly, Ye et al. reported a wearable aptasensor for the non-invasive monitoring of oestradiol, utilizing iontophoresis to generate sweat. The detection electrode, modified with an MXene-Au electrode, achieved ultra-high sensitivity with a low detection limit of 0.14 pM, establishing a strong correlation between sweat and blood estradiol levels in human subjects (Ye et al., 2023) (Fig. 3D).

Wearable Optical Epidermal Biosensors: In the field of wearable biosensors, optical sensors present an appealing avenue due to their potential for rapid readouts, especially colour changes (Li et al., 2021b; Mishra et al., 2022) (Fig. 3E). Xiao et al. introduced a microfluidic chip-based wearable colorimetric sensor for glucose detection from sweat, relying on the interplay of GOx-peroxidase-o-dianisidine reagents. The sensor, allowing simultaneous detection at five locations, achieved a LOD of 0.03 mM, although variations in the correlation between serum and sweat glucose levels were observed across subjects (Xiao et al., 2019). Ardalan et al. advanced this concept with an Internet of Things (IoT)-integrated cellulose-based microfluidic patch capable of fluorometrically detecting glucose, lactate, chloride, pH, and sweat volume. Challenges persist in real-time monitoring due to the static nature post-sweat interaction (Ardalan et al., 2020). Zhao et al. explored similar strategies on a flexible wearable fabric for optical detection of chloride, pH, and glucose on the forehead (Zhao et al., 2021). Recent work by Yang et al. incorporated microfluidic networks, integrated valves, and microscale optical cuvettes for copper and chloride ions, glucose, and pH detection in sweat (Yang et al., 2023). Despite these advancements, inherent challenges persist, such as sweat contamination, high evaporation rates, and low areal density on the skin surface in most sweat-based sensing systems (Mohan et al., 2020). Efforts to enhance sensitivity and overcome these limitations are imperative for the continued development of optical epidermal biosensors.

The predominant focus of wearable sensors has revolved around monitoring metabolites like glucose, lactate, cortisol, metal ions, and pH in sweat. However, recent developments highlight a surge in research dedicated to sensing disease biomarkers. For instance, Jagannath et al. designed a wearable platform for real-time monitoring of inflammatory bowel disease, detecting IL-1β and CRP through affinity-based interactions measured by EIS (Jagannath et al., 2020). This approach offers promise for early-stage diagnosis and prognosis. Another study by Upasham et al. demonstrated a similar strategy for detecting IL-31, a biomarker for atopic dermatitis, presenting a machine learning algorithm to predict disease flare-ups (Upasham et al., 2022). Additionally, efforts have extended to heart disease biomarkers, with Wei et al. introducing an electrochemical sensing system for simultaneous detection of cholesterol, transferrin, and potassium ions in sweat, demonstrating its potential for atherosclerosis detection (Wei et al., 2023). The same group expanded their efforts to detect sodium ions, ascorbic acid, and human NPY in sweat as potential cardiovascular health biomarkers (Wei et al., 2022).

Optical sensors offer rapid readouts and have the potential to revolutionize real-time monitoring applications. However, the practical implementation of these sensors faces challenges related to signal interference, post-sweat interaction dynamics, and calibration requirements. Improvements in sensor design, signal processing algorithms, and data interpretation methodologies are crucial for enhancing the reliability and accuracy of optical epidermal biosensors in practical settings. The utilization of nanomaterials in epidermal sensors for metabolite detection represents a promising avenue for enhancing sensitivity and selectivity. However, the translation of laboratory-based research into real-world applications necessitates rigorous validation and optimization processes. Furthermore, the integration of multiple functionalities, such as glucose and ketone sensing, demonstrates the versatility of wearable sensors. Yet, challenges persist in ensuring robust sensor performance under varying physiological conditions and environmental factors, such as temperature and humidity fluctuations.

The use of self-powered wearable sensors has been a promising avenue in epidermal sensing. Such an option allows the use to use the sensors with power derived from the human body. Yin et al. introduced a pioneering integration of sweat lactate biofuel cells with a rechargeable Zn–AgCl battery into a bioenergy module, enabling regulation-free, high-efficiency, and extended biochemical energy harvesting and storage (Fig. 3F). The integrated module demonstrates robust mechanical durability, enduring over 1000 cycles of repeated tensile deformation, and outstanding long-term autonomous operation, harvesting 2.9 J of energy overnight from just 20 min of exercise without measurable self-discharge. Furthermore, a fully integrated wearable electronic skin patch, powered by two such bioenergy modules, allows for wireless continuous monitoring of sweat pH, ascorbic acid, and lactate levels, presenting a practical, high-efficiency, and reliable solution for next-generation wearable electronics (Yin et al., 2023).

Wearable MN (Subdermal) Sensors for Comprehensive Well-being Monitoring: Wearable MN (subdermal) sensors have shown promising advancements in monitoring markers of well-being, particularly in human studies (Section F, Table 2). Freeman et al. introduced a 3rd generation sensor for lactate detection using metalized polycarbonate MNs (MNs). The sensor employed lactazyme (a recombinant LOx enzyme) immobilized on MN surfaces, utilizing direct electron transfer for lactate oxidation. The long-term wearable lactate sensing platform demonstrated significant correlations with blood lactate levels, albeit with variations between trials (Freeman et al., 2023). Future directions may focus on minimizing trial variability, mitigating the impact of pre-existing skin lactate, and improving sensor use duration. Recently, our group reported on the use of polyphenol-based immobilization of glucose and lactate oxidising enzymes. The immobilization was carried out on platinized subdermal patches, which were worn by a participant (Fig. 4A).

This report monitored changes in glucose levels over a 3 day period in addition to corelating variations in lactate to volume of O_2 uptake and exhaled CO_2 (Vulpe et al., 2024b). Capillary blood measurements and

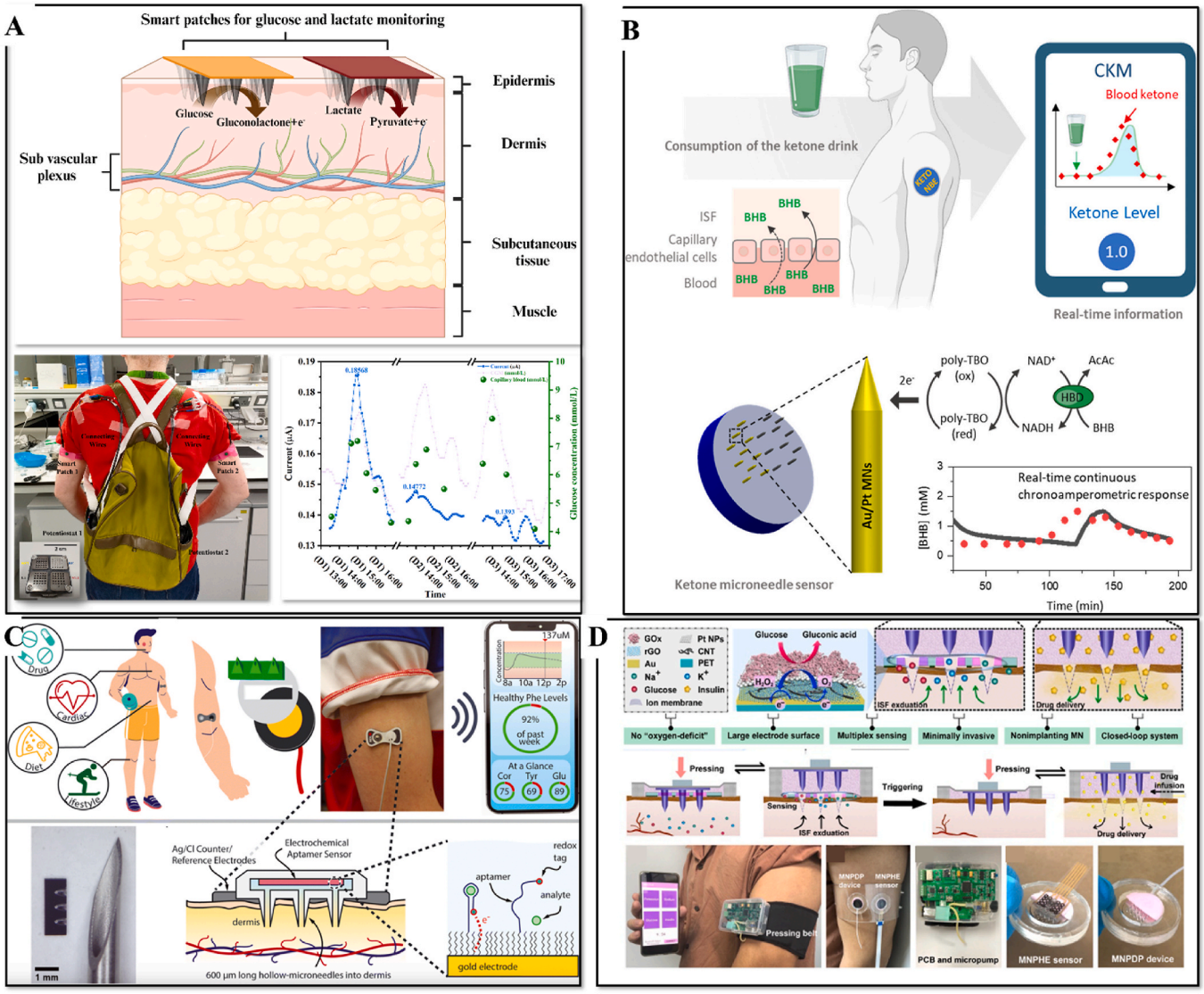

Fig. 4. (A) Wearable MN based monitoring of glucose over a 3-day period in ambulatory conditions (Reported with permission from Royal Society of Chemistry) (Vulpe et al., 2024b). (B) Wearable 3D printed subdermal wearable patch for the enzymatic monitoring of ketones from ISF *Reprinted (adapted) with permission from* (Moonla et al. 2024). Copyright American Chemical Society. Wearable MN based aptasensor aptasensor for the detection of cortisol and amino acids reported by Friedel et al. (Reported with permission from Royal Society of Chemistry) (Friedel et al., 2023). (D) Wearable MN based biosensing of glucose from exudated ISF animal mastication reported by Yang et al. (Open Access).

measurements obtained from a Freestle Libre were taken as primary and secondary standards in this study. Moonla et al. used 3D printed subdermal patches metalized with gold for the detection of ketones from ISF. The sensor was composed of β-hydroxybutyrate dehydrogenase enzyme, its co factor nicotinamide adenine dinucleotide, toluidine blue as mediator. These components were immobilized on the MNs along with CNTs followed by coating chitosan and polyvinyl chloride as protection layers (Moonla et al., 2024). The sensor was operated for a period of 4 h with blood ketone levels being adopted as the primary standard (Fig. 4B).

In second-generation lactate biosensors, Bollella et al. achieved a milestone by developing a sensor utilizing multi-walled carbon nanotubes, polymethylene blue, and lactate oxidase-modified gold MNs (Bollella et al., 2019). This biosensor offered real-time monitoring of lactate levels, showcasing the potential for dynamic lactate measurement. Tehrani et al. took a comprehensive approach, constructing a fully integrated MN array system for real-time detection of glucose, lactate, and alcohol (Tehrani et al., 2022b). The enzymatic nature of these sensors, along with their second-generation characteristics, allowed for simultaneous monitoring, responsive to daily activities like eating, drinking, and exercise. Zheng et al. contributed to the field by fabricating a MN extended-gate field-effect transistor (FET) designed for real-time sodium monitoring in ISF (Zheng et al., 2022b). The versatility of MN modifications enables the detection of various parameters such as pH, cortisol, and glucose. These innovations signify promising strides in wearable MN sensors, offering real-time, multifaceted monitoring capabilities for improved well-being assessment.

Subdermal wearable sensors hold promise for multifaceted well-being monitoring. However, challenges such as signal drift, biofouling, and biocompatibility issues need to be addressed to ensure the long-term reliability and safety of these sensors. Additionally, the scalability and cost-effectiveness of fabrication techniques for MN-based sensors warrant further optimization and standardization efforts.

Wearable MN (Subdermal) Sensors for Healthcare Monitoring: Wearable MN (subdermal) sensors hold substantial promise in therapeutic drug monitoring, presenting opportunities for commercialization (Section G, Table 2). Gowers et al. innovatively employed gold MNs (Au MNs) to continuously monitor β-Lactam antibiotic concentrations *in vivo*

(Gowers et al., 2019). The sensor, incorporating β-Lactamase immobilized within a hydrogel matrix, demonstrated a facile preparation method. An iridium oxide layer facilitated pH changes resulting from β-Lactam hydrolysis, with a low detection limit of 6.8 μM. In the realm of real-time drug monitoring, Rawson et al. conducted a ground-breaking first-in-human evaluation using MNs for phenoxymethylpenicillin (Rawson et al., 2019). Volunteers wearing β-lactam sensors were dosed, revealing a robust correlation between MN data, free blood, and microdialysis data. Future studies may involve actual patients to gather dosing information for incorporation into automated drug delivery systems. Friedel et al. reported a MN-based sensor for phenylaniline detection in interstitial fluid post-oral medicine intake (Friedel et al., 2023). The sensor design, extracting interstitial fluid to an ex vivo surface with specific aptamers, demonstrated clinically relevant detection within physiological ranges (Fig. 4C). Addressing signal stability challenges, Li et al. introduced an agarose hydrogel to filter high molecular weight biological components affecting aptamer sensors (Li et al., 2023). Hsieh et al. presented controllable-swelling MNs for interstitial fluid collection, employing functionalized moist cellulose papers for analyte recovery (Hsieh et al., 2023). This approach enabled colorimetric sensing of glucose and surface-enhanced Raman spectroscopy (SERS) sensing of nicotine, antibiotics, pesticides, and organic dyes. The study highlights rapid assays for diverse molecules but suggests the need for real-time detection by fixing cellulose papers to the MNs on the body.

Wearable Theranostics MN Patches: Wearable theranostics MN patches offer innovative solutions for diabetes management (Section H, Table 2). Xie et al. developed a closed-loop system integrating mesoporous MNs for real-time blood glucose tracking and treatment. The system comprises a glucose-sensing module using reverse iontophoresis, a flexible printed circuit board module with signal processing and wireless communication functions, and an insulin delivery module based on iontophoresis. This fully integrated wearable system precisely detects glucose changes, displaying fluctuations on mobile devices via Bluetooth. Additionally, Xie's group addressed safety concerns and the "oxygen-deficit" issue by introducing a non-implanted MN theranostics platform inspired by animal masticatory systems (Li et al., 2021c) (Fig. 4D). The platform includes a sensing module with MNs for ISF exudation and carbon nanomaterial-modified hybrid electrodes for glucose, K^+, and Na^+ sensing. The drug release module, controlled by a micropump, enables controllable rapid and sustained release. The pneumatic control ensures non-implantable characteristics, circumventing safety, and oxygen-deficit challenges.

Theranostics MN patches represent an innovative approach to diabetes management, offering real-time glucose tracking and treatment capabilities. However, the complexity of closed-loop systems and the integration of multiple functional components pose engineering and regulatory challenges. Moreover, ensuring the safety and efficacy of non-implanted MN platforms in long-term clinical use requires extensive validation studies and regulatory approvals.

Wearable Sensors for Veterinary Applications and Plant Health Monitoring: Wearable sensors play a vital role in veterinary applications and plant health monitoring (Section I, J, and K Table 2). For veterinary use, Odinotski et al. developed MNs for pH detection in animals using a hydrogel containing dopamine, conjugated hyaluronic acid, and PEDOT: PSS(Odinotski et al., 2022). Meanwhile, Yang et al. introduced a glucose-responsive MN patch for dual-hormone delivery (insulin and glucagon analogue) in a closed-loop system based on phenylboronic acid derivatives.

This system effectively regulates blood glucose levels under varying conditions (Fig. 5A) (Yang et al.). In plant health monitoring, Kim et al. utilized vapor print conformal conjugated polymer electrodes for continuous monitoring, while Lee et al. employed multimodal sensors on leaf surfaces for measuring volatile organic compounds, temperature/humidity, and environmental humidity (Fig. 5B) (Kim et al.; Lee et al.). Hossain et al. developed a sensor suite for crop health monitoring, including phytohormones, vapor pressure deficit, and radial growth of stems (Hossain and Tabassum 2023). Additionally, Perdomo et al. utilized reverse iontophoresis to extract glucose from plant leaves, offering a novel approach to monitor stress-induced changes (Perdomo et al., 2023). Lan et al. employed interdigitated laser-induced graphene-based electrodes to monitor transpiration in plants, showing potential for smart agricultural applications (Lan et al., 2020). Garland et al. used laser-induced graphene surfaces for monitoring soil ammonium and nitrate ions (Garland et al., 2018). In the context of plant growth, Zheng et al. designed a silk-MN patch embedded with wire electrodes for glucose monitoring in plant tissue (Fig. 5C), and Yi et al. developed hydrogel MNs with Ag nanoparticles for the sensitive detection of pesticide residues using surface-enhanced Raman spectroscopy (SERS) (Fig. 5D) (Yi et al., 2023; Zheng et al., 2022a). These advancements highlight the diverse applications of wearable sensors in veterinary and plant health, contributing to improved diagnostics and management practices. Parilla et al. reported a novel approach to plant health monitoring, addressing the pressing need to understand in situ physiological processes amidst the challenges of climate change and increased food demand. Utilizing a low-cost 3D-printed hollow MN array (HMA) patch coupled with biosensors, the study enables affordable analysis of biomarkers like glucose, peroxide, and pH in plant fluid, offering insights into plant stress. The developed electrochemical platform presents precise sensors for real-time monitoring of plant health, potentially enhancing precision farming practices to ensure sustainable agriculture in changing environmental conditions (Parrilla et al., 2024).

The comprehensive exploration of wearable sensors presented in this section underscores their transformative impact across human, animal, and environmental health. The convergence of technological innovations, interdisciplinary research, and real-world applications positions wearable sensors as crucial elements in advancing the "One Health" initiative. These applications not only exemplify the current state of the field but also lay the foundation for future advancements that hold the potential to revolutionize health monitoring and management practices across diverse ecosystems.

The application of wearable sensors in veterinary medicine and agriculture holds promise for improving diagnostics and management practices. However, the translation of sensor technologies from human to animal and plant systems requires consideration of species-specific physiological factors and environmental variables. Additionally, the development of robust sensor platforms for continuous monitoring in dynamic agricultural settings remains a formidable challenge.

While wearable sensors offer unprecedented opportunities for advancing health monitoring across diverse ecosystems, critical challenges related to sensor performance, reliability, safety, and regulatory compliance must be addressed. Collaborative efforts among interdisciplinary research teams, industry partners, regulatory agencies, and end-users are essential for realizing the full potential of wearable sensor technologies in transforming healthcare, veterinary medicine, and environmental monitoring.

Challenges: While wearable sensors hold immense promise for revolutionizing health monitoring, several challenges and opportunities lie ahead in their development and implementation. This section provides a critical assessment of current limitations and proposes future directions to address them effectively.

Sensor Performance and Reliability: One of the primary challenges facing wearable sensors is ensuring consistent and reliable performance over extended periods. Factors such as sensor drift, signal interference, and environmental influences can affect the accuracy and precision of measurements. Addressing these challenges requires advancements in sensor design, material selection, and signal processing algorithms to minimize noise and enhance signal-to-noise ratios. Additionally, the development of calibration protocols and quality assurance measures is essential for maintaining sensor accuracy and reliability over time.

Biocompatibility and Long-term Implantation: For subdermal wearable sensors, ensuring biocompatibility and mitigating tissue reaction are critical considerations. The long-term implantation of sensors may

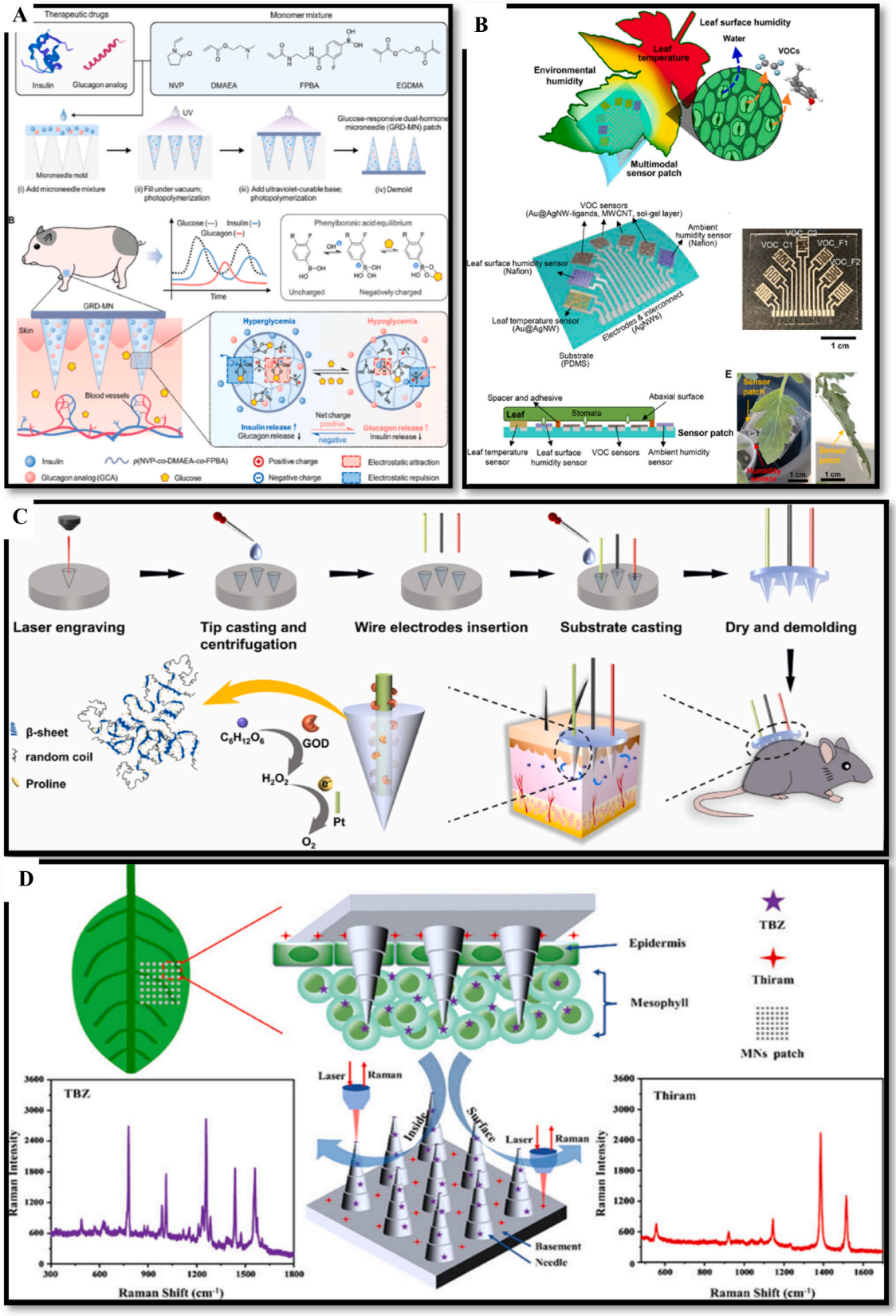

Fig. 5. (A) Glucose-responsive dual-hormone patch by Yang et al. from a silicone mold for glucose-triggered insulin and glucagon release (Open Access) (Yang et al.). (B) Resistive plant-based biosensors reported for the detection of VOC emanating from plants reported by Lee et al. (Open Access) (Kim et al.) (C) Silk MN based biosensors for the detection of glucose from plants and animals reported by Zheng et al. (Reprinted from with permission from Elsevier) (Zheng et al., 2022a). (D) A MN based patch for the detection of pesticide residues from leaf surfaces based on SERS reported by Yi et al. (Reprinted (adapted) with permission from. Copyright American Chemical Society (Yi et al., 2023)).

trigger immune responses or tissue damage, affecting sensor performance and patient comfort. Novel biomaterials with enhanced biocompatibility profiles and strategies for minimizing tissue trauma during sensor insertion are areas of active research. Furthermore, long-term studies evaluating the safety and efficacy of implanted sensors in real-world clinical settings are necessary to address regulatory concerns and ensure patient safety.

Standards and Guidelines: The lack of standardised protocols and guidelines for wearable sensor development and deployment poses significant challenges for regulatory approval and widespread adoption. Establishing consensus standards for sensor performance, data security, and privacy protection is essential for ensuring interoperability and facilitating regulatory clearance. Collaborative efforts among regulatory agencies, industry stakeholders, and academic researchers are needed to develop comprehensive guidelines that address the unique challenges of wearable sensor technologies.

Data Privacy and Security: With the proliferation of wearable sensors, ensuring the privacy and security of sensitive health data is paramount. Unauthorized access to personal health information or data breaches can have serious implications for patient confidentiality and trust in wearable sensor technologies. Robust encryption algorithms, secure data storage solutions, and transparent data sharing practices are essential for safeguarding patient privacy and maintaining data integrity. Moreover, ethical considerations regarding informed consent, data ownership, and data usage rights must be carefully addressed to protect patient rights and autonomy.

Clinical Validation and Real-world Utility: Despite promising research findings, the clinical validation and real-world utility of wearable sensors remain limited. Bridging the gap between laboratory-based studies and clinical practice requires rigorous validation studies in diverse patient populations and healthcare settings. Moreover, demonstrating the clinical efficacy, cost-effectiveness, and user-friendliness of wearable sensor technologies is essential for driving widespread adoption and reimbursement by healthcare payers.

User Acceptance and Engagement: User acceptance and engagement are critical determinants of the success of wearable sensor technologies. Designing intuitive user interfaces, minimizing device burden, and maximizing user comfort are essential for enhancing user acceptance and adherence to sensor usage protocols. Furthermore, incorporating feedback from end-users and healthcare providers during the design and development process is crucial for ensuring the usability and effectiveness of wearable sensor technologies in real-world settings.

6. Conclusions & future perspectives on use of sweat patches and MNs for overall healthcare

In conclusion, significant developments have been made in advancing wearable molecular sensing technology, particularly in the area of materials (Arjun et al., 2023b; Nguyen et al., 2019), biomarkers (Arjun et al., 2022), bioreceptors, device integration (Sanghavi et al., 2014), and microfluidics (Kasturi et al., 2021b; Torati et al., 2017). The incorporation of innovative 2D materials such as MXenes in sensor surfaces holds promise, with their ability to minimize immune responses upon skin contact (Arjun et al., 2023a; Fusco et al., 2023). Future research will explore the use of MXenes for immobilizing biologically active molecules and crafting MXene-based MNs tailored for metabolite detection in ISF and sweat (Ankitha et al., 2022). For prolonged wearable sensor performance, crucial studies on biofouling are essential, focusing on when and to what extent fouling occurs—a key aspect yet to be extensively explored beyond tissue phantoms or *in vitro* setups.

The emphasis on disease-specific biomarkers within the skin compartment, especially for early-stage detection of conditions like melanoma and dementia, signifies a pivotal shift in the trajectory of wearable molecular sensing devices. The evolution from real-time continuous monitoring to frequent surveillance of biomarker variations in both sweat and ISF underscores the imperative need for high-specificity biomarkers. A burgeoning interest in commercialization is poised to propel products encompassing microRNA detection in ISF (Kasturi et al., 2021a), wireless devices (Arjun et al., 2023b; Yoo et al., 2023), real-time monitoring of drug pharmacokinetics (Tai et al., 2018), and sophisticated big data analytics for early disease prediction (Vaghasiya et al., 2023).

Future directions in this dynamic field include the optimization of MN arrays for heightened extraction efficiency and the integration of microfluidic devices to manage volumes effectively. These directions include:

Multimodal Sensor Integration: The integration of multiple sensing modalities into wearable sensor platforms offers opportunities for comprehensive health monitoring and personalized healthcare delivery. By combining physiological, biochemical, and environmental sensors, wearable devices can provide a holistic view of an individual's health status and environmental exposures. Moreover, multimodal sensor integration enables real-time data fusion and analysis, facilitating early disease detection, intervention, and personalized treatment strategies.

Artificial Intelligence and Machine Learning: The integration of artificial intelligence (AI) and machine learning (ML) algorithms into wearable sensor technologies holds promise for enhancing data interpretation, predictive analytics, and decision support. By leveraging AI/ML techniques, wearable devices can learn from user data patterns, identify deviations from normal physiological parameters, and provide personalized health insights and recommendations. Furthermore, AI/ML algorithms can optimize sensor calibration, data pre-processing, and anomaly detection, improving the accuracy and reliability of wearable sensor measurements.

Longitudinal Health Monitoring: Longitudinal health monitoring using wearable sensors enables continuous tracking of health parameters over time, providing valuable insights into disease progression, treatment response, and wellness trends. By leveraging longitudinal data analytics and predictive modelling, wearable devices can detect subtle changes in health status, identify early warning signs of disease exacerbation, and facilitate timely interventions. Moreover, longitudinal monitoring enables the assessment of treatment efficacy, adherence, and patient outcomes, supporting personalized healthcare management and precision medicine approaches.

Collaborative Research and Innovation: Addressing the complex challenges of wearable sensor development and deployment requires collaborative research and innovation across interdisciplinary teams and stakeholder groups. By fostering partnerships between academic researchers, industry experts, healthcare providers, regulatory agencies, and patient advocacy organizations, collaborative initiatives can accelerate the translation of wearable sensor technologies from bench to bedside. Moreover, open-access data sharing platforms, collaborative research networks, and funding incentives can facilitate knowledge exchange, technology transfer, and rapid innovation in the field of wearable sensors.

Whilst wearable sensors offer unprecedented opportunities for advancing health monitoring and personalized healthcare delivery, critical challenges related to technological, regulatory, and clinical translation must be addressed to realize their full potential. By embracing interdisciplinary collaboration, innovative research methodologies, and stakeholder engagement, the future of wearable sensor technologies holds promise for transforming healthcare and improving patient outcomes across diverse populations and settings.

Abbreviation from Table	Full form
ASV	Anodic Stripping Voltammetry
CA	Chronoamperometry
OCV	Open Circuit Voltage
AlOx	Alcohol Oxidase
AscOx	Ascorbate Oxidase
NiHCF	Nickel hexacyanoferrate
PANI	Polyaniline

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Abbreviation from Table	Full form
PB	Prussian Blue
GOx	Glucose Oxidase
OCP	Open Circuit Potential
NCT	N doped carbon textile
LOx	Lactate Oxidase
CSSY	Core Sheath sensing yarn
CBCT	Carbon based Conducting thread
CFM	Carbon Fiber Membrane
SPCE	Screen Printed Carbon Electrode
TB	Toluidine Blue
HBD	Hydroxybutyrate Dehydrogenase
DTSSP	3,3′-dithiobis (sulfosuccinimidyl propionate
LIG	Laser Induced Graphene
PAN	Polyacrylonitrile
HRP	Horseradish Peroxidase
SPE	Screen Printed Electrode
CRP	C-reactive protein
CQD	Carbon quantum dots
CD	Cyclodextrin
CCP	conductive carbon paste
ZIF	Zinc imidazolate framework
IF	Index Finger
MF	Middle finger
RF	Ring Finger
BDDE	Boron-doped diamond electrode
pMB	Poly Methylene Blue
o-PD	o-phenylene diamine
PGMA	poly (glycidyl methacrylate)
PEG	Polyethylene Glycol
NW	Nanowire
GO	Graphene Oxide

CRediT authorship contribution statement

Georgeta Vulpe: Writing – original draft. **Guoyi Liu:** Writing – original draft. **Sam Oakley:** Writing – original draft. **Dimitrios Pletsas:** Visualization. **Guanghao Yang:** Software. **Rosa Dutra:** Writing – original draft. **Owen Guy:** Writing – review & editing. **Yufei Liu:** Writing – review & editing. **Mark Waldron:** Writing – review & editing. **Joe Neary:** Writing – review & editing, Writing – original draft, Validation. **Arjun Ajith Mohan:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Sanjiv Sharma:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This review on wearable biosensing technologies was performed during the duration of DASA/DSTL grant on “Simultaneous monitoring of glucose and lactate using wearable sensors in ambulatory conditions (DSTL 0000010329)”. The views expressed are those of the author(s) and not necessarily those of DASA/DSTL.

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