Biomicrofluidics REVIEW pubs.aip.org/aip/bmf

Advances in textile-based microfluidics for biomolecule sensing

Cite as: Biomicrofluidics 18, 051502 (2024); doi: 10.1063/5.0222244
Submitted: 6 June 2024 · Accepted: 23 August 2024 ·
Published Online: 17 September 2024

View Online Export Citation CrossMark

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ABSTRACT

Textile-based microfluidic biosensors represent an innovative fusion of various multidisciplinary fields, including bioelectronics, material sciences, and microfluidics. Their potential in biomedicine is significant as they leverage textiles to achieve high demands of biocompatibility with the human body and conform to the irregular surfaces of the body. In the field of microfluidics, fabric coated with hydrophobic materials serves as channels through which liquids are transferred in precise amounts to the sensing element, which in this case is a biosensor. This paper presents a condensed overview of the current developments in textile-based microfluidics and biosensors in biomedical applications over the past 20 years (2005–2024). A literature search was performed using the Scopus database. The fabrication techniques and materials used are discussed in this paper, as these will be key in various modifications and advancements in textile-based microfluidics. Furthermore, we also address the gaps in the application of textile-based microfluidic analytical devices in biomedicine and discuss the potential solutions. Advances in textile-based microfluidics are enabled by various printing and fabric manufacturing techniques, such as screen printing, embroidery, and weaving. Integration of these devices into everyday clothing holds promise for future vital sign monitoring, such as glucose, albumin, lactate, and ion levels, as well as early detection of hereditary diseases through gene detection. Although most testing currently takes place in a laboratory or controlled environment, this field is rapidly evolving and pushing the boundaries of biomedicine, improving the quality of human life.

INTRODUCTION

In recent decades, researchers have been seeking ways to reduce the volume of fluids required for analysis and laboratory work, such as blood and urine, due to the preference for non-invasiveness[1] and patient comfort.[2] Basically, only 100 μl[3] or even lower volumes of blood are used per test for laboratory work. However, a greater volume of blood is collected,[4] approximately 3–5 vials, each containing 8.5 ml. The sampling process is currently guided by the operator's experience, but this could be minimized through automation[5,6] and miniaturization.[7–9] Therefore, microfluidics has emerged as a promising solution to address this limitation in medicine due to the utilization of minuscule amounts of fluids to extract valuable information.[10–13]

Over the years, the field of microfluidics has continuously evolved while maintaining its advantages and addressing its drawbacks.[14–17] This field involves analyzing fluid characteristics and components in a controlled environment using minimal volumes of the targeted fluid. The field of microfluidics has found application in diverse industries, particularly through lab-on-chip devices, which can swiftly and efficiently detect pathogens in fluids such as blood.[18–22] This platform requires lower volumes of liquids than traditional laboratory methods, contributing to its efficiency and detection speed.[17]

For the past few decades, most researchers have shown interest in harnessing environmental advantages more through paper-based and cloth-based microfluidic devices.[23–26] This interest has led to an increased usage of microfluidic paper-based analytical devices

(μPADs) in numerous applications, such as diagnostics,[27–31] environmental testing,[32] food,[33–36] pharmaceutical,[37–39] and clinical samples.[30,31,37,40–42] To overcome the short durability of the μPADs, textile-based analytical devices (μCADs) have gained attention in biomedical applications.[43–46] From 2006, there has been a steady rise in papers related to textile-based microfluidic devices, where four papers were published that year. In the following years, up to 2012, the publication numbers were relatively constant, after which 11 papers advanced the field of textile-based microfluidics. Furthermore, 25 papers were published in 2019, followed by 28 papers in 2020, in 2021, 25 papers, and then in 2022, 19 papers were published. Finally, in 2023, the highest number of papers yet in this field were published, totaling 37 papers. Moreover, there is a decrease in the number of publications in the period between 2020 and 2023. As for all of the research in this field, fabrication and testing in laboratory settings has to be done, which was limited from 2019 to 2022. More precisely, due to the COVID-19 pandemic, there was limited access to laboratories, aside from restrictions in terms of the number of people using the laboratory at a time. With that in mind, a decrease in publications, which require practical testing, is expected during the pandemic.

Microfluidic textile-based analytical devices (μCADs) or microfluidic fabric-based analytical devices (μFADs) are a low-cost alternative to traditional laboratory testing. They were first introduced in 2011 with the aim of enhancing point-of-care testing and disease screening.[47] The concept of μCADs was initially introduced by Dendukuri and co-workers, using woven silk yarns.[47] Since then, μCADs have continued to evolve and gain attention among researchers. Various traditional Micro-Electro Mechanical System (MEMS) fabrication methods, such as photolithography, and other textile-based methods, such as weaving, stitching, and manual cutting, have been utilized. Additionally, wax has been commonly used to create hydrophobic channels for fluid direction.[48]

The development of simple, rapid, low-cost, and highly sensitive biosensors has contributed to the progress of personalized healthcare and ultrasensitive point-of-care disease biomarker detection. This has led to the extensive exploration of biosensor research and development.[49–51] As analytical devices used to detect specific chemical components in substances, biosensors have naturally found their way into the field of microfluidics, particularly in developing microfluidic analytical devices. Moreover, in recent decades, the integration of electrochemistry in textile electronics has led to the emergence of textile-based biosensors, which offer promising advancements in the field of sensor technology.[31,46,52,53]

The integration of microfluidics and biochemistry has led to advancements in biosensing. Textile-based biosensors use materials, such as cotton, neoprene, Gore-Tex, and combinations of polyamide and cotton, as the base for sensing.[54–56] Additionally, conductive materials, such as carbon and its derivatives, silver, and other conductive materials, are layered onto the substrate to create a sensing region.[54] Electrodes woven from conductive threads and yarns have been utilized after functionalization.[57]

The ability of wearable biosensors to monitor vital physiological characteristics, such as blood oxygenation, respiration rate, skin temperature, movement, brain activity, blood pressure, and sweat composition, *ex vivo* has garnered significant attention in recent years.[58–63] Wearable biosensors made from textiles demonstrate the feasibility of creating functional biosensors on fabric, indicating that textile-based biosensors should also be used for chemical sensing. However, current wearable chemical sensors are prone to mechanical damage and often need large rigid electronic components.[63] Therefore, incorporating these textile-based biosensors in a closed, microfluidic system should be the next landmark in research in this field.

The development of microfluidic cloth-based analytical devices has become crucial at the intersection of diverse multidisciplinary fields, including biomechanics, bioelectronics, and portable sensing, as well as fundamental sciences, such as medicine and materials science.

Textiles, especially conductive threads, fibers, and yarn, and those coated with conductive materials, show significant sensing capabilities, with and without additional functionalization. Moreover, textile thread coated with wax creates a hydrophobic path, enabling the traversing of analytes.[48] Polydimethylsiloxane (PDMS) and other materials widely used in microfluidics have a detrimental effect on the environment and require a harsher fabrication process. In contrast, textiles utilize far more environmentally friendly fabrication methods.[55,64,65]

A new avenue in the development of bendable, stretchable, conductive materials in the past decade has been the use of liquid metals.[66,67] More precisely, metal alloys, for example, gallium-based, are liquid at room temperature, enabling easy moldability and adhesion onto irregular surfaces.[67] With that in mind, there has been much interest in these alloys, especially in the field of microfluidics, successfully being integrated into micropumps, microvalves, mixers, and droplet generators.[67] Furthermore, their high conductivity has been an effective sensing parameter in sensorics. Moreover, they have been used to develop strain, pulse, and motion sensors, which can be placed on the human body.[68–70] Liquid metals can be molded into microfibers, and they have potential use in textile electronics.[68] With this high diversity in application, liquid metals pose a great research direction in textile-based microfluidics and even more so, as they have not yet been used in this field at all.

The primary challenge in microfluidics that limits their application in biosensing is the lack of standardization,[71] as well as the difficulties in using a minimal volume of fluids in complex systems to fully describe specific behavior or to detect the target analyte of interest.[72] Moreover, these problems compound the challenges in the field of biosensing, creating an even greater obstacle to overcome.[73] It is important to note that one of the main problems in this field is a lack of experiments that deal with real patient samples using biosensors. This is evident in the papers reviewed, as the focus is on the laboratory environment. In addition to current developments in textile-based microfluidics and biosensors in biomedical applications, this will be the main focus of this review.

The main objective of this paper is to identify the gaps in the application of textile-based microfluidic analytical devices in biomedicine. Additionally, it needs to provide an overview of fabrication techniques and materials used, which can lead to various modifications and advancements. Furthermore, novel ways of use and inspiration can be discovered by presenting the diverse applications of textile-based microfluidic analytical devices.

Figure 1 summarizes this review paper and its crucial structural points.

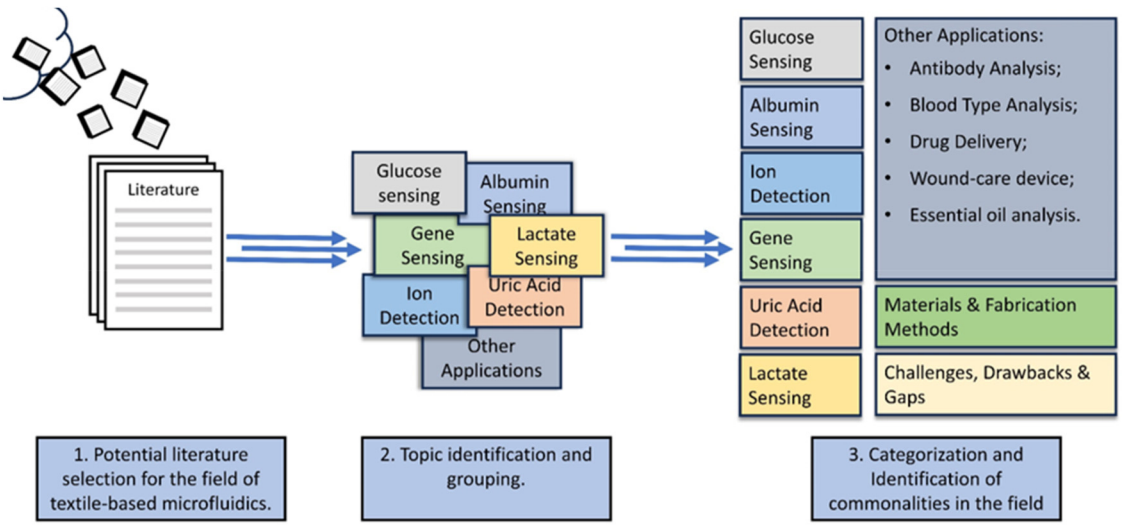

FIG. 1. Review summary of the presented review paper on textile-based microfluidics for biomolecule sensing.

MATERIALS AND FABRICATION TECHNIQUES

In μCADs, cotton fibers are the most common materials used in their fabrication.[55,74–86] Moreover, materials, such as carbon fibers[87–89] and cloth,[56,90–92] nylon,[74,75,93,94] silver,[57,95] cellulose,[64,65] and polyester threads,[86,96,97] are utilized as well. This is due to the widespread accessibility of cotton, polyester, and nylon used in manufacturing hollowed fibers. It is important to note that extensive research was done in the field of thread flow direction in microfluidic devices, where a consistent flow rate on cotton threads of 0.38 μl s^{-1} was achieved.[98] Table I shows the characteristics and use of these base materials, as well as if they have been tested in a clinical or laboratory setting. Similarly to Table I, a graphic depiction of the number of papers published, which made functional realizations, is shown in Fig. 2.

Furthermore, cost analysis was conducted to better present these materials' availability. As of 2024, we have compiled prices of carbon fibers, nylon thread, carbon cloth, polyester thread, silver thread, raw cellulose, and cotton. The cost analysis was done by comparing prices on different sites; therefore, these are approximations. Carbon fibers cost around €9–€30 per kg, while nylon thread €10–€20 per km and carbon cloth approximately from €27 to €54 per m^2. Furthermore, polyester thread costs between €3 and €10 per km, which, alongside cotton (€1–€2 per kg) and raw cellulose (€4–€10 per kg), presents one of the cheapest options in the fabrication of cloth-based microfluidic devices. Finally, silver thread has the highest cost per kg, going from approximately €100 to €200. These prices are indicators of the availability of the materials; cotton presents the most common material used in μCADs. On the other hand, silver thread, even though it is the most expensive option, its usefulness, as a conductive thread may be a reason for its wide presence in published papers in Fig. 2.

Different substrate materials have been used in biosensors, each with their advantages and limitations. Cotton is one of the most researched and used substrate materials in the field of biosensors. Being a natural material with wide availability, cotton has become the most cost-effective substrate material in biosensor development.[74–86] It has good biocompatibility and is suitable for immobilizing biological elements, such as enzymes or DNA, which in turn aids in the process of sensing. By providing a non-reactive and porous surface for effective immobilization, cotton, as a substrate, allows for efficient binding of targeted biomarkers.[84,86] On the other hand, carbon fibers offer unique properties, some contrasting the properties of cotton, making the fibers suitable for use as substrate materials in biosensors.[87–89] These properties include high mechanical strength, excellent electrical conductivity, and a large surface area, which, similar to cotton, enables efficient immobilization of biological elements and enhances biosensor sensitivity.[87–89] As a synthetic representative, nylon thread has been found to be useful, especially for its higher chemical and temperature stability, compared to the aforementioned substrate materials.[93,94] As a key component of cotton, cellulose has been used as a substrate material, having a crystalline structure that gives high tensile strength.[64,65] Its greater insolubility in water and chemical stability are favorable properties that enable better compatibility with textiles and easier use on the body. This aspect of cellulose should be explored more in the future, as it has only been done in laboratory settings with simulated, artificial analytes.[65] One of the least used materials, silver thread presents an unexplored avenue for substrate use in biosensors. Moreover, its good temperature, electrical stability, and antibacterial properties are vital aspects that contribute to its potential to integrate textile-based microfluidic biosensors in everyday clothing.

The specific coatings, which are put on substrate materials, with the aim of making it sensitive to certain biomarkers are specifically related to the targeted analytes of interest. Therefore, those materials and coatings will be described in detail in the Applications section of this paper.

TABLE I. Materials with their characteristics used in textile-based microfluidics.

Material	Characteristics	Stability	Use in textile-based microfluidics	Clinical/ laboratory setting	Pros/cons	Reference
Cotton	Biocompatible; affordable; lightweight; biodegradable; 95% cellulose; 1.3% proteins; 1.2% minerals; can be treated with polymers for greater endurance	Good thermal conductivity (degrades between 130 and 340 °C); water absorbability may affect the functioning of specific biosensors	Substrate material for various biosensors; coated with wax to create hydrophobic paths for liquids; treated; used as the sensing part for different biosensors (e.g., adrenaline, mercury, uric acid, ion, etc.)	Laboratory setting only	Pros: cheap; good thermal conductivity Cons: water absorbability; needs to be treated with polymers for better endurance	55 and 74–86
Carbon fibers	High degree of mechanical strength; high rigidity; light weight; expensive; biocompatible	Superior chemical resistance; exceptionally little thermal expansion	Used as the scaffold for detecting biomarkers in sweat	Laboratory setting only	Pros: superior chemical resistance; high degree of mechanical strength; light weight Cons: expensive; rigid	87–89
Nylon thread	More resistant to chemical abrasion than cotton or silk; cheap; non-biodegradable and biocompatible	Good stability over time; good resistance to alkalis, but is susceptible to destruction in acidic environments; thermoplastic material; degrades from 240 to 260 °C	Substrate material; stable for addition of different conductive; sensitive inks; for detecting alkaloids, antibodies in blood, and glucose	Laboratory setting only	Pros: cheap; resistant to chemical abrasion compared to cotton or silk Cons: non-biodegradable; UV sensitive; heavy pollutant	74, 75, 93, and 94
Carbon cloth	Due to their more complex nature, carbon cloth is more flexible than carbon fibers; expensive; biocompatible	When activated, it is highly homogenous during joules effect heating	Substrate material; glucose and heavy ion sensing	Laboratory setting only	Pros: highly flexible; biocompatible; highly homogenous Cons: expensive; environmental impact; limited flexibility	56 and 90–92
Polyester thread	Not biodegradable; stretchable; high strength, durability, and extensiveness; hydrophobic nature; biocompatible	Can deteriorate under direct sunlight	Substrate material; reported use in adrenaline biosensors	Laboratory setting and human preliminary test	Pros: biocompatible; hydrophobic nature; durable Cons: UV sensitive; non-biodegradable	86, 96, and 97
Silver thread	Biocompatible; durable; heat and humidity can affect its properties; highly conductive; expensive	Resistant to friction; stable conductance values up until 200 °C; decomposition at 370 °C; oxidation	Modified and treated with a chlorine salt; can be used as a reference Ag/AgCl electrode	Laboratory setting only	Pros: highly conductive; durable; biocompatible; resistant to friction Cons: expensive; susceptible to oxidation	57 and 95
Cellulose	Biocompatible; biodegradable; cheap; high tensile strength; crystalline structure	Do not rapidly degrade; chemically stable; insoluble in water	Used as a substrate material	Laboratory setting only	Pros: biocompatible; biodegradable; chemically stable; high tensile strength Cons: lack of elasticity; moisture absorption; shrinkage over time	64 and 65

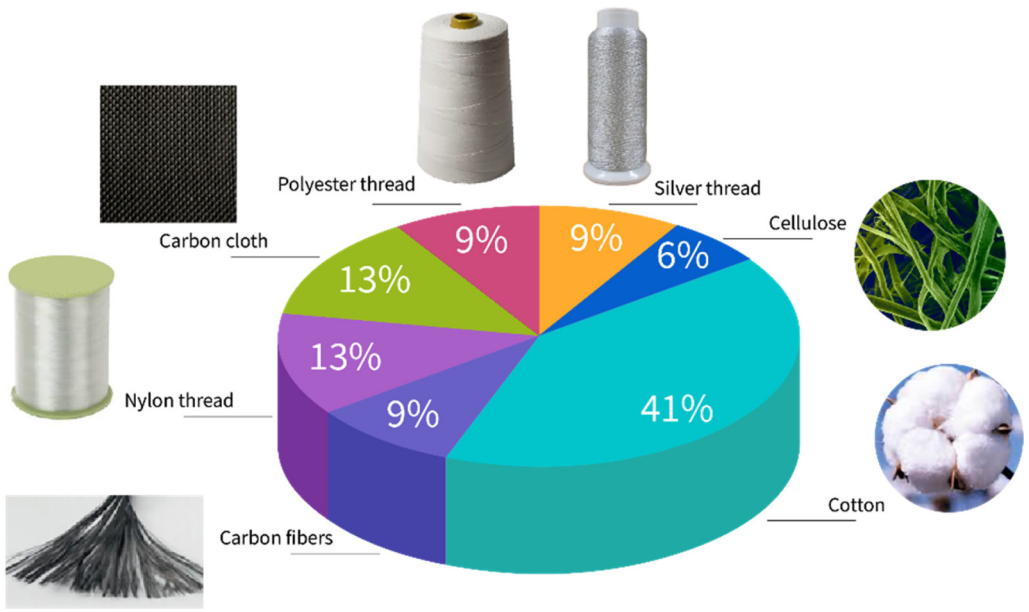

FIG. 2. The percentage of papers published on the materials used in textile-based microfluidics.

Finally, all the previous substrates, as well as the targeted biomarkers, have only been used in laboratory settings, except polyester thread. This gap of non-on-patient experiments simulating real-life settings should be filled and explored in the near future, as it is a vast plane for improvement.

Noting that the fabrication of μCADs and textile-based biosensors is an interdisciplinary field, there are a myriad of fabrication methods that ought to be used with the goal of manufacturing a functional μCADs biosensor, as seen in Table II. From embroidery,[55,57] digital and hand-done, 3D printing,[74,99,100] screen printing,[48,78,80,101–103] grafting,[77] laser utilization,[74,79,104] to the use of functionalization methods, such as immersion,[99] coating,[93,100,105] evaporation,[90] adsorption,[48] acid treatment,[106] drop casting,[65] and deposition,[55,75] there is vast potential to be found in new and modified fabrication methods by bridging these two fields. In μCADs, one of the main methods of fabrication is the combination of embroidery and screen printing. More precisely, screen-printing methods are used to print wax as a non-conductive and hydrophobic layer onto textile, while with embroidery, conductive channels are made.[55,57] Screen-printing methods are more common, as the hydrophobic wax layer and the conductive sensing layer can be fabricated.[74,99,100] Of the presented fabrication techniques, screen printing was used the most often, followed by embroidery, 3D printing, laser utilization, and coating. The least used fabrication techniques were deposition, immersion, drying, adsorption, evaporation, acid treatment, and drop casting.

Figure 3 represents a decision matrix based on the cited literature and Table II. Each fabrication technique was categorized into one of three groups (high, medium, or low) depending on the criteria (cost, precision, scalability, safety, speed of production, material versatility, and number of publications). Finally, based on the previous criteria, application suitability was determined.

APPLICATIONS IN BIOMEDICINE

With the dawn of the Internet of Things (IoT), many developments have been made in the field of telecommunications, making it integral in wireless and miniaturized biomedical and healthcare applications. As an extension to this, IoT has enabled faster ways of communication in nano-integrated wearable biosensor devices, especially in healthcare. Biosensors, with their wide applications in biomedicine, upgraded with 5G in IoT, have enabled further advancements in telemedicine, as well as in curing, monitoring, and disease detection.[107] As a solution to the need for miniaturization but not degrading the characteristics of biosensors, μCADs have been introduced. These devices can be integrated into textiles, be wearable, and not obstruct the user's day-to-day life. Moreover, in a previous review, functional components, such as microvalves, micromixers, microfilters, and velocity control elements, were described in detail. Finally, the future outlook, which gave concern on stability, automatization, as well as integration of flow control components, will be addressed, now that a few years have passed. The development of cloth-based multiplex assays through the following biosensor applications will also be addressed.[43]

Much interest in recent years has been focused on developing threads with specific properties, which can be implemented as transducers in sensing applications. Chemiluminescent detection systems have been exploited in food analyses through the investigation of the aforementioned cloth and thread systems.[108] This effect is not only present in the food analysis domain, but it has also

TABLE II. Overview of fabrication methods for manufacturing functional μcAD biosensors.

Fabrication technique	Advantage	Drawbacks	Use in μCADs	Reference
Embroidery	Digital or hand-done; fast process; can be used for rapid and mass production	Thread needs to have a certain mechanical resistance; thread is damaged during fabrication	Common practice; used to fabricate the channels	55 and 57
3D printing	Fast and cheap fabrication; easily modifiable; can be used as an assistive method for other fabrication techniques	Spending on the building material; can be easily destroyed; hard to print on smaller scales; prone to variation in size	Used as a mold or an underlying structure	74, 99, and 100
Screen printing	Fastest fabrication technique; even distribution of ink on the designated area; can be used for mass production	Limited to the number of molds on the frame; more material is lost than in other techniques	Used for creating hydrophilic and hydrophobic paths	48, 78, 80, and 101–103
Laser utilization	Extremely precise fabrication method; fast	Expensive; dangerous	Creates hydrophilic and hydrophobic paths by activating the photoresist	74, 79, and 104
Deposition	Precise control over thickness and uniformity; creates high-quality films with good adhesion; suitable for various materials	Limitation in scalability for large areas for deposition; expensive and may require special work conditions	Good for specific precise functionalization of certain areas; good for development of sensor arrays	55 and 75
Immersion/ drying	Cost-effective; can be used in mass production; not substrate specific, high versatility, and applicability	Film thickness and uniformity can vary; less precise in comparison with deposition	Can be applied to various fabric types; used for large-scale production	99
Coating	Simple and cost-effective; versatile; can be used in large-scale production	Limited control over thickness of the coated area; uneven coatings	Used for applying multiple different layers	93, 100, and 105
Adsorption	Can be applied to complex structures to little consequence; simple and cost-effective	Limited process, as it is surface dependent; requires optimization as it depends on the materials used; limited control over uniformity and thickness	Adsorption is employed for attaching bio-recognition elements onto fabric surfaces; useful for modifying cloth to make it receptive to specific analytes; practical for developing cloth sensors with enhanced specificity through the adsorption of biomolecules	48
Evaporation	High purity of deposited material; good control over film thickness	Vacuum is needed, especially for high purity deposition; complex equipment is needed	Used in creating thin films with enhanced sensitivity on cloth; applicable in small-scale settings where precise deposition is needed	90
Acid treatment	Effective in functionalization and surface modification in any way; can enhance wettability and adhesion	Dangerous; requires careful handling; limited control over specific modifications; if not used properly, it can result in the destruction of the material	Complex use, as it can easily damage the cloth; used to improve the adhesion quality of the cloth	106
Drop casting	Versatile and suitable for a wide range of materials; cost-effective; safe	Limited control over uniformity and thickness; less precise in comparison to deposition techniques	Applicable to point-of-care or on-site sensor fabrication	65

been used in many biosensing applications, such as glucose in urine and serum detection and the detection of H_2O_2 in milk.[109] With their seamless and non-toxic contact with human skin, textiles possess the potential to passively and non-invasively harness information from biological fluids excreted from the human skin. Most of these biosensors are based on sweat analysis and detecting specific biomarkers that can indicate an imbalance in the examinee's system in real-time. Some of these biomarkers are metabolites, such as glucose, electrolytes, neuropeptides, cytokines, trace elements, and small molecules, from which significant research has been done in the field of urea and cortisol detection.[110] Through the investigation of the aforementioned biomarkers, the

	Cost	Precision	Scalability	Safety	Speed of Production	Material Versatility	Number of Publications	Application Suitability
Embroidery	Low	Low	Medium	High	Medium	Low	Medium	Medium
3D Printing	Medium	Medium	Medium	High	Medium	Medium	Medium	Medium
Screen-printing	Low	Medium	High	High	High	Medium	High	High
Laser Utilization	High	High	Low	Low	High	Low	Medium	Low
Deposition	High	High	Low	Low	Low	Low	Medium	Low
Immersion/ Drying	Low	Low	High	Medium	High	High	Low	High
Coating	Low	Low	High	Medium	High	High	Medium	High
Adsorption	Medium	Medium	Medium	Medium	Low	Medium	Low	Medium
Evaporation	High	High	Low	Low	Low	Low	Low	Low
Acid Treatment	Medium	Medium	Low	Low	Medium	Low	Low	Low
Drop Casting	Low	Low	Medium	Medium	Medium	High	Low	Medium

FIG. 3. Graphical depiction of the number of papers using different fabrication methods in textile-based microfluidic biosensors.

physiological status of the human body can be tracked, with the possibility of sending real-time nutritional information, as well as grading athletic performance, to the examiner or physician.[55] When engaging in physical activity, the assessment of sweat loss could accurately indicate how dehydrated the human body is. When a person is very dehydrated, their body's electrolyte concentration will rise, which could result in homeostasis disbalance. To better understand the interaction between μCADs and various biological fluids, we present a detailed summary of the key properties of sweat, blood, and saliva (Table III). This summary includes fluid composition, typical biomarker content, and the challenges and advantages of using each fluid in μCADs.

The selection of biological fluids for μCADs significantly influences sensor design. For example, low concentration of biomarkers in sweat requires highly sensitive sensors, whereas blood's complex matrix necessitates robust separation and detection technologies. Saliva's fluctuating pH and enzyme content require μCADs that can operate effectively under variable conditions.

Keeping in mind the liquids mentioned above, the importance of the selected biomarkers (glucose, albumin, lactate, uric acid, ions, and genes) in this section is reflected in their integral part in the stable functioning of the human body as a whole. The significance of monitoring and detection of these biomarkers is as follows:

Glucose: Glucose presents a significant biomarker in the human body, as its significance stems from the possibility of monitoring the well-being of patients who have diabetes through it. Moreover, through glucose and its fluctuation in blood or sweat, different pathological states can be identified and caught early, preventing serious complications, which can lead to loss of life. For example, aside from diabetes, hypoglycemia and hyperglycemia can be monitored through glucose sensing.[116]

Lactate: Lactate is a key biomarker in biomedicine, essential for assessing metabolic conditions, exercise physiology, and clinical scenarios. Lactate levels are crucial for understanding anaerobic metabolism, especially during high-intensity exercise with limited oxygen. Elevated levels indicate reliance on anaerobic pathways, informing training in sports medicine.[117]

Albumin: Serum albumin levels indicate the health and function of the liver, as these proteins are produced by it. Moreover, a decrease in albumin levels can be an indication of inflammation. Furthermore, low albumin levels can result from rapid fasting or malnutrition.[118]

TABLE III. Summary of key properties of biological fluids of interest used in μCADs.

Biological fluid	Key properties	Common biomarkers	Challenges in detection	Advantages in detection	Reference
Active sweat	Produced during physical activity; higher protein content, variable pH	Glucose, electrolytes, lactate	Variability in sweat rate, contamination, limited volume	Can provide real-time information on metabolic activity	111
Passive sweat	Produced while at rest; lower protein content, more stable pH	Electrolytes, cytokines	Less variation, but lower volume and lower biomarker concentration	More stable and less influenced by external factors	111
Blood	High protein content, neutral pH, contains a wide range of biomarkers	Glucose, hormones, proteins (e.g., albumin)	Requires anticoagulants, risk of infection	Broad range of biomarkers, well-established detection methods	112
Saliva	Moderate protein content, enzymes, fluctuating pH	Hormones, antibodies, glucose	Influence of food intake, diurnal variations	Non-invasive collection, can be collected easily	113
Urine	Contains waste products, electrolytes, and metabolites	Creatinine, urea, electrolytes, drug metabolites, hormones	Concentration variability, sample handling, complex matrix, limited biomarker range	Reflects renal function and metabolism, easy to collect	114
Interstitial fluid	Similar to blood plasma but with lower protein content	Glucose, lactate, cytokines, proteins, cortisol	Collection method, fluid dynamics, variability, limited research	Provides localized biomarker information, less invasive than blood	115

Ion: Ions, especially metal ions, are crucial for functioning underlying biological processes, such as catalysis, osmotic regulation, metabolism, and cell signaling. For example, ions, such as Na+ and K+, maintain fluid and electrolyte balance. Variations in levels of these ions can indicate different significant problems in the human body.[119]

Gene: Through the development and use of precision medicine, species identification, and pathogens detection, gene monitoring and detection have become significant. Monitoring and detecting genes in clinical practice can provide improved solutions for accurate diagnosis and precise therapy of different complex and severe illnesses.[120]

Uric acid: Uric acid is a major product of purine nucleoside breakdown in humans, primarily excreted through the kidneys with a concentration of 2–10 mM in sweat. High levels of uric acid can pose risks for various diseases, such as cardiovascular diseases, type 2 diabetes, renal diseases, and gout.[121]

Previously presented applications are still in the investigation stage and/or done in laboratory settings. They are yet to be executed on human volunteers, which provide vast space for research. The lack of standardization in the field of microfluidics and biosensors is found in this merged field as well. With the growing rate of publications and research done in the field of textile-based microfluidic analytical devices, standardization should be considered. It would greatly speed up the fabrication process and leave more room for the development of sensing and monitoring aspects. Moreover, the high variability of sensitivities and limits of detection indicates that there is a consequence of the fabrication process, as well as the choice of structural elements. Through further testing, these shortcomings can be evened out.

Despite significant advances in textile-based microfluidic devices for various biomedical applications, several challenges remain unaddressed. These include scalability of production processes, reaching clinically relevant sensitivity and specificity, integration with broader healthcare systems for data analysis and monitoring, and ensuring long-term stability and functionality of the embedded sensors in diverse environmental conditions. The prohibitive cost of microchip fabrication and poor sensitivity due to small sample volumes in a microfluidic format poses a challenge.[122] Second, the need for complex surface modifications and selective functionalization of textile materials to create microfluidic channels with switchable water transport adds complexity to the manufacturing process.[123] Additionally, while simple methods, such as painting hydrophobic zones on cotton cloth, have been proposed for fabricating microfluidic devices, ensuring dimensional reproducibility and barrier integrity remains a concern.[124] These factors altogether affect the scalability of textile-based microfluidic device production processes, highlighting the need for further research and innovation to address these challenges and enhance the viability of these devices for widespread biomedical applications.

Future research should focus on the development of novel nanomaterials that enhance the sensitivity and selectivity of μCADs for biomarker detection. Additionally, integrating these devices with wireless technology could pave the way for real-time health monitoring systems. Research could also explore the use of biocompatible and robust materials to ensure that devices can withstand long-term use without degradation, particularly in wearable formats.

For instance, enhancing the sensitivity of glucose detection in sweat could greatly benefit diabetes management, while advancements in the detection stability of albumin could improve the monitoring of kidney and liver diseases. Moreover, innovative designs for ion detection in sweat could lead to better hydration strategies for athletes and individuals in extreme environments.

Finally, before describing the state-of-the-art and current trends of the most prolific types of biosensors, it is important to

emphasize that these systems require energy. With that in mind, great strides have been achieved in the field of flexible fuel cells, which have power-storage properties or energy-harvesting methods implemented in them.[125]

Textile-based microfluidics have covered many biosensing areas through the detection of various biomarkers. From that, ion detection (17 publications) and glucose sensing (14 publications) garnered the most research interest. Furthermore, lactate, albumin, and uric acid have lower detection success, as indicated by around five published papers, per biomarker. Notably, gene detection through textile-based microfluidic devices has gained interest in recent years.

Glucose detection

Blood glucose level is a crucial sign of diabetes and needs to be closely monitored for the treatment of the aforementioned condition. The intense regulation of blood glucose concentration in diabetic patients would be made possible by continuously monitoring the glucose level *in vivo*, non-invasively. Long-lasting implantable sensors lessen the frequency of implantation and replacement, which in turn decreases patient discomfort. The ability to implant thread-based sensors in the body with the least amount of invasiveness makes glucose measurement intriguing for long-term monitoring. Diet and degree of activity impact a person's blood glucose levels. Monitoring glucose concentration in perspiration is a straightforward, non-invasive method to determine the relevant health status, which is helpful to check the level of the body's metabolism and brain activity.[80,103]

Textile-based microfluidics and biosensors have been widely used to detect glucose, a vital component in diabetes monitoring. These devices integrate microfluidic networks and biosensors with textile materials to measure glucose levels in the body. Microfluidic networks enable the flow and distribution of fluids, while biosensors respond to specific chemical or biological signals to generate an electrical output that is proportional to the concentration of glucose. One of the main advantages of textile-based glucose detection systems is their comfort and ease of use. These devices can be integrated into wearable clothing, allowing for continuous and non-invasive monitoring of glucose levels. Additionally, these devices have been shown to have a high level of accuracy and reliability, making them suitable for use in clinical settings. For example, a study by Chib *et al.* found that a textile-based glucose biosensor fabricated on cotton could accurately measure glucose levels in human sweat with a high degree of reproducibility.[126] Furthermore, the use of textile-based microfluidics and biosensors for glucose detection has the potential to improve the lives of people with diabetes. By providing real-time and continuous monitoring of glucose levels, these devices can help individuals better manage their condition and avoid potentially dangerous fluctuations in glucose levels. In addition, integrating these devices into wearable clothing eliminates the need for frequent finger pricks, making the monitoring process less painful and more convenient.[126]

In all wearable sensors, microfluidic devices must be integrated to perpetually refill sweat on the sensing electrode during measurement to continuously monitor sweat glucose levels with high precision over long periods. In developing microfluidic devices for wearable platform integration with biosensors, it is imperative to attain low power consumption, small size, and durability. Therefore, to achieve daily sweat glucose monitoring using wearable electrochemical biosensors, various features must be met, including detection accuracy, sensitivity, stability, user convenience, and cost-effectiveness. These features ought to be similar to those found in electrochemical biosensor strips that blood glucose meters utilize. It will take a while before wearable biosensor systems with all these features are a reality.[127] Figures 4(g) and 4(h) show an example of a wearable system.

Moreover, different approaches have been done for non-invasive *in vivo* and *in vitro* glucose monitoring. Mostafalu *et al.* have extensively reported on the usability of thread in the construction of three-dimensional (3D) microfluidic circuits and systems.[129] Adding nanomaterials, such as carbon nanotubes, carbon nanopowders, polyaniline, and other materials, with their combinations as well, opens a new avenue for biomarker detection integrated into microfluidic systems.[129]

The relevant physiological range of glucose in sweat has a detection limit of 0.125 M and 0.05 mM. Zhao *et al.* have employed surface-enhanced Raman scattering and colorimetric sensing modalities in core-shell structured gold nanorods on fabric-based microfluidic devices to detect *ex situ* glucose content detection in sweat.[128] Mathematical formulas were developed to accurately detect the content of glucose in sweat using data fitting characteristics of samples with known concentrations. The accuracy of this system in a textile-based sensing band was tested on healthy participants in various body positions. The participants' sweat samples found 51.86–67.19 M of glucose, as seen in Figs. 4(i) and 4(k).[128] A microfluidic cloth-based photoelectrochemical analytical device for detecting glucose in saliva has been recently introduced.[48] It has been possible to test salivary glucose non-enzymatically, sensitively, and rapidly by integrating photoelectrochemical μCADs with multiwalled carbon nanotubes and cadmium sulfide quantum dots. The cadmium sulfide quantum dots constantly oxidize glucose to produce an electrical signal for glucose detection when they are in the presence of an excitation source and glucose. This process creates a powerful oxidizing electron hole. Furthermore, a linear relationship with a detection limit of 15.99 nM is found between the photoelectrochemical signal and glucose concentrations in the range of 0.05–1000 μM under ideal circumstances. The cloth-based device also exhibits respectable selectivity, repeatability, and long-term stability within the detection range. Additionally, the technique has been used to identify glucose in actual saliva samples, indicating promising prospects for biochemical uses. A publication has been done on a one-step polymer screen-printing technique for creating microfluidic cloth-based analytical instruments. The levels of albumin and glucose in human serum under control were measured. According to the results, glucose and albumin levels did not differ significantly at 95% confidence intervals.[103] Aside from utilizing the photoelectric effect,[48] the effect of electrochemiluminescence was exploited by Liu *et al.*[80] Moreover, glucose determination has been done with it. This easy-to-use and cost-effective instrument has been efficiently utilized to test glucose levels in clinical urine and blood samples as well as hydrogen peroxide in milk.[80]

Even though previous research articles have given significant resolution, it is important to note that using chitosan/multi-walled carbon nanotubes/graphene quantum dots-gold nanoparticles, a higher sensitivity of cloth-based glucose biosensors was achieved.[91]

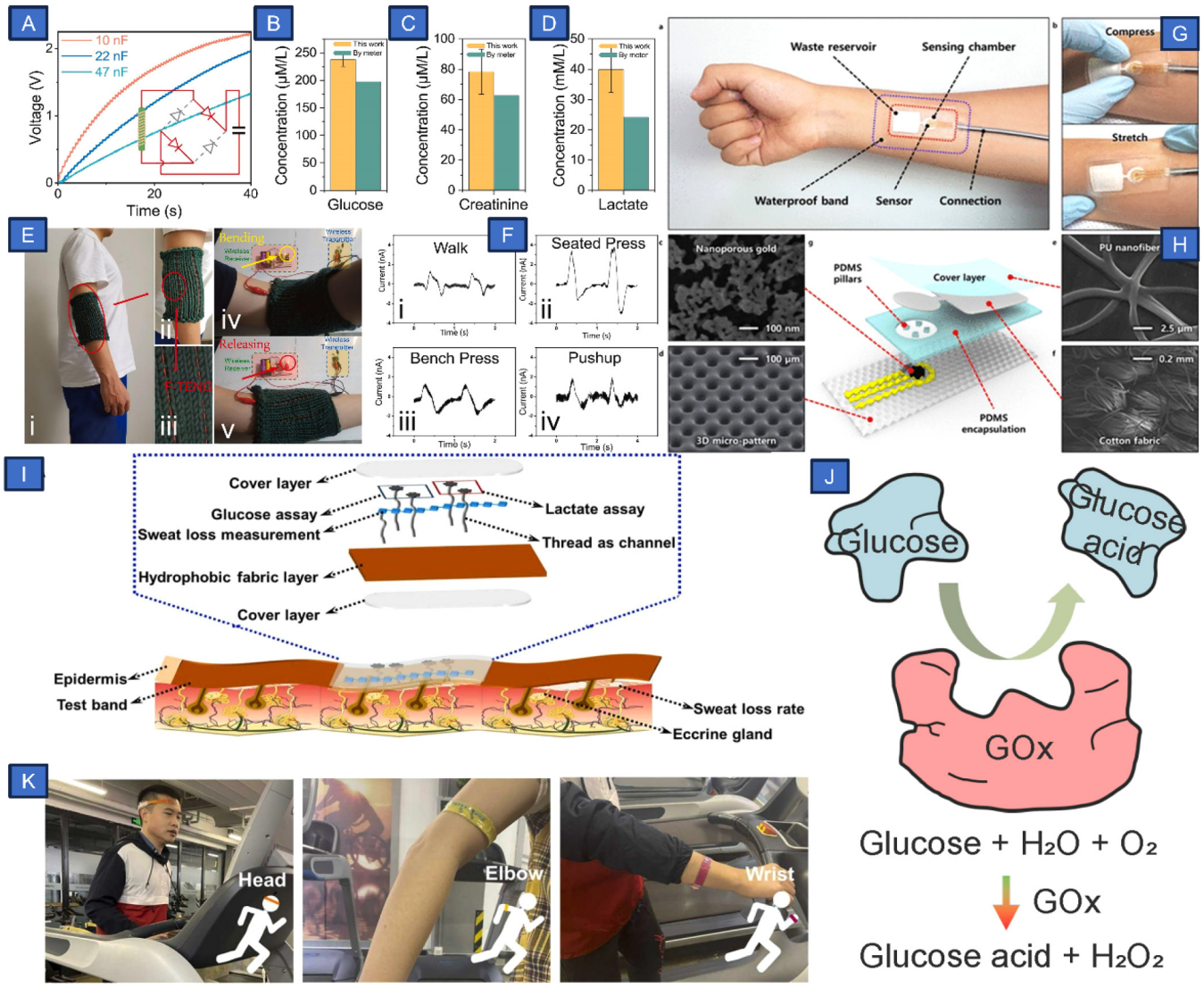

FIG. 4. Different fabrications of textile-based microfluidic biosensors, all in a patch form: (a)–(f) core-shell structured gold nanorods on a thread-embroidered fabric-based microfluidic device (a) dependence of voltage from time of the capacitors powered by F-TENG, (b) comparison of biosensing performances between F-TENG and commercial devices for glucose, (c) creatinine, (d) lactate, (e) smart clothing integrated with F-TENG , and (f) body motion captured by f-TENG. Reproduced with permission from Zhao *et al.*, Biosens. Bioelectron. **205**, 114115 (2022). Copyright 2022 Elsevier. (g) Capillary microfluidics-integrated nanoporous gold electrochemical sensor. (h) Layered components in the fully stretchable microfluidics-integrated biosensor patch and the FESEM of different parts of the device. Reproduced with permission from Bae *et al.*, ACS Appl. Mater. Interfaces **11**(16), 14567–14575 (2019). Copyright 2019 American Chemical Society. (i) Illustration view of the embroidered/fabric sensing band and its interface with skin.[128] Reproduced with permission from Zhao *et al.*, Sens. Actuators B: Chem. **353**, 131154 (2022). Copyright 2022 Elsevier. (j) Underlying process of glucose detection. Reproduced with permission from Zhao *et al.*, Biosens. Bioelectron. **205**, 114115 (2022). Copyright 2022 Elsevier. (k) Sensing band as a wearable device on different parts of the body. Reproduced with permission from Zhao *et al.*, Sens. Actuators B: Chem. **353**, 131154 (2022). Copyright 2022 Elsevier.

The suggested sensor has been demonstrated to have a large dynamic range, high detection sensitivity, and respectable selectivity, repeatability, and stability. Last, the sensor's validity and usefulness for detecting glucose in human serum samples are shown.

Microfluidic thread-based electrode systems have also been used to detect glucose and acetylthiocholine.[93] A phosphate buffered saline (PBS) solution containing glucose oxidase and potassium ferricyanide as a mediator was dried onto the thread for the glucose system. For the second system, a solution of acetylcholinesterase in PBS was added to the nylon thread. As a result, the glucose oxidation's current production was proportional to the glucose concentration. The amount of acetylthiocholine

supplied to the thread increased directly to the present output of thiocholine oxidation.

Stretchable fiber-based triboelectric nanogenerators are the basis for wearable biosensors that Zhao *et al.* have developed for real-time sweat analysis and body motion capture.[130] A stretchable conductive fiber coated in polyaniline and varnished wires makes up these nanogenerators. Utilizing the surface-triboelectric coupling effect—a coupling effect between a triboelectric effect and an enzymatic reaction—wearable biosensors can detect glucose, creatinine, and lactic acid in sweat in real-time, in addition to accurately detecting motion states. These wearables are significant because they can respond to glucose, creatinine, and lactic acid up to 103%, 125%, and 38%, respectively, without needing an external power source. The fabricated result can be seen in Fig. 4. Figure 4(a) represents the circuit configuration powered by the F-TENG, and the time-voltage dependence of the shown capacitors, while Figs. 4(b)–4(d) show a comparison between F-TENGs biosensing performances and commercially available devices. An example of smart clothing integrated with the device as mentioned earlier is shown in Fig. 4(e), and the results of body motion measurements from the device are shown in Fig. 4(f). The mechanism of glucose detection utilized in these devices is represented in Fig. 4(j). The underlying mechanism is based on the reaction of glucose, facilitated by glucose oxidase, with oxygen, producing gluconic acid and hydrogen peroxide. Through measurement of the concentration of hydrogen peroxide, the initial glucose concentration is calculated.[130] For this particular biosensor application, the sol-gel process was used to manufacture zinc-doped magnesium oxide nano-flakes, which were then distributed in a chitosan solution to create a nanocomposite thin layer over a carbon electrode.[131] To avoid the degradation or unexpected reactions and instability of glucose oxidase enzymes,[132] copper oxide-based electrochemical biosensors were developed, which do not utilize enzymes to detect glucose. These portable biosensors use graphene paste printed on cellulose cloth. Electrodes were made out of copper oxide-coated graphene.[65] With a sensitivity of 1082.5 $\pm$ 4.7% μA/mM cm^2 on copper oxide-coated glassy carbon electrodes and 182.9 $\pm$ 8.83% μA/mM cm^2 on copper oxide-coated graphene printed electrodes, the developed biocompatible, disposable, and reproducible sensors demonstrated sensing performance in the range of 0.1–1 mM glucose, making them a strong candidate for future portable, non-invasive glucose monitoring devices on biodegradable substrates. One more successful detection method revolves around the refractive index of glucose. Tang *et al.* have proposed a cavity biosensor designed and fabricated for the fast detection of glucose concentration in serum.[104] The purpose of this cavity biosensor is to quickly detect the amount of glucose in serum. Findings showed that the suggested biosensor had high detection sensitivity for a refractive index and that, at a wavelength of 1590 nm, its sensitivity for glucose was around 0.185 nm/(mg/ml). The cavity biosensor exhibits considerable promise for use in family healthcare for the detection of glucose concentration in diabetes patients because of its small structure, high sensitivity, and quick reaction time.

Lactate detection

Lactate detection is based on either the use of lactate oxidase (LOD) or lactate dehydrogenase (LDH).[133] Recent studies have not yet explored the use of LDH in textile-based biosensors. However, there are other non-conventional ways lactate has been detected, such as colorimetric detection,[134] graphene-based nanocomposite materials,[57] as well as the use of F-TENG material,[130] aside from LOD.[135]

Incorporating lactate oxidase-based biosensors in a wearable textile-based microfluidic device was done by Baysal *et al.*[135] It provides a non-invasive, semi-quantitative, and rapid way of detecting lactate levels in simulated sweat solutions. This study was done in a laboratory setting using artificial sweat. The hydrophilic microchannels and reservoirs surrounded by hydrophobic barriers were created with photolithography. An SU-8 negative photoresist was used to make the barriers hydrophobic, while the reservoirs were functionalized by LOD and horseradish peroxidase enzymes. Textile-based biosensor systems integrated with microfluidics could assist in expediting the detection process with semi-quantitative visual inspection, classifying lactate levels into normal (<5 mM) and high (>5 mM), from a light to dark purple change, with the starting color being green. Following that, colorimetric detection of lactate in real human sweat samples was done by analyzing the influence of enzyme, ABTS, and gelatin ratios, which based on the lactate level influence the color formation in the microfibrous nonwoven microfluidic system. The biosensor showed a difference when artificial and real sweat were used.[134] Khan *et al.* reported that using a three-electrode system in a smart textile biosensor showed promising results in lactate detection. The working and counter electrodes were modified with G-PU-RGO-PB (graphite–polyurethane–reduced graphene oxide–phosphate buffered) paste. The printed electrodes were fixed to the textile-based biosensor using embroidered conductive silver yarn. The electrode performance was carried out using cyclic voltammetry in a ferricyanide solution. The system's transfer function was linear with a relative standard deviation of ~0.2%.

Figure 5(a) illustrates the fabrication process, while testing and evaluating are shown in Figs. 5(b)–5(e) for the modified graphene-based nanocomposite material used in detecting lactate in human sweat.[56] Figures 5(f), 5(g), and 5(i) present SEM images of tetraethylenepentamine reduced graphene oxide, XPS spectra of C1s GO with a fitted curve, and laser scanning microscopic images of a G-PU-RGO-PB non-coated and coated working electrode with enzymes immobilized, respectively.[56] In Fig. 5(h), the underlying detection mechanism used in this analytical device is shown. Similar to glucose sensors [Fig. 4(j)], lactate sensors detect lactate concentration by measuring the amount of hydrogen peroxide produced in the reaction, facilitated by lactate oxidase (LOx).

Finally, F-TENG, a stretchable conductive fiber made of Ecoflex coating with polyaniline and varnished wires, was used for real-time sweat analysis.[130] This textile-based wearable biosensor was used for glucose sensing but is employed as a lactate acid sensor in real-time sweat sensing. It is shown in Fig. 4.

Albumin detection

Different ways of albumin detection have been described in this section. The most common one using a BCG or bromocresol green solution has been reported by Tasaengtong and Sameenoi[103] By utilizing screen printing for fabrication of the microfluidic

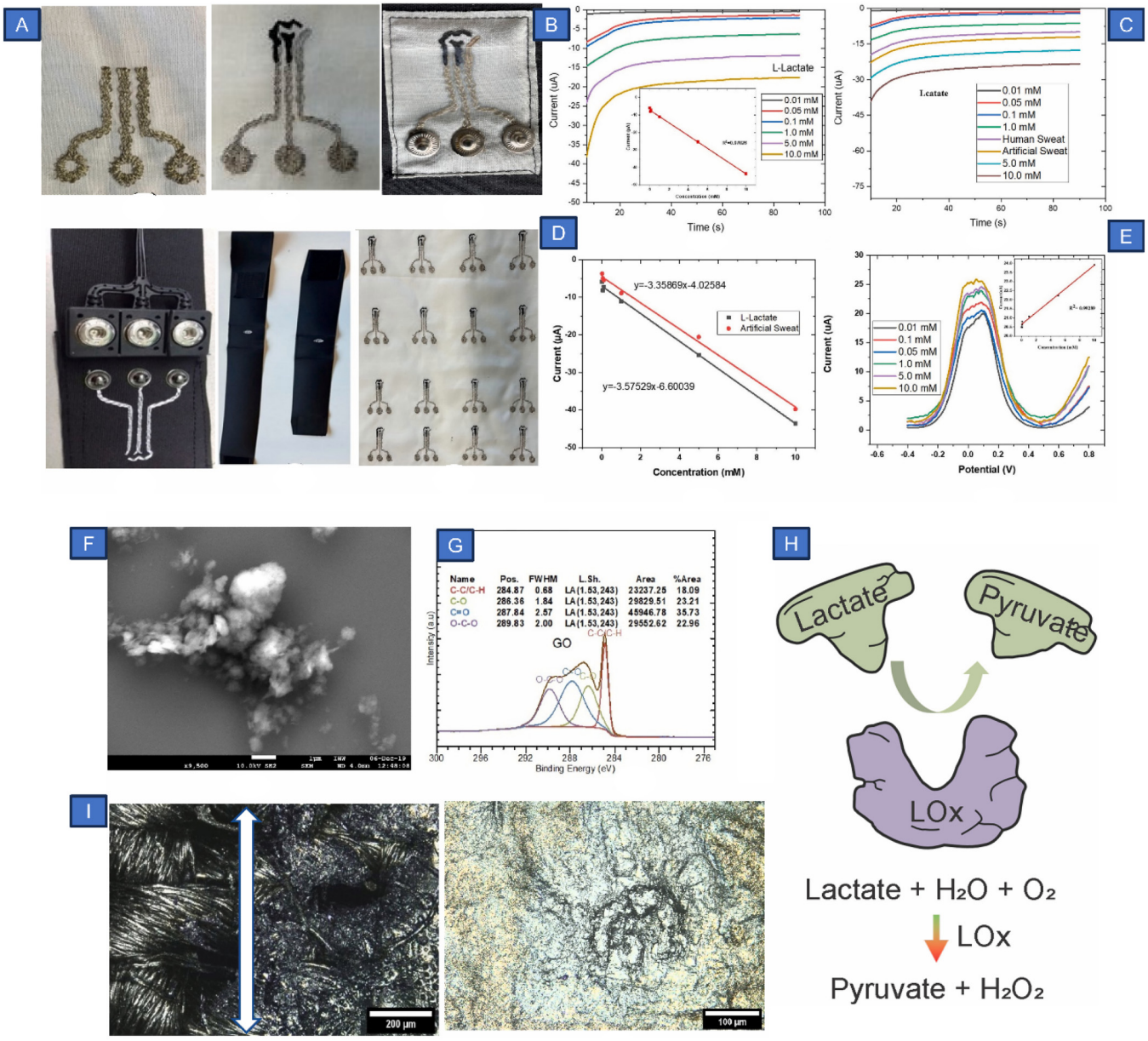

FIG. 5. Modified graphene-based nanocomposite material for lactate detection in human sweat:[56] (a) step-by-step depiction of the fabrication of the lactate detection system. (b)–(e) Lactate content measurement using amperometry (b) at different concentrations of lactate. (c) as (b) but with addition of human and artificial sweat. (d) Linear calibration curve for artificial sweat and L-lactate. (e) Differential pulse voltammogram of different concentrations of lactate. (f) SEM images of tetraethylenepentamine (TEPA) reduced graphene oxide (TEPARGO). (g) XPS spectra of C1s GO with a fitted curve. Reproduced with permission from Khan *et al.*, Biosens. Bioelectron.: X **10**, 100103 (2022). Copyright 2022 Elsevier. (h) Underlying detection mechanism of lactate sensors. Reproduced with permission from Zhao *et al.*, Biosens. Bioelectron. **205**, 114115 (2022). Copyright 2022 Elsevier. (i) Laser scanning microscopic images of (left to right) G-PU-RGO-PB noncoated and coated (left) working electrode with enzymes immobilized (right). Reproduced with permission from Khan *et al.*, Biosens. Bioelectron.: X **10**, 100103 (2022). Copyright 2022 Elsevier.

CAD, they have created a method for rapid, one-step detection of albumin and glucose in human serum. After administration of albumin, the biosensors sensing area turned yellowish-green signifying the presence of the analyte of interest. Moreover, the results showed no significant difference at 95% confidence intervals of the glucose and albumin levels.[103]

The following articles provide an overview of recent developments in the field of textile-based microfluidic biosensors that

pertain to the detection of albumin. These articles discuss challenges and opportunities related to the field of textile-based microfluidics.[136–140] Albumin detection, through the use of textile-based microfluidic platforms, is of great importance in clinical application, as it provides a convenient and reliable way to monitor changes in albumin levels in the body. Albumin is a protein found in blood plasma and is an important indicator of overall health and disease. Changes in albumin levels can provide important information about a wide range of medical conditions, including liver and kidney disease, malnutrition, and inflammation. The use of textile-based microfluidic biosensors for albumin sensing offers several advantages over traditional diagnostic methods. For example, these sensors are often flexible, portable, and wearable, making them well-suited for use in point-of-care settings.[136] They also provide rapid and accurate results, allowing healthcare professionals to make treatment decisions more quickly. More precisely, Cabot *et al.* investigated the movement of albumin, aside from other substances, traveling on surgical sutures, having a speed of $0.33 \pm 0.07\,\mu$m/s.[137] Additionally, the textile-based design of these sensors makes them durable and easy to maintain, which is vital for long-term use.[138] The use of textile-based microfluidic biosensors for albumin sensing can potentially transform the way that albumin levels are monitored in the clinical setting. By providing a convenient and reliable way to monitor changes in albumin levels, these sensors can help healthcare professionals make informed treatment decisions and improve patient outcomes.[136–140]

The detection limits for albumin sensing using textile-based microfluidic biosensors vary depending on the specific study and sensor design. However, these sensors generally have shown the ability to detect albumin in a range of concentrations with high accuracy and sensitivity. For example, Ulum *et al.* reported that the limit of detection for albumin was 114 mg/l.[136] Paul *et al.*, on the other hand, reported a remarkable limit of detection of 10^{-4} mg/l, with the use of zinc oxide nanowires.[139] Moreover, Chen *et al.* in a different study reported an improved detection limit of 3.5 mg/l.[140] These studies demonstrate that textile-based microfluidic biosensors have the potential to detect albumin at low concentrations, making them suitable for a wide range of clinical applications, bearing in mind that conventional blood analysis has a limit of detection of 133 mg/l.[136] However, it is important to note that the exact detection limit may vary depending on the specific sensor design and the measurement conditions.

In Fig. 6, critical zones from μTAD testing are shown on Fig. 6(a), where different tested dilutions and mixing of blood are shown. More precisely, the images (color, gray, and negative) show the separation of different blood solutions into plasma and formed elements. Semi-quantitative results of albumin are demonstrated in Figs. 6(b) and 6(c) (artificial blood) and Figs. 6(d) and 6(e) (sheep whole blood). Moreover, in Figs. 6(b) and 6(d), bare eye inspection on thread color changes in time is shown, while in Figs. 6(c) and 7(e), quantitative color intensity analysis is shown after separation and centrifugation. The underlying mechanism is based on albumin binding with bromocresol green (BCG). The binding introduces color changes, which can be measured spectrophotometrically.[136]

When developing textile-based microfluidic biosensors to detect albumin, some obstacles can be encountered. For example, due to its location, it can be challenging to detect albumin without interference from other components. This is, especially, probable in non-laboratory clinical settings. Therefore, precise separation needs to be done beforehand. Moreover, considering this detector's use in clinical settings, the stability of both the reagent and the sensor can pose an issue. Calibration and standardization are critical for assuring the accuracy of albumin detection. However, biosensors for the detection of albumin have important applications, especially in point-of-care testing, notably in remote areas of the world. Being made of textile or thread, their flexible design enables easy cleaning and sterilization on one hand and continuous real-time monitoring on the other.

Non-woven fabrics, knitted fabrics, and electro-spun nanofibers are widely used in textile-based microfluidic platforms for albumin detection. For example, some studies have used polypropylene non-woven fabrics for albumin detection in urine and plasma samples, while others have used electro-spun nanofibers for highly sensitive and specific albumin detection in serum and plasma samples. The choice of textile will depend on the specific requirements of the application, including the desired sensitivity, specificity, and ease of sample preparation.[141–143]

Ion detection

The detection of ions in biological fluids, as well as water, is important in preventing contaminants from entering human bodies or detecting irregularities in secretions, which ought to indicate a more serious underlying disease. The detection of mercury and lead ions in water, as well as the detection of sodium in sweat, has been researched in depth.[85]

Wang *et al.* developed a microfluidic device made of both cloth and paper for simultaneous sensing of mercury and lead ions in water.[77] The aforementioned fusion of paper-based and cloth-based analytical devices has been achieved through intertwined synergy between the rotary paper-based microfluidic device and the sensing cloth-based part. Quantum dots were grafted on the cotton cloth and modified with polymers to achieve the needed fluorescence sensing components. Simultaneous detection of Hg^{2+} and Pb^{2+} was achieved by a layering paper with hydrophilic channels and hydrophobic barriers, as seen in Figs. 7(a) and 7(b). In Fig. 7(c), the underlying mechanism and the functionalization procedure of a cotton fiber are depicted. The detection mechanism primarily relies on the fluorescence quenching effect resulting from an electron transfer from quantum dots to targeted metal ions, while the ion-imprinted polymer plays a crucial role in enhancing the specificity and sensitivity of the detection of targeted ions. The preparation process of the sensing area is shown in Fig. 7(c), where cotton fibers are grafted with amino groups, and then quantum dots are attached to the surface by amide linkages, creating the fluorescent sensing area. Furthermore, the ion-imprinted polymer is applied to the fluorescent area using a sol-gel process. The presence of template ions causes quenching of the fluorescence signal, which is restored once the template ions are removed.[77]

A similar approach was done by Qiu *et al.* using a photoelectrochemical cell aided with ion imprinting, with the goal of testing divalent mercury ions.[85] What differs from the technique, which utilizes both paper and cloth-based analytical devices, is that wax screen printing, in addition to carbon-ink screen printing, was done only on a cloth-based analytical device. However, this

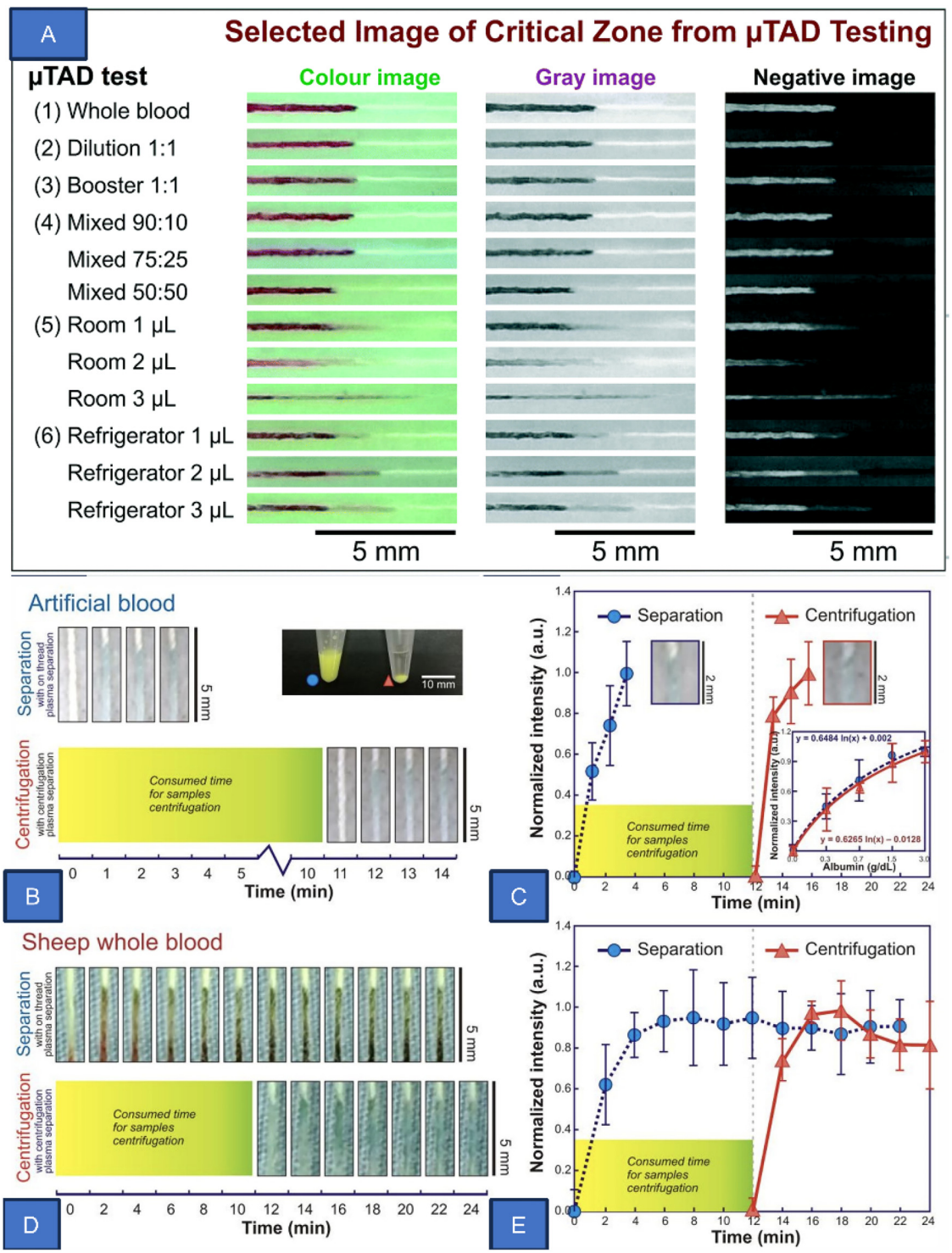

FIG. 6. Cotton-thread microfluidic device for separation of blood plasma and assay to detect albumin: (a) visual representation of different parameters for quantifying separation of blood plasma and assay. Semi-quantitative analysis of albumin by an EDTA treated textile-based microfluidic analytical device: (b) and (c) artificial blood and (d) and (e) sheep whole blood. Reprinted with permission from Fakhrul Ulum *et al.*, Lab Chip, **2016**(16), 1492–1504. Copyright 2016 Royal Society of Chemistry.[136]

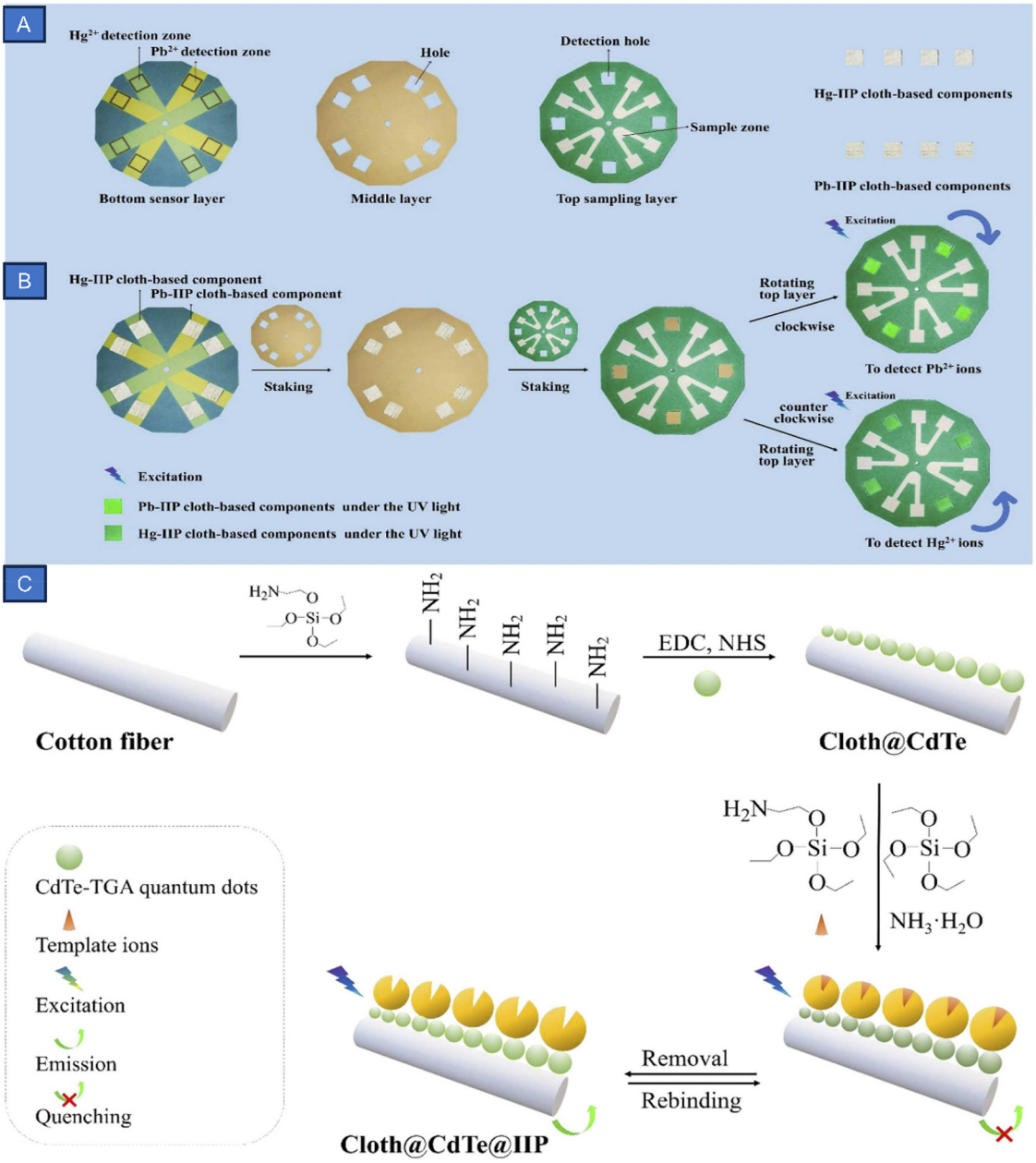

FIG. 7. Textile-based microfluidic device for separation of Hg^{2+} ions and Pb^{2+} ions: (a) illustration of each layer from the top and the detection process of the rotary μCAD. (b) Illustration of each layer from the bottom and the detection process. (c) Functionalization process and the underlying detection mechanism of the textile-based microfluidic device for ion separation. Reprinted with permission from Wang *et al.*, J. Hazard. Mater. **428**, 128165 (2022). Copyright 2022 Elsevier.[77]

approach gives an economic and simplistic way of fabrication. Moreover, this device is portable and low-cost, with the potential for body use, as well as used in the food industry.

Heavy metal ions, such as copper, nickel, zinc, and silver ions, on the other hand, have been detected and filtrated with carbon-cloth integrated microfluidic devices.[56] The ionic mixture of copper and zinc has been reduced as an alloy on the carbon cloth, but other previously mentioned metals, in a salt form, have also been detected.

With the goal of perspiration monitoring, Ma *et al.* have developed a wearable capillary microfluidic device utilizing a polyester thread. Aside from being a thread-based, wearable, capillary

microfluidic device, the presented realization addresses several drawbacks of conventional on-skin perspiration sensors, such as skin irritation and lack of precise fluidic manipulation units. An apparent advantage of this method is the low cost of the used materials and layering; therefore, there is no direct skin-to sensor contact, which avoids irritability. *In situ* collection, transportation, and analysis of Na^+ ions were successful, paving the way for continuous perspiration monitoring and showing the potential of capillary thread-based microfluidic devices.[97] Additionally, Quero *et al.* developed a novel thread-based microfluidic device that utilizes electrophoresis with the goal of separating ions (potassium, sodium, and lithium).[96] They achieved good separation efficiency, with detection limits of 1 μmol/l. Additionally, sensitivity was raised by covering copper electrodes with an enamel coating that was 7.5 μm thinner than the original. Threads could be employed without reducing separation efficiency and detectability for at least three days (around 20 runs per day).

Gene detection

In textile-based microfluidic sensing, gene detection has been thoroughly researched, and some successful realizations have been presented.[78,84,144] Screen printing has mostly been done for the fabrication of these biosensors. DNA, K-ras, and p53 genes have been detected using different electrochemiluminescence methods. First, Su *et al.* have described a cloth-based microfluidic DNA biosensor that can detect specific DNA using label-free proximity hybridization and electrochemiluminescence.[78] When carbon screen-printing ink is applied to cloth-based electrodes, a foldable three-dimensional device can be used as a sensing interface for detecting K-ras genes, as seen in Fig. 8(a). Moreover, different transfer characteristics can be seen in Fig. 8(b). In Fig. 8(c), the underlying gene detection mechanism and sensor preparation are shown. After fabricating the 3D cloth-based device, the working electrode (WE) was modified to construct the biosensor. First, MWCNTs-CS was applied to the WE surface and dried at room temperature, after which glutaraldehyde (GA) was added, incubated, washed with PBS, and air-dried to form a modified electrode with aldehyde groups. Then, the electrode was incubated with amino-modified HP-DNA and washed with a Tris–HCl buffer to remove excess HP-DNA. Finally, a bovine serum albumin (BSA) blocking buffer was added to block nonspecific binding sites. The reported linear range is from 0.001 up to 2500 pM, with a detection limit of 0.13 fM. The device exhibits relatively high sensitivity,

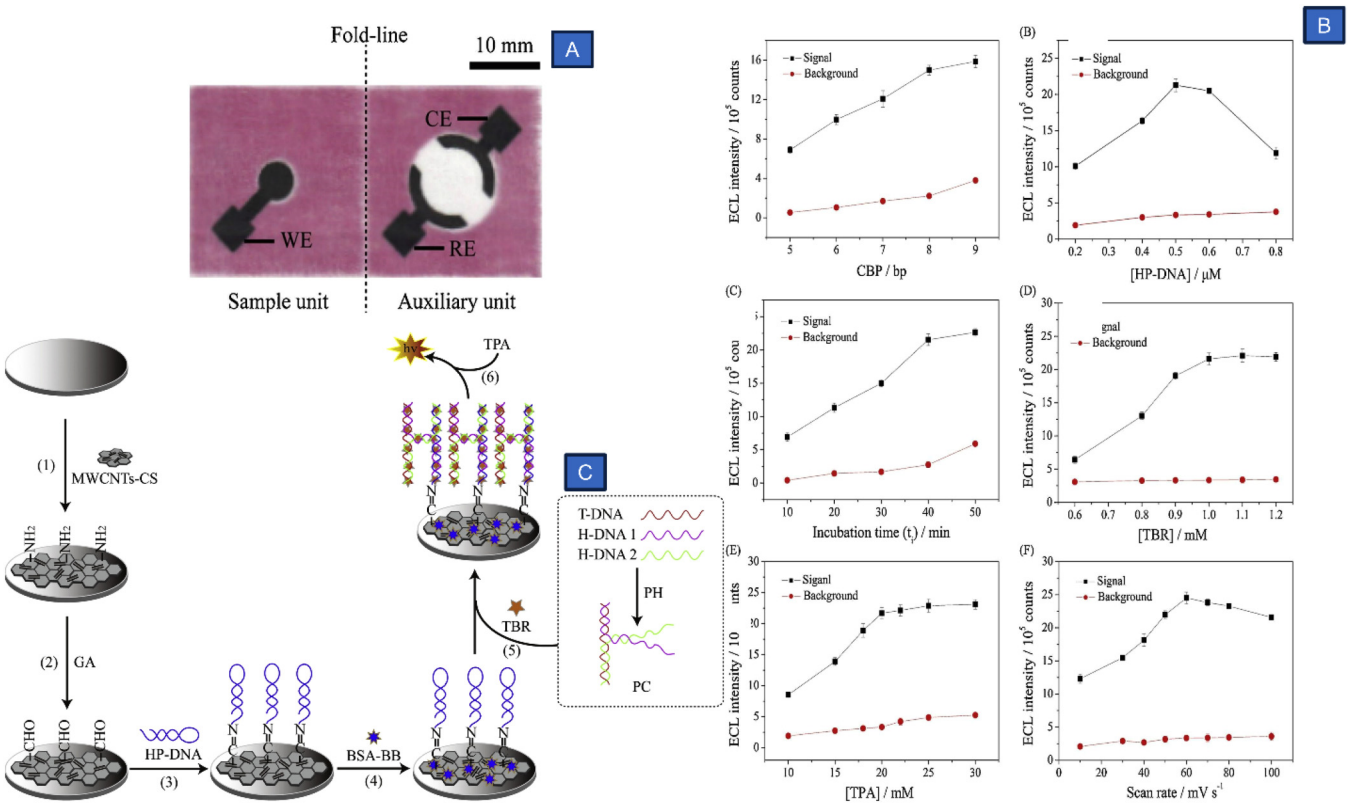

FIG. 8. Cloth-based microfluidic biosensor for ultrasensitive detection of a K-ras gene: (a) cloth-based microfluidic biosensor. (b) Electrochemiluminescence intensity graphs showing the detection of the K-ras gene, as well as the background noise. (c) Underlying detection mechanism used for gene detection and sensor preparation. Reprinted with permission from Su *et al.*, Sens. Actuators B: Chem. **296**, 126654 (2019). Copyright 2019 Elsevier.[78]

stability, reproducibility, and specificity. Another gene that was detected using a cloth-based microfluidic biosensor employing the electrochemiluminescence effect is the p53 gene. Moreover, the use of luminol-gold nanoparticles and hybridization chain reaction amplification gave a greater detection limit of 0.02 fM. Wax-based screen printing has been used as the main principle of manufacturing this biosensor. After the dropping of target DNA, signal nanoprobes, and hydrogen peroxide onto the sensing interface, the aforementioned p53 gene is detected with the linear range of 0.0001 up to 1000 pM. It was reported that the p53 gene can be detected in a complex cellular homogenate sample. Zhang *et al.* reported the use of magnetic immobilization/enrichment and CBP-ECL with electrochemiluminescence for cloth-based biosensor detection of an *invA Salmonella* enteritis gene.[84] The sensitivity is good, and there is a wide linear range, high specificity, and stability.

Uric acid detection

As an avenue for detecting different imbalances in the human body, such as cardiovascular diseases, gout, excessive drinking, and many more, the detection of uric acid has become a focal point in biosensor research over the past few decades. Moreover, with the integration of these biosensors into cloth-based devices, new possibilities have risen.[145] In this review section, the focus is on uric acid detection using microfluidic biosensors based on cloth.[146,147]

With the accelerated growth of textile-based sensors and its advances, a cloth-based multiway bipolar ECL biosensor has been developed with the goal of uric acid detection by Liang *et al.*[83] With optimized conditions, uric acid has been detected from 0 to 1 mM. The intensity of ECL increases linearly in two ranges (between 0.01 and 0.1 mM, as well as 0.25 and 1 mM). The electrodes were wax and carbon-ink based screen printed, with three functional closed bipolar electrodes (C-BPE) in a single microchannel. After voltage application on the anodes, the ECL is activated simultaneously. Moreover, aside from the linearity and the limit of detection of 5.2, 5.3, and 4.9 μM, the ability to detect uric acid in blood samples, as well as duplex detection of glucose and uric acid, had been successfully done. Acceptable selectivity, stability, and reproducibility have been achieved as well. A similar approach to uric detection in blood had been done by Kuswandi *et al.*[146] Additionally, aside from urea, the developed device has monitored pH. The thread-paper-based microfluidic device system had been used for passive and simple monitoring of urea and pH. The aforementioned device has been integrated into a menstrual pad, named a smart menstrual pad, as it combines a threaded part that handles the blood samples and a paper part that is sectioned off for the reaction of plasma with immobilized bioreagents. The smart menstrual pad gave successful results in agreement with well-confirmed methods for the detection of pH and urea in menstrual blood, with the primary goal of kidney function monitoring. The limit of detection is 72.55 μg/ml. The precision of pH detection is approximately 0.8%, while the precision for urea is around 1.68%, in accordance with the limit of detection. Similarly to the uric acid biosensor developed by Liang *et al.*, the smart women's pad showed significant stability, reliability, and selectivity. The calibration curves for detecting urea and pH in the smart women's pad showed linearity

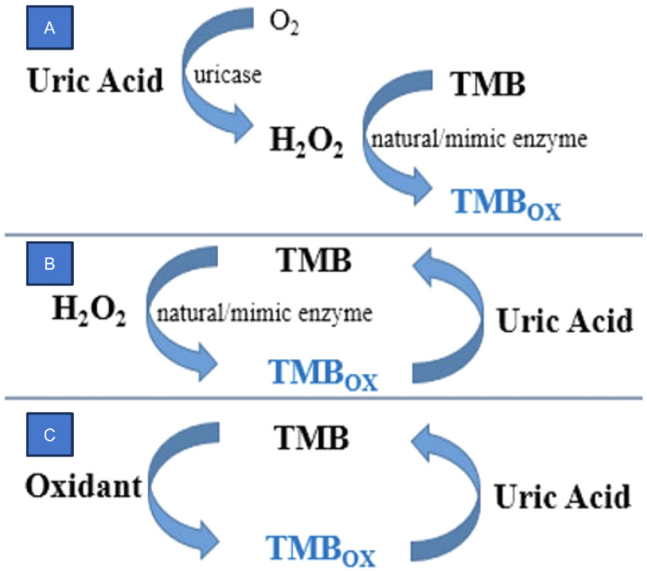

FIG. 9. Different types of detection strategies for uric acid: (a)–(c) Uric acid detection based on UV detection.[140] Reproduced with permission from Wang *et al.*, Crit. Rev. Anal. Chem. **50**(4), 359–375 (2020). Copyright 2020 Taylor & Francis Publishing.

over the whole range of acceptable values. However, there is still room for growth as these biosensors have not been tested on humans yet, which gives room for certain advancements and drawbacks in the previously described fabrication and testing processes.

In Figs. 9(a)–9(c), the UV method for the detection of uric acid is shown. More precisely, these are different strategies for UV detection of uric acid, employing uricase and the uric acid—TMB (3,3′,5,5′-tetramethylbenzidine) system (substitutes hydrogen peroxide as a substrate). Uric acid is oxidized by uricase in this method, producing hydrogen peroxide, which then catalyzes the oxidation of TMB to produce blue TMBox. A similar inverse process is shown in Fig. 9(b), where hydrogen peroxide oxidizes TMB, which then is reduced by uric acid to a colorless TMB. Figure 9(c) indicates that there is a possibility of oxidation of TMB through oxidants, such as NaClO.[140]

Common applications summary

Table IV summarizes all previous applications in μCAD. The highlighted characteristics are sensing mechanism, sensor characteristics, tested liquids, and limitations.

Other applications

As biomedicine is a broad field, enveloping many different avenues of medicine and biology, some applications are not as widely tested as others. Glucose testing, pH testing, sweat analysis, and albumin detection are commonly done, not only because the analytes are more available for testing, but the need for monitoring

TABLE IV. Summary of key properties of common μCAD sensing applications.

Application	Sensing mechanism	Characteristics	Tested liquids	Limitations	Reference
Glucose detection	Surface-enhanced Raman scattering; colorimetry, photoelectrochemical sensing; electrochemiluminescence; triboelectric effect; refractive index	Detection limit of 15.99 nM with a linear range in saliva; detection limit of 0.125 M and 0.05 mM in sweat; high sensitivity	Sweat; saliva; serum; urine	Enzyme stability; biomarker dependence from person to person, reproducibility, and selectivity	48, 80, 103, 126, and 128–132
Lactate detection	Lactate oxidase; lactate serum; urine nanocomposite transducers; triboelectric effect	Linear transfer function with a relative standard deviation of ~0.2%; through colorimetry, precise classification of lactate levels	Simulated sweat solutions; artificial sweat; human sweat	Laboratory setting; non-quantitative detection; enzyme stability; real-time analysis	57, 130, and 133–135
Albumin detection	Bromocresol green (BCG) solution; zinc oxide nanowires (electrochemical)	Various limits of detection: 0.0001 mg/l to 3.5 mg/l	Human; serum; urine; plasma	Stability; calibration; high variability in separation; real-time monitoring; cross-interference	103 and 136–140
Ion detection	Fluorescence sensing, quantum dots and various substances sensitive to specific ions in liquids; electrochemical basis mostly	Limit of detection is approximately 1 μmol/l for sodium, potassium, and lithium ions	Water; sweat; ionic mixtures with the goal of filtration	Complex fabrication process; potential interference in non-controlled, non-laboratory settings	56, 85, 96, and 97
Gene detection	Electrochemiluminescence; magnetic immobilization	High sensitivity; linear range; detection limit in the range of fM for tested genes	Complex cellular homogenate	Fabrication; sample FM setting	78, 84, and 144
Uric acid detection	Electrochemiluminescence; electrochemical sensing	Detection range: 0–1 mM., ECL intensity linear in two ranges: 0.01–0.1 and 0.25–1 mM, Limits of detection: 5.2, 5.3, and 4.9 μM	Blood	Laboratory testing only; complexity of fabrication; variability in results	145–147

of these biomarkers can be a precursor to changes in the human body.

The development of microfluidic devices for rapid blood analysis is one of the main paths of research paths in this area, as presented before, with the detection of different significant blood analytes. Furthermore, as plasma separation from blood can yield significant information about the number of antibodies in the blood, Shimazu *et al.* have developed a thread-based microfluidic device for this means.[75] The device was optimized in terms of applied NaCl concentration in the coated solution and the number of twisting turns on the used thread. The developed device uses a sample volume of 2 μl, and the device's response time is 2.5 min. Moreover, it can be stored at −20 °C for approximately one month. The fabrication process of this thread-based microfluidic device is simple in terms of deposition of NaCl and BSA in PBS solutions, adding hydrophobic layers. However, BSA is expensive to acquire.[75]

Rapid blood type analysis, using small amounts of blood, can expedite the process of treatment in emergency rooms. With this in mind, Su *et al.* have developed a cloth-based microfluidic device for blood type analysis.[78] The developed device has achieved high potential; however, there are limitations in the fabrication results. For example, such challenges include miniaturization limitations regarding weaving and photolithography, as their resolution is ~mm.

A silver thread-based microfluidic platform was developed with the goal detecting essential oils using impedance spectroscopy.[93] The range of measurement of variation of electrical parameters is between 1 Hz and 200 kHz. Increasing the concentration of oils decreased the capacitance. However, it increased the resistance, which in turn increased the overall impedance. This platform can be used as a way of rapid determination of the type and quality of essential oils.

Even though, in the fields of wound-care and drug delivery, which are tightly intertwined, there has not been a significant amount of crossover with textile-based microfluidics, the development of microfibers and integration of conventional microfluidics in wound-care and drug delivery point to significant overlaps and implementation of μCAD and μTAD in the aforementioned field.

Wound-care and drug delivery inherently require exact amounts of liquids delivered in a precise and timely manner to the

wound or the patient himself. Microfluidics presents an adequate field for these requirements. Moreover, by integrating microfluidics in textiles, enabling the devices to be portable and directly carried on the body, automating treatment and delivering prescribed medicines become even more feasible.

The main structural elements for integrating wound-care and drug delivery systems into textile are microtubes and microfibers, which can reliably deliver drugs or ointments to the body part in question. With that in mind, Rahimi *et al.* developed highly stretchable and flexible micro-tubing made of commercially available Tygon® micro-tubes for fluid transport in wearable applications.[148] For the substrate, stretchable polyester fabric was used. Before embroidering, micro-tubes were cleaned, sonicated, and treated with oxygen plasma for outer surface functionalization. This was done to increase the hydrophobicity of the surface. They have prepared the embroidered structures for various wearable applications by fully mechanically and electrically characterizing them. Furthermore, they tested the drug delivery performances of the developed structures, presenting and characterizing functional drug delivery channels.[148] Additionally, bio-inspired one-dimensional materials, inspired by spider silk and cactus spines, were developed by Ju *et al.*, with the goal of directional liquid transport.[149] By chemical modification and variation of surface roughness of their artificially made spider silk and cactus spines, they have accomplished one-directional and reversible liquid transport. Moreover, tunable transport was investigated as well. This accomplishment can lead to future integration of these artificial, bio-inspired materials in wound-care and drug delivery through textile-based microfluidic devices.[149] Similarly to the previous publication, Lin *et al.* developed a patterned duplex fabric for innovative wound management.[150] More precisely, they have used a genetically modified spider silk protein to create a patterned microarray with a controllable size and capillary effect to guide liquid flow to the wound of interest. Moreover, these microarrays can control fluid flow pump-free. Finally, they have implemented this modified spider silk protein duplex fabric on chronic diabetic wounds. The healing process was monitored by hematoxylin-eosin staining of wound skin tissues. Wounds treated with the modified duplex fabric showed a dense regenerated epithelial tissue structure, while immunohistochemistry showed almost no staining on the wounds where the modified fabric was used.[150]

CHALLENGES AND SOLUTIONS

Most of the aforementioned textile-based microfluidic analysis devices have been used in laboratory-controlled settings, which do not account for the high variability and unpredictability of real-life applications. Furthermore, there is plenty of room for advancements and research for continuous monitoring of different biomarkers, such as glucose or albumin. Moreover, the stability and selectivity of these sensors should be explored as well, as the influence of other substances can affect the sensing results. Most importantly, the repeatability of textile-based sensors must be explored, and how well the process of washing the sensor removes the previously administered analyte, aside from the question of how much it damages the device itself.

These obstacles could be overcome by patient testing and simulations and, of course, with higher amounts of samples. The reusability of textile-based sensors can be improved by adding hydrophilic layers onto the textile to lower its liquid retention properties. Furthermore, in terms of fabrication techniques, inkjet printing of hydrophobic layers or even conductive layers on cloth, with the goal of creating a textile-based microfluidic system, should be explored. This technique, in contrast to some other fabrication techniques previously presented, uses significantly less material during fabrication, aside from being capable of achieving higher resolution than screen printing, embroidery, and many different fabrication techniques. Aside from the limitations of textile-based microfluidic sensors, there are still unexplored avenues of detection, which could be done. For instance, detecting different microorganisms, bacteria, and viruses could be explored. This has the potential, as their presence is apparent in excretory fluids, such as sweat, saliva, and breath.

Textile-based microfluidic analytical devices will benefit from rapid advancements in the field of artificial intelligence, enabling the development of point-of-care devices, which can give ready results and enable rapid testing.[151] Additionally, the use of 3D and 4D printing and bioprinting opens up an avenue of fast channel production on a micro- and nanoscale, enabling more precise and less variable structure fabrication.[151] Nonetheless, printing on such a small scale comes with its drawbacks. For example, the direction of the printing process is important, as on a microscale, the placement of filament during fabrication plays a significant role on the smoothness of the interior walls of microfluidic channels. With incorporating, already miniaturized microfluidic devices into textiles, the user will be able to have the device on him at all times, passively collecting data and evaluating it. On the other hand, the question of repeatability and reliability of the measured results needs to be addressed. With the use of small, microliter-sized samples, these devices are approaching the detection limit for specific biomarkers, which presents an obstacle in miniaturization and sensing. Moreover, the variation of biomarkers, from person to person, can influence the results.[152] These aspects concern the rapid development of textile-based microfluidic analytical devices and microfluidic sensing as a whole.[152] In biosensing in general, and with that in textile-based microfluidic devices, the occurrence of false positive results is present. This obstacle should be minimized before commercialization. Aside from that, there is a need for standardization of these analytical devices, not only in their production process but in the sample preparation stage, as well as in the testing stage.[152]

Furthermore, an important aspect of using microfluidics in biomedicine is using small quantities of liquids and achieving precise and accurate results. This is extremely important in drug detection. A large-area mesh-structured microfluidic gradient generator for drug testing has been developed.[153] This development could be transferred onto textile, as it has potential to be integrated into wearables.

FUTURE PERSPECTIVES AND EMERGING TRENDS

As there is an ever-present need for innovative and reliable wearable devices, textile-based microfluidics can easily, moreover

naturally flow into this area of innovation and development. Moreover, when the field of textile-based microfluidics passes on to on-patient testing, the possibilities of this field will be even more apparent. Furthermore, the addition of eco-friendly, biocompatible, and biodegradable materials is of the utmost importance in the field of electronics, considering the ever-growing amount of e-waste around the world. Textile-based microfluidics encompasses this green idea, extending without any obstacles into the field of green electronics.

Moreover, engineering textile-based microfluidic analytical devices to be more eco-friendly can be done by employing natural fibers and materials, such as silk, cotton, and even wool in the fabrication process. Developing and upgrading biodegradable polymers to enhance coatings and structural components goes hand in hand with green electronics. Chemical pollutants can be bypassed with the use of water-based inks and dyes. Furthermore, in-depth research has been done on developing edible inks for coatings in edible electronics. These inks can be repurposed as sensing materials and coatings in textile-based microfluidic devices.[154,155]

Additionally, wound-care can be revolutionized by textile-based microfluidic systems, where aside from monitoring the wound itself, through the presence of different biomarkers in it, the microfluidic system can deliver needed drugs to the injured area, if need be.

Finally, with the development of the electronic nose and mouth, there is a need to develop multiplexed assays that can accurately differentiate between certain types of analytes in fluids. Then, these textile-based microfluidic devices can move across another dimension, being fully capable of not only on-patient monitoring of different biomarkers but their use in environmental monitoring as well.

CONCLUSION

This review paper has discussed the current trends, challenges, and potential solutions in textile-based microfluidics for biomedical applications. As emphasized earlier, research in this field is limited to laboratory settings. The development of more reliable and stable microfluidic devices is crucial to facilitate their application to clinical research. Over time, this field may adopt eco-friendly materials and techniques, including fiber substitutions for conventional plastics and using recycled clothing substrates to enhance sustainability and reduce costs. Despite progress, many detection capabilities remain unexplored, and there is untapped potential for transferring applications from paper-based and conventional microfluidics to textile-based platforms. Overall, this field offers promising opportunities for future development.

ACKNOWLEDGMENTS

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie Grant Agreement No. 872370.

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Lazar Milić: Conceptualization (equal); Investigation (lead); Methodology (equal); Writing – original draft (lead). **Nor Syafirah Zambry:** Formal analysis (equal); Supervision (equal); Validation (supporting); Writing – review & editing (equal). **Fatimah Binti Ibrahim:** Conceptualization (equal); Methodology (equal); Writing – review & editing (equal). **Bojan Petrović:** Conceptualization (equal); Supervision (equal); Validation (equal); Writing – original draft (equal); Writing – review & editing (equal). **Sanja Kojić:** Conceptualization (equal); Formal analysis (equal); Project administration (lead); Supervision (equal); Writing – original draft (equal). **Aung Thiha:** Writing – review & editing (lead). **Karunan Joseph:** Resources (equal); Visualization (equal); Writing – review & editing (equal). **Nurul Fauzani Jamaluddin:** Investigation (equal); Project administration (equal); Writing – review & editing (equal). **Goran M. Stojanović:** Conceptualization (equal); Formal analysis (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Resources (lead); Supervision (lead); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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