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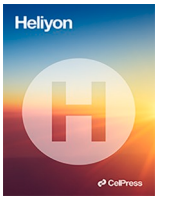

Review article

# Advancing biological investigations using portable sensors for detection of sensitive samples

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ABSTRACT

Portable biosensors are emerged as powerful diagnostic tools for analyzing intricately complex biological samples. These biosensors offer sensitive detection capabilities by utilizing biomolecules such as proteins, nucleic acids, microbes or microbial products, antibodies, and enzymes. Their speed, accuracy, stability, specificity, and low cost make them indispensable in forensic investigations and criminal cases. Notably, portable biosensors have been developed to rapidly detect toxins, poisons, body fluids, and explosives; they have proven invaluable in forensic examinations of suspected samples, generating efficient results that enable effective and fair trials. One of the key advantages of portable biosensors is their ability to provide sensitive and non-destructive detection of forensic samples without requiring extensive sample preparation, thereby reducing the possibility of false results. This comprehensive review provides an overview of the current advancements in portable biosensors for the detection of sensitive materials, highlighting their significance in advancing investigations and enhancing sensitive sample detection capabilities.

## 1. Introduction

A biosensor is a device that integrates an electrochemical element with a biological molecule, such as an enzyme or antibody, to produce a measurable or detectable signal. The electronic component of the biosensor detects, stores, and transmits information regarding the presence of different chemical or biological substances or physiological changes in their environment [1,2]. Biosensors come in various sizes and forms, and some are sensitive enough to monitor pH levels or detect very low concentrations of certain pathogens [3,4]. The main components of a biosensor system include an analyte, a bioreceptor, a transducer, an electrical component, and a display. Fig. 1 gives a general overview of the working of biosensors. An analyte is a material being analyzed to identify its components (e.g., alcohol, glucose, ammonia, and lactose). A bioreceptor is a biomolecule or biological element (such as an enzyme,

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cell, aptamer, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), or antibody) capable of recognizing the target substrate (i.e., an analyte). The signal produced by the biorecognition of the bioreceptor during its interaction with the bioreceptor can be in the form of light, charge, mass change, heat, etc. A transducer changes this signal into a measurable signal that changes the form of energy. Quantifying the presence or amount of a chemical or biological target turns the biorecognition event into either optical or electrical signals that are usually proportional to the amount of analyte. The signal that has been transduced is processed and prepared for presentation. The resultant output is amplified and then transformed into a digital format. The display module then provides

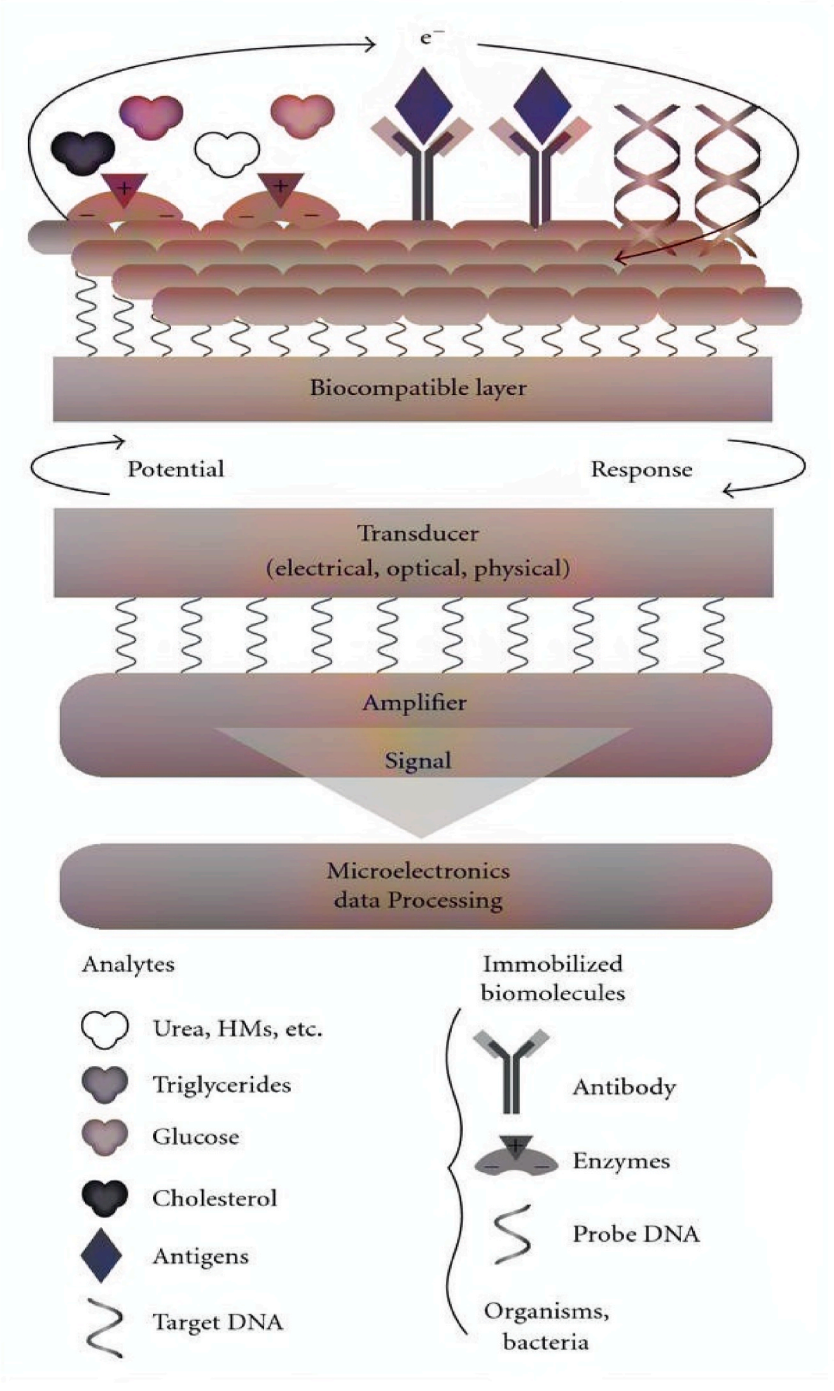


**Fig. 1. Schematic displaying the working principle biosensor.** Typically, the design of a biosensor is comprised of three main components: a molecular recognition element (protein, receptor, enzyme, antibody, DNA, RNA, oligonucleotides, etc.), a signal-transducing element (electrochemical, Raman, fluorescence, optical, thermal, etc.), and a signal amplification/processing element [55].

quantitative analysis of the processed signals presented on display (computer or printer) and provides the output to the user so that they can read and comprehend it [5–8].

In the past 20 years, biosensors have gained tremendous popularity. Modern life have significantly benefited from innovative biosensors, scientific, and technological advancements. In recent years, the use of biosensors for ongoing monitoring of biological and synthetic processes in both industrial and clinical chemistry has increased. Biosensors are becoming increasingly popular in the fields of food analysis [9–11], bioterrorism [12–14], environmental [15–20], and human health monitoring and diagnostics [21–23]. In biomedical studies, biosensors have been useful in the diagnosis and treatment of cancer [24,25], diabetes [26,27], neurodegenerative disorders, including Alzheimer's disease [28,29] and Parkinson's disease [30,31], and other chronic conditions. These biosensors may chemically analyze body fluids, including saliva, blood, urine, perspiration, etc., to reveal the condition of various diseases [32]. Besides that, various biosensors have been developed to detect environmental contaminants and toxins [33–37]. Biosensors for detecting food analytes have developed extensively, yet only a small fraction have found practical use.

The concept of biosensors emerged during the 1950s with the introduction of electrochemical devices for detecting analytes. One of the earliest and most renowned examples was the electrochemical oxygen biosensor, pioneered by Leland Clark Jr in 1956 [38]. This biosensor utilized a platinum cathode for oxygen reduction and a silver/silver chloride reference electrode. Later, Clark and Lyons combined this setup with glucose oxidase in a dialysis membrane to measure glucose concentration in a solution [39]. Subsequently, in 1967, Updike and Hicks introduced the first "enzyme electrode" to quantify glucose in solution and tissues *in vitro* [40]. They achieved this by immobilizing glucose oxidase in a polymerized gelatinous membrane coating a polarographic oxygen electrode. Another milestone came in 1969 when Guilbault and Montalvo developed the first potentiometric enzyme electrode, known as the urea sensor [41]. This biosensor involved immobilizing urease onto an ammonium-selective liquid membrane electrode.

Over the years, many biosensors have been developed for diverse *in vitro* and *in vivo* applications. These biosensors vary in their nature, ranging from enzymatic, antibody, polypeptide, and aptamer, to nucleic acid-based sensors. Moreover, the transduction mechanisms of biosensors have evolved alongside technological advancements and demands. These mechanisms encompass electrochemical and electronic biosensors, thermic biosensors measuring temperature changes associated with enzyme-catalyzed reactions, microbial biosensors that integrate microorganisms with physical transducers, immune biosensors utilizing recombinant antibodies or antibody fragments for target recognition, and optical biosensors relying on optical diffraction and changes in light emission upon target recognition [42]. As numerous scientific and technological sectors have advanced, so too have sensors designed for use in forensic investigations. These sensors have come a long way since their early 20th-century beginnings as crude equipment used in primitive forensic investigations. The advent of electrochemical biosensors in the 1960s marked the beginning of the forensic sensors' journey. The electrochemical oxygen biosensor that Leland Clark Jr. Developed is a major advance. This biosensor for oxygen detection made use of platinum cathodes and silver/silver chloride reference electrodes. Later, in order to quantify glucose concentrations in liquids, Clark and Lyons integrated glucose oxidase into a dialysis membrane. These early accomplishments paved the way for future progress [43].

Potentiometric enzyme electrodes and enzyme transducers were first proposed by Updike and Hicks in the late 1960s [40]. They created an enzyme transducer by covering a polarographic oxygen electrode with a polymerized gelatinous membrane containing glucose oxidase. This method may determine glucose concentrations in *in vitro* cultured solutions and tissues. In addition, Guilbault and Montalvo made great strides when they immobilized urease on an ammonium-selective liquid membrane electrode to create the first potentiometric enzyme electrode, the urea sensor.

As biosensor research advanced, the field spawned a variety of biosensor technologies, such as enzymatic, antibody-based,

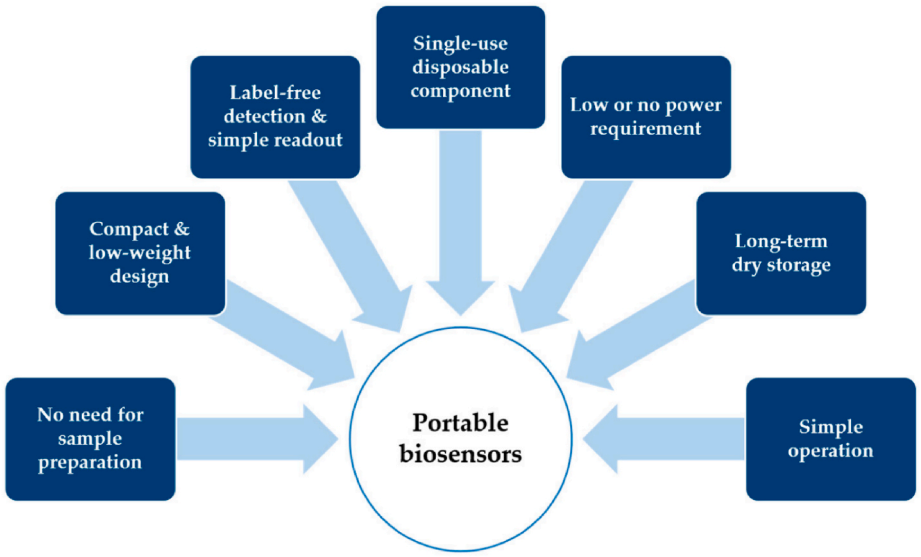


**Fig. 2.** Key characteristic features that are integrated into the design of novel portable biosensors [32].

polypeptide-based, aptamer-based, and nucleic acid-based sensors. These biosensors had unique strengths in detecting specific forensically important analytes [44–47]. Aptamers and molecularly imprinted polymers (MIPs) are two examples of novel recognition elements incorporated into biosensors to increase their sensitivity and selectivity, allowing them to detect a wider variety of chemicals. Improvements in microfabrication, nanotechnology, and sensing technologies allowed biosensors to be made smaller and more portable [47–49]. These advancements made it possible to conduct forensic analysis directly at the scene of an incident, drastically cutting down on investigation turnaround times. Fig. 2 illustrates the essential elements and attributes incorporated into the development of innovative portable biosensor devices. These biosensors are likely designed to provide advanced capabilities in terms of rapid and accurate detection of specific biological molecules or analytes in various applications.

Biosensors have made important advances in forensic DNA analysis in recent years, allowing for multiplexing and rapid DNA profiling. They can speed up the process of identifying criminal suspects and victims by allowing for the simultaneous detection of several analytes inside a single sample, thanks to their multiplexing properties. The advent of rapid DNA profiling technology has changed the face of forensic investigations forever by allowing for rapid and precise identification of suspects [50–52].

Forensic biosensors have been used in a wide variety of fields, from forensic toxicology and trace evidence analysis to the detection of explosives and the identification of gunshot residue. They have helped reconstruct crime scenes and provided key evidence in court thanks to their sensitivity to minute levels of chemicals [53,54]. This article aims to present a comprehensive overview of biosensors' development and their potential applications, with a particular focus on portable biosensors in various forensic fields. While acknowledging the existence of related review articles in the literature, our review provides a consolidated and comprehensive resource for researchers and practitioners interested in the on-spot detection of forensic samples using biosensors. By highlighting the advancements in portable biosensor technology and their suitability for forensic analysis, this review serves as a convenient and informative reference, encompassing diverse branches of forensic science.

## 2. Biosensors in a forensic toxicological analysis

Detecting pollutants and poisons of forensic relevance that may be harmful to humans or the environment has led to the development of several portable biosensors. These biosensors are used for sensitive and selective detection of heavy metals (HMs) [56–58], phenols [59], pesticides [60], ammonia [61], herbicides [62], polycyclic aromatic hydrocarbons [63], etc. Industrial processes or agricultural practices introduce most of these toxic substances into the soil or water. Such contaminants are ingested and may devastate human health [64]. The potential of HMs and their ions to accumulate for a more extended period of time in the biological system makes them especially hazardous to the environment. As a result, numerous analytical techniques for detecting them, such as inductively coupled plasma mass spectrometry (ICPMS), have been developed. However, these approaches are either quite costly or need specialized knowledge to implement. Biosensors provide a simple, quick, sensitive, and focused method for monitoring environmental toxins in comparison to traditional methods.

**Table 1**
Biosensors for the detection of heavy metals of forensic interest.

| Analyte | Detection Method | Detection strategy | LOD | Ref. |
|---|---|---|---|---|
| Lead | Colorimetric | Based on DNAzyme labeled gold nanoparticles and graphene oxide | 100 pM | [95] |
| | Colorimetric | Magnetic bead DNAzyme gold nanoparticle complex used for the development of paper-based sensor | 0.3 nM | [96] |
| | Colorimetric | Gold nanoparticles functionalized with DNAzyme and barcode DNA are used for the development of test stip-based sensor | 20 nM | [97] |
| | Fluorescence | flow cytometric method based on DNAzyme | 0.6 nM | [98] |
| | Electro chemiluminescence | Signal-on ECL DNAzyme-based biosensor | 1.4 pM | [99] |
| | Impedance spectroscopy | G-quadruplex-based DNA sensor | 0.1 pM | [100] |
| | Amperometric | Cascade DNA and quantum dots amplification-based DNA sensor | 6.1 pM | [101] |
| Arsenic | Amperometric | The use of acetylthiocholine iodide as a substrate results in an AChE inhibitory action. AChE immobilized on SPCE; thiocholine detected at +0.6 V | – | [102] |
| | Voltammetric | An open circuit on a (DNA/SWCNT/PDDA)n/GCE accumulates As(III). Re-dissolution of As to As (III) through oxidation | 0.05 μg/L | [91] |
| | Amperometric | Using 2-phospho-L-ascorbic acid as a substrate, AcP activity is inhibited. AcP immobilization on SPCEs; monitoring reduction in substrate oxidation response with increasing As(V) concentration | – | [103] |
| | Colorimetric | Aptamers-cationic surfactant complexes inhibited the formation of AuNP aggregates; The aptamer-As (III) complex was formed by a particular interaction between As(III) and the aptamer, and cationic surfactant could assemble AuNPs, leading to a color shift and an increase in RS intensity. | 0.6 μg/L | [104] |
| $Pb^{2+}$ | Electrochemical | ion-dependent split DNAzyme and a template-free DNA extension reaction, | 30 pM | [105] |
| | Optical | DNAzyme-modified $Fe_3O_4$@Au@Ag nanoparticles | 5 pM | [79] |
| | Optical | DNAzyme-based sensor using optical fiber sensor platform | 0.03 nM | [106] |
| | Colorimetric | $Pb^{2+}$-dependent GR-5 DNAzyme and the self-replicating catalyzed hairpin assembly (SRCHA) reaction | 2.6 nM | [107] |

### 2.1. Inorganic hazardous materials

Mercury (Hg) is a toxic heavy metal abundantly distributed in nature. Seafood and dental amalgam are the two primary sources of mercury exposure for humans [65,66]. Mercury poisoning diagnosis may be difficult, although acquiring reliable results is possible. This heavy metal is known to cause public health catastrophes in Minamata Bay, Japan, and Iraq [67–69]. Several studies have been conducted to develop innovative and portable biosensors to detect mercury (Table 1). Recently, a disposable, efficient, portable, cheap, and user-friendly biosensor for real-time detection has been developed for electrochemical detection of Hg(II) with LOD and LOQ 3.94 μM and 6.50 μM, respectively [70]. The biosensor was developed by modifying the surface of a screen-printed carbon electrode (SPCE) using silver nanowire/hydroxypropyl-methylcellulose/chitosan/urease (AgNWs/HPMC/CS/Urease) composite and used for detection of Hg(II) I real water samples.

The prepared biosensor showed remarkable linearity and recovery of Hg(II) in drinking water samples, making it convenient and effective compared to conventional methods such as inductively coupled plasma optical emission spectrometry (ICP-OES). In another study, Haider et al. developed a portable biosensor based on surface plasmon resonance (SPR) to detect $Hg^{2+}$ in tap water [71]. In this biosensor, gold nanorods (AuNRs) were immobilized on the surface of Au electrodes for selective and sensitive detection of $Hg^{2+}$ with LOD of $2.28 \times 10^{-19}$ M. Glass substrate functionalized with (3-mercaptopropyl) trimethoxysilane (MPTMS) and chemically bound to gold nanorods were used to estimate the concentration of Hg in tap water. The immobilization of the glass substrate with MPTMS not only improved the sensitivity of the sensor for Hg detection but also improved LOD. In this study, the sensitivity of the sensor was measured using micromolar concentrations of Hg, and LOD was found to be $2.28 \times 10^{-19}$ M.

Pourreza et al. employed paper-based analytical devices (PADs) with curcumin nanoparticles (CURNs) to detect the concentration of $Hg^{2+}$ [72]. The paper-based probe containing CURNs as the sensing reagent was made using the wax dipping method, and the analytical signal was determined to be an increase in the mean color intensity across all test zones when the $Hg^{2+}$ concentration was raised. The proposed sensor proved effective for detecting $Hg^{2+}$ with the LOD of 0.003 g/mL and successfully recovered $Hg^{2+}$ from spiked samples across a range of concentrations in a variety of water samples. In order to digitally measure mercury concentration utilizing a plasmonic AuNP and aptamer-based colorimetric assay, Wei et al. proposed a smartphone-based $Hg^{2+}$ ion sensor platform that uses an optomechanical reader coupled with a smartphone camera. Using LEDs tuned to 523 and 625 nm and custom-built Android software, the sensor was able to quickly digitally process the transmission pictures acquired by the phone and analyze the concentration of mercury in ppb levels [73].

Besides electrochemical biosensors, DNA-based biosensors have emerged as a preferred tool for rapid, sensitive, and selective onsite detection of mercury. Long et al. proposed a thymine-thymine (T-T) containing DNA probe immobilized onto an optical fiber sensor that binds exclusively to mercury ions to produce a T-$Hg^{2+}$-T complex to create a DNA-based evanescent wave optical biosensor for quick and sensitive detection of $Hg^{2+}$ ions with a detection limit of 2.1 nM [74]. In another study, a simple and reusable method for developing DNA biosensors for the detection of $Hg^{2+}$ ions based on electrochemical signal change was proposed. In this study, a DNA-modified Au electrode was able to capture a complementary probe, forming a double helix structure that blocked electron transmission. Strong T-$Hg^{2+}$-T interactions with T-T mismatches enabled $Hg^{2+}$ ions to be detected with a detection limit of 0.05 nM [75]. DNA-functionalized silica NPs have been synthesized to rapidly detect $Hg^{2+}$ in an aqueous solution with a low detection limit (4 ppb) [76]. In this study, dye-trapped silica NPs were capped by two DNA strands in the presence of $Hg^{2+}$. The pore of the silica NP is uncapped by the rehybridization of two DNA strands, thereby releasing the dye with measurable increases in fluorescence signal.

Lead (Pb) is another highly toxic metal that a forensic expert usually encounters. Lead complexes are very persistent inside the body and cannot be quickly metabolized or eliminated, leading to lead poisoning. As a result, it is critical to develop a method for detecting lead at low concentrations. A straightforward label-free technique employing random dsDNA templated synthesis of CuNPs as fluorescent probes has effectively detected $Pb^{2+}$ [77]. The proposed dsDNA-CuNPs were highly selective for $Pb^{2+}$ while also being sensitive, with a detection limit of 5 nM. In another study, AuNPs and DNAzyme were used to develop a label-free colorimetric sensor to detect $Pb^{2+}$ [78]. The sensor's dynamic range was found to be tunable with a detection limit in the nanomolar range. In the presence of $Pb^{2+}$, DNAzyme released ssDNA, which is absorbed onto and stabilized AuNPs against salt-induced aggregation. The uncleaved complex could not stabilize the AuNPs in the absence of $Pb^{2+}$, resulting in purple-blue AuNP aggregates. The sensor proved to be effective with detection limit of 3 nM. Xu et al. used DNAzyme-modified $Fe_3O_4$@Au@Ag nanoparticles to develop a surface-enhanced Raman scattering (SERS) biosensor for $Pb^{2+}$ detection with an LOD of 5 pM [79]. In another study, Guo et al. developed an FRRT-based sensor to detect $Pb^{2+}$ [80]. They used ethidium bromide (EtBr) to intercalate in double-stranded DNA (dsDNA) grooves. This allowed EtBr to intercalate between the two strands of 17E DNAzyme and the FAM-labeled substrate. When $Pb^{2+}$, FAM, and EtBr are in close proximity, and when FAM is excited at 490 nm, FRET occurs, resulting in a drop in FAM fluorescence intensity. DNAzyme cleaves the substrate in the presence of $Pb^{2+}$, releasing EB, which then blocks the FRET between FAM and EB, resulting in bright fluorescence. This sensor reportedly has a detection limit of 0.53 nM. Wang et al. developed a portable aptasensor based on a graphene field effect transistor to detect lead in blood samples [81]. This device showed sensitive and selective detection of $Pb^{2+}$ with an LOD of 37.5 ng/L. The device was also found to be selective toward the detection of other metal ions such as $Na^+$, $Mg^+$, $Ca^+$, and $K^+$. Xiao et al. proposed a nanomolar sensitivity electrochemical sensor for the detection of $Pb^{2+}$ by attaching a redox-active group modified DNAzyme to the electrode surface [82]. In another study, Shen et al. developed a technique where DNAzyme was immobilized onto the electrode, and $Pb^{2+}$ was detected by amplifying the signal using a DNA-Au biobar code and enabled the detection of $Pb^{2+}$ with a detection limit of 1 nM [83]. Various other biosensors for the detection of lead have been summarized in Table 1.

Arsenic (As) is one of the metal poisons that has been misused since ancient times to poison humans as well as animals. Arsenic in the form of As(III) and As(V) is naturally found in high concentrations in the groundwater of several countries. In its inorganic form, arsenic is highly toxic [84]. Long-term arsenic exposure through drinking water and food may result in cancer and skin problems

[85–87]. In medicolegal investigations, arsenic and its derivatives are used for homicidal and suicidal purposes. Since it is tasteless and colorless in homicidal cases is mixed with food articles and brewages [88]. Therefore, the straightforward detection of arsenic has been the center of interest for the global scientific community. Biosensors have been found selective and effective for determining arsenic with significantly lower detection limits (Table 1). Truffer et al. developed a compact portable biosensor using *Escherichia coli (E. coli)* bioreceptor cells for the detection of As(III) in water [89]. The expression of green fluorescent protein by *E. coli* was found to be linearly dependent on the arsenic concentration. The sensor was designed to house a microfluidic chip made of polydimethylsiloxane, which is responsible for holding the agarose-encapsulated bacteria and a complete optical illumination, collection, and detection system for the purpose of performing automated quantitative fluorescence measurements. This sensor can independently collect water samples, regulate the measurement process, and transfer data through GSM networks. There is significant potential for whole-cell bacterial biosensors as a useful supplementary strategy for the detection of arsenic. Elcin et al. established the feasibility of immobilizing a selected bacterial bioreporter in agar and alginate biopolymers for use in arsenite and arsenate concentration measurements [90].

The immobilized bioreporter cells in the minimal medium could detect arsenite, whereas immobilized bioreporter cells in phosphate-limited minimum media could detect both arsenite and arsenate. These agar and alginate immobilized bioreporter systems could identify arsenite and arsenate concentrations of 10 g/L and 200 g/L within 5 h and 2 h, respectively. Recently, a DNA-functionalized single-walled carbon nanotube (SWCNT) modified glassy carbon electrode (GCE) for As (III) detection was proposed [91]. The detection was carried out by directly observing the oxidation of As(0) (reduced by guanine in DNA) to As (III). At pH 7.0, an LOD (LOD) of 0.05 g/L was observed. Another study used a label-free colorimetric approach for detecting arsenite with excellent sensitivity and selectivity based on the difference in adsorption characteristics on Au NPs of random coil G-/T-rich ssDNA and folded DNA bound to arsenite [92]. Using this proposed sensor, arsenite detection could be accomplished visually or quickly via UV/Vis spectroscopy; neither sophisticated equipment nor an in-depth understanding of electron or energy transfer is necessary. Liu et al. designed a fluorescent nanoprobe consisting of dye-labeled single-strand DNA encapsulated in single-wall carbon nanotubes for the detection of arsenite [93]. It was found that the nanoprobes could detect arsenite ions at the femtogram (fg) level in a lysosome of a living cell. In another study, double-stranded *calf thymus*-DNA immobilized onto β -mercaptoethanol-gold (MCE/Au) electrode has been proposed for the detection of arsenic trioxide (As2O3) with a detection limit of 0.01 μg g $mL^{-1}$ [94].

### 2.2. Organic toxins

#### 2.2.1. Alcohol

Alcohol is one of the most often poisonous substances strongly linked to health problems and traffic accidents [108]. Over the years, the rapid and accurate assessment of ethanol in biological samples has gained increasing relevance in forensic and clinical medicine. Over the last decade, a lot of progress has been made in the field of portable and flexible wearable biosensors. Various wearable biosensors have been developed for the real-time detection of alcohol in the human body (Table 2). SCRAM™ unit is a commercially available sensor that tests alcohol consumption through the skin. The SCRAM™ is built as an ankle bracelet with a sensor compartment and a digital signal processing compartment, which communicates the gathered data to an in-home modem [109]. This device has been developed for law enforcement officials to monitor individuals with alcohol-related crimes. The WrisTAS$^{TM}$ relates to the first wrist bracelet developed for use in medical settings to regulate alcohol abstinence [110]. In 2015, a new generation wrist-worn bracelet for alcohol monitoring became available, which links through Bluetooth to an app on a user's smartphone [111]. Kim et al. developed a noninvasive method for detecting alcohol levels in induced sweat using a wearable tattoo-based biosensing device [112]. The temporary tattoo system was coupled with an iontophoretic biosensor that was outfitted with flexible wireless electronics on the skin-monitoring platform. Furthermore, pilocarpine medication transdermal administration causes sweat through iontophoresis, which is evaluated by amperometry using an alcohol oxidase (AOx) coated screen-printed and Prussian blue (PB) electrode transducer. The zinc oxide thin films incorporated into the nano porous flexible electrode system has been used to develop a lancet-free, label-free

**Table 2**
Wearable biosensors for monitoring alcohol concentrations in the human body.

| Device | Company/Developed by | Body localization | Working Principle | Ref |
|---|---|---|---|---|
| SCRAM CAM | Alcohol Monitoring System (AMS), USA | Ankle | The SCRAM CAM bracelet uses transdermal testing to check for alcohol levels every 30 min. It can tell the difference between alcohol that has been consumed and alcohol that has been exposed to the skin (such as lotions or perfumes that contain alcohol. | [115] |
| Proof$^{TM}$ | Milo Sensors, California, USA | Wrist | Bracelet is utilized for detection of alcohol using enzymatic electrochemical biosensor cartridge coupled with a smartphone app. | [116] |
| BACtrack Skyn | BACKtrack, San Francisco, California | Wrist | BACtrack Skyn is able to detect intoxication by monitoring the concentration of ethanol molecules in the sweat. This is referred to as Transdermal Alcohol Content or TAC. In contrast to breathalyzer tests, the TAC measurement is constanly changing and does not require blowing into a device. Once BACtrack receives a reading, TAC is processed algorithmically to estimate BAC. | [117] |
| Quantac Tally | Quantac Inc., New York, USA | Wrist | It was designed to provide the user with individualized insights into the effects of alcohol intake on their health by combining alcohol monitoring data from its connected smartphone app with health-related measures. | [118] |
| AlcoWear | McAfee et al., California, USA | Wrist | AlcoGait is an application that can be coupled with any smartwatch to monitor the accelerometer and gyroscope data of the user. | [119] |

biosensor for the simultaneous measurement of glucose and alcohol in sweat [113]. Without any external stimulation, detection was possible from human sweat at very low quantities (1-3 μL). Using AOx-functionalized zinc oxide thin-film electrodes for alcohol monitoring allowed for a dynamic range of 0.01–200 mgdL$^{-}$1 and LOD value of 0.01 mgdL$^{-}$1 ethanol [[133,134]39].

The use of novel nanomaterials that enhance the analytic characteristics for detection purposes also stands out among the more recent approaches. Using single-walled carbon nanotubes (SWCNTs) covalently functionalized with polytyrosine have been used to develop an ethanol biosensor by immobilizing ADH through Nafion entrapment and amperometric detection in the presence of $NAD^+$ [114]. The quinones produced during primary tyrosine oxidation contributed to the electrocatalytic activity of electrode material towards NADH oxidation. Therefore, a potential value as low as 0.2 V vs. Ag/AgCl was employed for the amperometric detection, and an LOD of 0.67 mM was achieved [31].

### 2.2.2. *Toxins from microalgae species*

Toxins generated by toxic microalgae species and contaminated shellfish are among the most severe global concerns owing to their high toxicity and widespread dispersion. Consuming contaminated seafood may have devastating health consequences, including death. There have been reports of human poisoning outbreaks all over the globe that have been ascribed to toxic cyanobacteria. These outbreaks have been linked to drinking contaminated water or after recreational exposure [120–123]. The most tragic event connected to cyanotoxins to date took place in Caruaru (Brazil) in 1996 [124]. An accidental lethal poisoning at a hemodialysis clinic resulted in the deaths of over fifty renal patients. Therefore, the detection of such toxic compounds is often encountered by forensic professionals. Various portable biosensors have been designed for detection of selective and sensitive detection of such toxins (Table 3).

The marine algae of the genus *Pseudo-nitzschia* are responsible for producing the amnesic shellfish toxin domoic acid [125]. Due to concerns over the contamination of shellfish with domoic acid, a quick field assessment of toxin levels in shellfish and saltwater is necessary. In order to detect domoic acid, Steven et al. developed a portable SPR biosensor device [126]. Antibodies against domoic acid were produced and then sorted by their affinity. Employing a portable six-channel SPR system designed, competition- and displacement-based assays were developed using these antibodies. This competition-based SPR test detected domoic acid with an LOD of 10 nM with linearity ranging from 13 to 200 nM.

Microcystins (MCs), a class of cyclic heptapeptides generated by several species of bloom-forming cyanobacteria, have received the most significant attention among cyanotoxins. Various studies have been conducted to develop biosensors for the detection of such toxins. Herranz et al. developed an SPR biosensor for the sensitive detection of MCs in drinking water [127]. In this study, microcystin-LR (MCLR) was immobilized onto the SPR chip functionalized with a self-assembled monolayer. The proposed biosensor was able to detect MCLR with a detection limit of 73 ± 8 ng/L. In another study, Lin et al. developed an electrochemical impedance biosensor for the detection of MC-LR [128]. In the presence of the target (MC-LR), MC-LR aptamers were immobilized on a gold electrode through Au–S interaction, and the binding of MC-LR and the aptamers probe caused a complex formation change on the electrode surface, resulting in a decrease in impedance. The reduction rate was logarithmically proportional to the MC-LR concentration between $1.0 \times 10^{-7}$ and $5.0 \times 10^{-11}$ mol/L, with a detection limit of $1.8 \times 10^{-11}$ mol/L. Tetrodotoxin (TTX) is another example of toxin, characterized lately as possessing molecular mysticism, is a one of the low-molecular-weight neurotoxins with multiple recognized analogues of differing toxicities found in diverse marine species. Campbell et al. developed SPR based optical biosensor for detection of TTX with detection limit of 200 μg/kg [129]. TTX immobilization on an optical biosensor chip in this work provided a highly sensitive and stable test for screening TTX in gastropods and puffer fish. Although the acquired detection capacity is ten times lower than the legal limit allowed in Japan, it is nonetheless helpful as an early warning monitoring tool for low-level TTX outbreaks.

The neurotoxin saxitoxin and similar compounds are a global health concern because they cause paralytic shellfish poisoning (PSP). Effective monitoring of potentially polluted fishing sites and seafood sample screening is essential to safeguard the public. There are a variety of analytical approaches for identifying paralytic shellfish toxins (PSTs), but each has its own set of problems when used routinely. SPR bioassays are a relatively new technology that overcomes the drawbacks of existing methods, such as those relating to ethics or performance. Yakes et al. proposed an immunoassay-based SPR biosensor for the effective detection of PSP [130]. This study refined an immunoassay for the detection of PST and expanded the use of a biosensor substrate for this purpose. The technology is superior to previously used sensors because it allows for quick chip fabrication, utilizes less saxitoxin during conjugation, and allows for triplicate measurements to be taken during each test run, all of which enhance the analytical validity of the data. This assay streamlined the quantitative analysis of natural samples by eliminating the need for extensive sample dilutions. Furthermore, this SPR biosensor can analyze a triplicate sample in under 5 min, suggesting that the technique might be extended to high-throughput analysis.

**Table 3**
Biosensors for the detection of toxins generated by toxic microalgae species.

| Toxin | Transduction | Detection strategy | LOD | Ref. |
|---|---|---|---|---|
| Microcystin-LR | SPR | MC-LR immobilized covalently on an SPR chip functionalized with a SAM. | 13 ng/mL | [131] |
| Microcystin-LR | EIS | A gold electrode with immobilized MC-LR aptamer, Variations in impedance as a function of measuring MC concentration | $1.8 \times 10^{-11}$ μg $L^{-1}$ | [128] |
| Okadaic acid | SPR | Binding of OA to immobilized anti-OA antibody | 31 μg $g^{-1}$ | [132] |
| Palytoxin | SPR | Palytoxin binding with anti-Palytoxin | 2.8 ng m $L^{-1}$ | [133] |
| Domoic acid | SPR | Binding with anti-domoic acid antibody | 10 nM | [126] |
| Okadaic acid | Amperometric | Immobilized protein phosphatase inhibition, catechyl monophosphate used as a substrate for detection | 2.69–171.87 μg/L | [134] |

Okadaic acid (OA) is a toxin produced by several species of dinoflagellates and is known to accumulate in shellfish and sponges. It is one of the primary causes of diarrhetic shellfish poisoning and is a potent inhibitor of specific protein phosphatases. It is also known to have a variety of adverse effects on cells. An electrochemical enzyme biosensor based on d protein phosphatase (PP2A) has been developed to detect OA effectively [128]. The biosensor relies on the toxin's ability to inhibit the immobilized enzyme in conjunction with the electrochemical measurement of enzyme substrates. This key constraint of PP2A may be overcome by immobilizing the enzyme by entrapment in a polymeric matrix, which keeps the biomolecule in a flexible conformation and considerably preserves the enzyme activity, creating a durable screening device. As an enzyme substrate, catechyl monophosphate simplifies the biosensor process by eliminating the need for oxygen-dependent enzymes, which are often used for this purpose. In another study, an indirect competitive immunoassay using an electrochemical immunosensor for the detection of OA has been designed and successfully used in an automated flow environment. This study used a screen-printed carbon electrode (SPCE) in the flow system to insert OA-modified magnetic beads to create the biosensor. There was a competition between the immobilized OA and the OA in the sample for binding the anti-okadaic acid monoclonal antibody (anti-OA-MAb). For electrochemical detection, a secondary antibody was tagged with alkaline phosphatase. As the quantity of free OA in the sample increased, the current response of the labeled alkaline phosphatase to 1-naphthyl phosphate was reduced. The sensor effectively showed its application for the detection of OA with an LOD of 0.15 μg/L and a linear range of 0.19–25 μg/L.

## 3. Biosensors for the detection of explosives

Sensing explosives is vital for countering terrorism, enhancing security, and protecting the environment [135]. Generally, mass spectrometry, gas chromatography, ion mobility spectrometry, infrared spectrometry, colorimetric assay, electrophoresis, Raman scattering, fluorescence spectrometry etc., are used for the forensic detection of explosives. Most of these techniques are advantageous in one way or another, but these are mostly bulky, expensive, and time-consuming [136]. Biosensors show specificity and sensitivity towards explosives through biological components such as aptamers, antibodies, and molecularly imprinted polymers [137]. The specific nature of biorecognition components helps overcome cross-reactivity, which is common in chemosensors [138]. Trained animals are attributed with highly sensitive noses, which is significantly more essential than most of the other explosive detection techniques [139].

A sensory array-based electronic nose mimicking animal behavior is effective in the detection of explosives [140]. The olfactory sensor-electronic nose has been widely applied for detecting chemicals [141]. These bio-based sensors are composed of the chemosensory array and artificial neural network. Considering the adaptable nature of microorganisms, engineered microorganisms have been used as biosensors in detecting hazardous materials [142,143]. The detection of trinitrotoluene (TNT) has been studied extensively because it is the most used explosive in landmines. Synthetic biology has opened a gateway to the detection of hazardous materials. Since TNT can induce physiological responses in *E. coli,* it is possible to define sensing elements from *E. coli*. Junjie et al. identified five elements, i.e., topA, recA, yadG, yqgC, and aspC, with high TNT sensing ability having a minimum responding concentration of 4.75 mg/L [144]. The microbial bioreporter for explosive detection was described in a patent granted to Burlarge et al. [145]. However, they did not describe the sensor element. Yagur-Kroll et al. screened the *E. coli* gene promoter with a green fluorescent protein (GFP) transcriptional fusion for TNT and dinitrobenzene (DNB) detection [146]. Table 4 highlights some of the bacterial sensor strains with the ability to detect explosives. The vapors leaking from landmines offer an advantage in their detection without relying on the metal used. A cost-effective and wireless biosensor was developed by combining a portable and compact optical device with recombinant bacterial cells for 2, 4-Dinitrotoluene (DNT) detection [147].

Large-scale monitoring of low concentrations of explosives like TNT/RDX is an arduous task. Biosensors that insert aptamers with high specificity and affinity are novel strategies for RDX detection. A riboswitch-based biosensor was developed and characterized by using *E. coli* with fluorescence as the detection element [148]. RNA aptamers are short sequences of nucleic acids that show high target specificity when combined with a riboswitch that initiates GFP translation, thus useful in developing an effective biosensor for detection. DsRed fluorescent protein was used in the detection of RDX. The process spans target binding at the molecular level to fluorescence detection at the macroscale, involving several physical and biochemical changes [149]. A common challenge in aptamer-based biosensors is effectively translating target-binding interaction into a detectable signal. This has paved the way for the development of other transducing platforms. Amplifying such signals while maintaining stability, specificity, and affinity is also challenging [150]. For the growing security threats worldwide, developing sensitive analytical devices to detect small traces of explosives in less time is imperative. Unfortunately, an ideal system for detecting explosives does not exist. The probability of false positives needs to be zero for efficient biosensors, which is difficult to achieve. The immunosensor system works on the principle of kinetic competition and is fast with reduced limitations affinity.

**Table 4**
Use of biosensing microorganisms for the detection of explosives.

| Microorganisms | Sensing element | Explosive material | Detection limit | (References) |
|---|---|---|---|---|
| *Saccharomyces cerevisiae* | GFP | DNT | 25 μM | [154] |
| *Pseudomonas putida* | luxAB, and GFP | DNT | 2 mM | [155] |
| *E. coli* | Flagellar motion | Nitrate | 12 mM | [156] |
| *Dictyosphaerium chlorelloides* | Chlorophyll α fluorescence | TNT | 2.2 μM | [157] |
| *E. coli* | *luxCDABE, GFPmut2* | *TNT and DNT* | 27 μM and 22 μM | [158] |

The immunosensor consists of a monolithic column with an immobilized hapten that traps fluorescently tagged antibodies when no explosive is present. In the presence of explosives like TNT, the antibody binding sites are blocked, leading to a breakthrough of tagged protein detected through fluorescence using a complementary metal-oxide semiconductor camera [151]. A sandwich antibody-aptamer immunoassay for TNT detection was developed using TNT-specific aptamer and antibody recognition using a fluorescence resonance energy transfer (FRET) system. The FITC-tagged aptamer and rhodamine isothiocyanate tagged antibody were used as the recognition elements with a 0.4 nM LOD [152]. Cyclodextrins, peptides, algae, yeast, and bacteria-based systems have been used for explosive detection. Some are based on immunometric assays, while others rely on plasmon resonance technology. However, not enough antibodies are available against the explosives because high affinity is needed for optimal assay performance. Aptamers, single-stranded molecules, have high target binding capability and have been demonstrated in various fields like biotechnology, medicine, and diagnostics. Aptamers have been developed for the detection of explosives like TNT using the systematic evolution of ligands by exponential enrichment (SELEX). The aptamer selection is achieved by double-stranded DNA partitioning using streptavidin-tagged silver nanoparticles. The aptamer with $10^{-7}$ M affinity is applied in the aptasensor to detect TNT [153].

## 4. Biosensor for detection of body fluids of forensic interest

Detecting and identifying bodily fluids at a crime scene is crucial in forensic science. The presence or absence of a bodily fluid and the subsequent identification of that fluid is a necessary first step in forensic investigations. Therefore, it is essential to identify the body fluid present at the crime scene to connect a link between the victim and the criminal. However, many stains from bodily fluids are either not visible to the human eye or might be mistaken for stains from other fluids or substances, making this a challenging undertaking [159–161]. Even though it seems evident to a forensic investigator what a stain is made of, it does not mean it can be used to establish or deny facts in court. A stain might include several bodily fluids from different donors. Crime scene investigators and laboratory professionals may use physical tests on these suspicious stains to either positively identify a fluid or rule it out, depending on the circumstances [161]. While blood, sperm, and saliva are the most frequent bodily fluids recovered at crime scenes, others, such as vaginal fluid, urine, and perspiration, may also play essential roles, such as contributing vital DNA evidence. Preliminary testing may be performed on each of these fluids; for some, more definitive tests can be performed to establish positive identification. Some tests are deemed confirmatory because they can determine the species of a given fluid. Recently, biosensors have evolved as a significant approach for the selective and sensitive detection of different body fluids. Although few studies have been conducted on developing portable biosensors for body fluid detection and their application in forensics, various other studies have been performed to detect

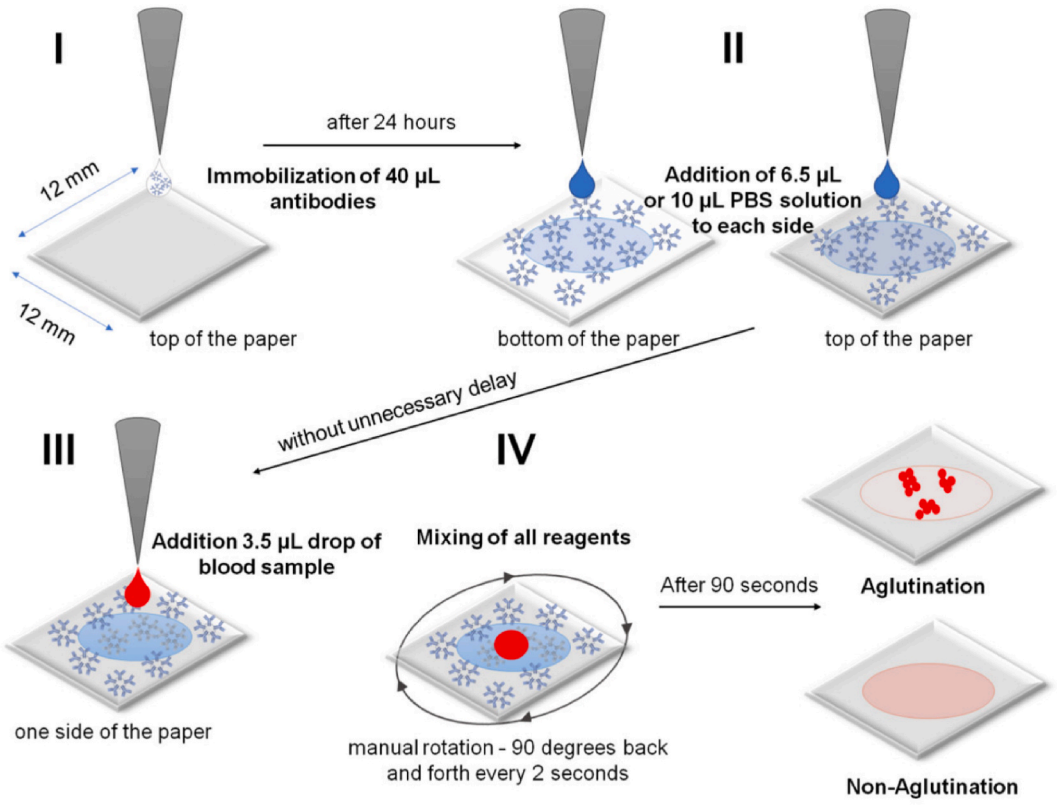


**Fig. 3.** Preparation of the paper-based lateral-flow immunostrips for blood typing: (I) immobilization of antibody, (II) dropping of PBS solution, (III) Addition of blood sample, and (IV) mixing of reagents and reading out of the results [166].

different biomarkers in body fluid. These studies may be employed in forensics for the detection of body fluids present at crime scenes. A brief summary of portable biosensors for the detection of body fluids has been described below.

### 4.1. Blood

Blood is one of the common pieces of physical and biological evidence found at crime scenes. It is crucial for forensic experts to determine whether the suspected sample is blood or not. Also, if the given sample is blood, what is the origin of the blood (animal vs human)? If human blood, what is the blood group (A, B, AB, or O)? Using biosensors could be an effective and errorless technique for detecting blood for forensic studies. Although no such study has used biosensors to detect blood, several other biomedical studies have been performed to detect blood and its biomarkers. These studies can be employed in forensics for effective and on-spot detection of blood. SpinDx, developed by Sandia National Laboratories, is a centrifugal platform for conducting multiplexed immunoassays and WBC counts from a drop of blood in less than 15 min [162]. The concentration of hemoglobin in human blood can be determined quickly and accurately using this centrifugal microfluidic platform. This device can be used in forensics to determine the origin of blood at the crime scene. Sang et al. developed a biosensor consisting of a multifunctional di-electrophoresis manipulation device and a surface stress biosensor to separate and detect red blood cells for the detection of hemolytic anemia [163]. The biosensor allows for the detection of live and dead red blood cells, and the diagnosis of hemolytic anemia can be made from capacitance readings from the biosensor. The device was successfully able to sort live/dead red blood cells. Although this study has no relevance to forensics, such a technique can be used to identify blood evidence found at the crime scene. Campbell et al. developed an immuno-biosensor for the detection of antibodies recognizing the Rh (D) blood group antigen [164]. This device incorporated a conducting polypyrrole and polyelectrolyte matrix with human erythrocytes. Following this, oximetry and light microscopy were used to show that the erythrocytes were intact in the polymerization solution and the polymer matrix. Cyclic voltammetry and resistometry were used to characterize the electrochemical properties of the polymer. Finally, agglutination, ELISA techniques, and cyclic resistometry were used to analyze the immune response from antigen/antibody binding. By cycling the polymer between +0.35 V and −0.7 V (vs. Ag/AgCl), the sensor could qualitatively identify antigen/antibody binding using resistometry. After Anti-Rh (D) antibody (250 g/mL) was added, the resistance changes throughout the resistogram dropped by 1.1 (p0.0008) in polymers containing Rh (D) positive erythrocytes, but no significant change was seen in polymers lacking erythrocytes.

Noiphung et al. introduced a novel paper-based blood typing device using a hybrid of wax printing and wax dipping techniques that enables the simultaneous assessment of ABO and Rh blood types [165]. In this study, blood was diluted 1:2 for forward grouping, and entire blood was taken for reverse grouping. Hemagglutination was performed using a 30 % cell solution of either A-cells or B-cells on the reverse grouping side. The presence of the appropriate antigen or antibody could be determined by the ratio between the distance traveled by the red blood cells and plasma separation. Ratajczak et al. developed portable paper-based immunostrips for on-spot blood typing of a blood sample (Fig. 3 [I, II, III, and IV) [166]. They introduced a novel biosensing devices utilizing a microporous cellulose matrix, with a specific emphasis on portable paper-based immunostrips (IMS) designed for rapid blood typing in emergency scenarios requiring blood transfusion. Through the functionalization of cellulose fibrils using antibody-supramolecular interactions, the immunostrips are engineered to establish hydrogen bonds between IgM pentamers and cellulose fibers, demonstrated by quantum mechanical calculations. Employing a carefully chosen paper membrane with 3 μm diameter pores, the immunostrips enable channel functionalization with antibody molecules while preventing the entry of red blood cells (RBC). This innovative approach enables naked-eye determination of all AB0 and Rh blood types, even with a mere 3.5 μL blood sample. Durability tests of the IgM immunostrips underscore their potential for sustained use, while a newly proposed statistical evaluation method for digitized blood agglutination images opens avenues for automated blood typing using machine vision and digital data processing.

### 4.2. Saliva

Saliva is another common body fluid often found at crime scenes. Saliva is a biologically complex fluid secreted by the salivary glands' acinar cells. It acts as an indicator for several plasma constituents. Its use as a diagnostic and forensic tool has been studied and evaluated extensively in the past few years. Besides serving as an important source of DNA, saliva samples can be used for toxicological and drug monitoring. Various biosensors have been developed for the detection of various biomarkers present in saliva for biomedical applications. However, the application of biosensors for the detection of saliva and its biomarkers in forensics is yet to be fully explored. A smartphone-based bacteria sensor that tests for two oral bacteria in real samples has been developed for saliva identification [167]. This bacterium sensor consists of a series of test strips made out of blue-emitting silicon carbide quantum dots (SiC Qds) and red-emitting gold nanoclusters (AuNCs). This approach has been shown to be very sensitive in its detection of two types of oral bacteria *(S. salivarius and S. sanguinis)*. Under a 365 nm UV light, test strips, when exposed to bacterial solutions, cause a dose-dependent change in color, which can be captured by a smartphone camera and processed using a color detector app. This method offers a novel method for the visual, quick identification of two bacteria in saliva and for screening saliva samples among forensic bodily fluids. α-amylase is an isoenzyme produced by ciliary glands for the digestion of starch and can serve as an essential biomarker for detection. Rebelo et al. designed a MIP-based biosensor consisting of disposable gold screen printed electrodes to detect α-amylase in human saliva [168]. Molecular imprinting technology and electrochemical techniques were used to design and make artificial receptors on the sensor's surface that can recognize the stress biomarker amylase. Detection was also carried out in a simple manner. Using small, portable, disposable chips called AuSPEs made detection easy and cheap. This MIP-based biosensor detected the target analyte with an LOD of less than $3.0 \times 10^{-4}$ mg $mL^{-1}$. Lactate is a significant biomarker that may be detected in saliva. Petropoulos et al. presented a Prussian Blue-modified screen-printed electrode for detecting hydrogen peroxide from a reaction catalyzed by lactate

oxidase enzyme [169]. The integrated biosensor with portable instrumentation was effective for detection purposes with a working range of 0.025–0.25 mM and LOD of 0.01 mM. Roda et al. developed a 3D-printed small cartridge that may transform a smartphone or tablet into a luminometer. The sensor was developed by combining lactate oxidase and horseradish peroxidase in a working prototype for selective detection of lactate in saliva with LOD in saliva was found to be 0.5 mmol/L [170]. Yao et al. produced carbon electrodes and electrochemical chambers screen-printed on hydrophilic fabric for the detection of lactate in saliva. The electrochemiluminescence signals are then read by smartphone for detection of lactate with an LOD of 0.35 mM and a dynamic range of 0.05–2.5 mM [171]. In another study, Ahmed et al. developed an impedimetric immunosensor for the effective detection of *Streptococcus pyogenes* present in saliva [172]. Although this study has little to do with forensics, *S. pyogenes,* as a biomarker of saliva, can be used to analyze the suspected body fluid collected as physical evidence.

### 4.3. Semen

Su et al. developed a lightweight automated semen analysis assay based on a holographic on-chip imaging system using a lens-free on-chip microscope to conduct semen analysis for quantification of the count of motile sperm in semen samples [173]. To automatically quantify the number and dynamic trajectories of motile sperm, digital subtraction of successive lens-free holographic frames with the reconstructed images then being processed appropriately, while Immotile sperm counts can be analyzed by summation of the same frames. Besides this, various other smartphone and paper-based devices have been developed for sperm count analysis in semen samples [174–177]. Although these studies have been conducted for male fertility tests, using such techniques in future studies for forensic examination of suspected semen samples could be beneficial in dealing with sexual assault cases.

Prostate-specific antigen (PSA) is a serine protease produced by the prostate epithelium. Its primary function is the liquefaction of that seminal fluid. PSA detection has become the forensic method in sexual assault cases to detect and determine semen. The existing conventional methods of assays for the detection of PSA in forensic samples may often lead to false results owing to the presence of other fluids, presence of foreign material (such as fabric in the case when the dry samples are collected from the clothes of a victim), and in cases when the collected sample is not enough for analysis. The rapid evolution in the research and development of biosensors has made it possible to get rapid and reliable results for the detection of PSA. Koukouvinos et al. proposed a biosensor based on white light reflectance spectroscopy for determining PSA as a sperm biomarker in forensic samples [178]. This proposed biosensor relies on using a two-stage immunoassay that utilizes polyclonal anti-PSA antibodies for collection and detection steps, followed by the addition of streptavidin to enhance the detection signal. This assay requires a sample quantity of a few nanoliters and could detect PSA concentration in semen samples with an LOD of 0.5 ng/mL. In another study, A compact capacitive biomarker-based sensor was developed by Mishra et al., allowing for direct, quick quantification and ultrafast detection of PSA specifically [179]. In this study, an interdigitated capacitor (IDC) was functionalized to detect PSA concentrations between 0.1 and 10 L/mL with a reaction time of 3 s. The resultant IDC-based PSA biosensors exhibited high repeatability and reusability for real-time biosensing of targeted biomolecules in situations where low-concentration detection is crucial.

## 5. Biosensors for food forensics

Rapid determination of food safety and quality is vital for the food industry and the health of consumers, and the forensic lab often receives samples to determine the quality or presence of contamination [180–182]. For ameliorating the risks of food-borne disease outbreaks, stringent real-time monitoring of food products throughout the food supply chain is necessary [183]. Portable biosensors could be paramount in detecting toxins, pesticides, antibiotics, and allergens in food, food spoilage, and food contamination [184–188]. These sensors can sense the food spoilage by analyzing the biochemical changes that occur during the microbial food spoilage, detecting food-specific pathogenic microbes, or detecting specific gases such as hydrogen sulfide, nitrogen dioxide, ammonia, cyclohexanone, carbon dioxide that are released during food spoilage [184]. Various types of portable biosensors, such as portable cell-based biosensors, smartphone-based quantum dot fluorescence biosensors, lab-on-chip biosensors, lateral flow immunoassay-based smartphone biosensors, charge-coupled device-based portable lens-free optical biosensor, and portable fluorescent microsphere-based lateral flow biosensor have been developed for the assessment of food quality and safety [189–194]. Santovito et al. have developed a handheld portable phosphorescent oxygen-based sensor for the detection of microbial contamination and enumeration of microbes by determining total viable counts in meat samples within 1–8 h in the range of 0.65–7.87 Log (CFU/cm$^2$) [195].

Similarly, a portable and wireless bio-electronic nose device has been developed for monitoring food freshness by sensing food spoilage indicators, like the release of biogenic amines (cadaverine and putrescine) [196]. The bio-electronic nose device consists of olfactory receptors, namely trace amine-associated receptor 13c and trace amine-associated receptor 13d, which are specific to biogenic amines [196]. The nose device is highly sensitive and has a detection limit of 1 fM for biogenic amines, cadaverine, and putrescine [196]. Another biogenic amine histamine that accumulates in food due to microbial activity and can be toxic to consumers has been detected in fish samples by a portable electrochemical biosensor in the range of 0.01–100 μg/mL [197]. Similarly, portable biosensors have been developed to detect food-borne bacteria like *E. coli, Salmonella typhimurium,* and *Campylobacter* spp [198–200]. A biosensor that uses a sandwich enzyme-linked immunosorbent assay with an antibody specific to *E. coli* and a fluorescent imager on the smartphone has been developed for the detection of *E. coli* in egg and yogurt with a detection limit of 10 CFU/mL and 1 CFU/mL respectively [198]. Vizzini et al. developed a portable DNA biosensor modified with silica nanoparticles for the detection of *Campylobacter* spp. in chicken meat [199]. Apart from monitoring food spoilage, various portable biosensors have been developed for determining antibiotics in different food samples [190,193,194,201].

Ye et al. have developed a smartphone-based portable biosensor for the on-site detection of antibiotics in food samples [190]. The portable biosensor is based on the induction of yellow-green fluorescent quenching of quantum dots by the target analyte via a photo-induced electron-transfer process [190]. It can detect the gatifloxacin antibiotic in milk samples within 5 min and has a low detection limit (0.26 nM) [190]. In another study, a charge-coupled device-based portable lens-free optical biosensor that has live bacterial strains integrated for luminescence detected ciprofloxacin antibiotic in milk and egg white in 60–80 min and had an LOD of 8 ng/mL [194]. A portable lateral flow immunoassay-based biosensor that uses fluorescent microspheres for labeling antibodies was able to detect polypeptide antibiotics like bacitracin and colistin in milk samples with an LOD of 7.85 ng/mL and 1.89 ng/mL for bacitracin and colistin respectively [193]. Similarly, another antibiotic, tetracycline, was determined in milk samples by a portable biosensor made by immobilizing NADPH-dependent TetX2 protein on a glassy carbon electrode with polythionine modification [201]. The portable biosensor could detect tetracycline in milk samples in the range of 0.1–0.8 μM and had a detection limit of 40 nM [201]. Advances have been made in developing portable biosensors for the detection of different allergens in food samples [191].

Chiriaco et al. have developed portable immunochip biosensors for the detection of gliadin (alcohol-soluble fraction of the allergen gluten) in different food samples such as beer, potato flour, wheat flour, and rice flour [191]. The immunochip biosensor based on electrochemical impedance has a detection limit of 0.5 ppm, which is 20 times less than the established limit of gluten-free food [191,202]. Additionally, a mast cell-based portable paper biosensor modified with graphene/carbon nanofiber/gelatin methacryloyl composite has been developed for the detection of casein, an allergen present in milk [202]. A portable B-cell-based biosensor has been designed for the detection of botulinum toxin secreted by pathogenic bacteria belonging to *Clostridium* spp [203]. The B-cell-based biosensor could sense the botulinum toxin serotype A in milk (LOD = 7.4-7.9 ng/mL), acidified juices (LOD = 32.5-75.0 ng/mL), ground beef (LOD = 14.8 ng/mL), smoked salmon (LOD = 62.5 ng/mL), and green bean baby food (LOD = 16.6 ng/mL) [203]. Furthermore, a portable biosensor has also been developed to determine saxitoxin, a harmful toxin in shellfish [204].

Zhong et al. developed a smartphone-based device for colorimetric analysis and enzyme-linked immunosorbent assay to determine saxitoxin and had a 1-50 ng/mL detection range [204]. Similarly, a smartphone-based portable chemiluminescence biosensor has been made for the detection of mycotoxin ochratoxin A in coffee and wine samples with an LOD of 0.3 μg/L and 0.1 μg/L, respectively [192]. The chemiluminescence biosensor is based on the lateral flow immunoassay technique and utilizes a smartphone's camera for light detection [192]. The mycotoxin ochratoxin A was also detected in spiked wheat samples by a portable evanescent wave biosensor in the range of 0.73–12.50 μg/L and had a detection limit of 0.39 μg/L [205]. Another mycotoxin, deoxynivalenol, was detected in beer samples without a preconcentration step by a portable nanostructured surface plasmon biosensor with a detection limit of 17 ng/mL [206]. Moreover, portable biosensors have been developed for the detection of environmental pollutants like melamine, sulfadimidine, atrazine, and bisphenol A [207]. Sulfadimidine was detected in milk, baby formula, and yogurt by a reusable and portable biosensor made with a combination of microfluidics technology and an evanescent wave immunosensor with an LOD of 0.5 μg/mL [207]. Table 5 highlights various other biosensors used for the detection of toxins in foods.

## 6. Biosensors for detection of drugs abuse

Abuse of illegal substances poses a substantial risk to public health and a significant burden on the healthcare system. Drug misuse and overdose deaths have surged dramatically over the past few years, approaching epidemic proportions. The illegal sale, consumption, and smuggling of these drugs have been challenging tasks for law enforcement agencies. As a result, point-of-care diagnostic and monitoring devices are gaining prominence in various disciplines, including clinical diagnosis, crime scene investigation, employee testing, and roadside drug detection [218,219]. Recent advancements in biosensing technologies have enabled rapid, on-the-spot detection of drugs or illegal substances [220,221].

Conventional approaches such as LCMS, GCMS, and HPLC are the primary methods to detect illegal substances and their

**Table 5**
Biosensors for food quality and detection of toxins in foods.

| Type of biosensor | Biomolecule coupled with transducer | Analyte | Application | Level of detection | References |
|---|---|---|---|---|---|
| Enzyme | Choline esterase immobilized on fiber optic | Carbaryl and dichlorvos | Carbaryl and dichlorvos in water sample | 5.0–30 ppb and $10^{-8}$–5.2 ppb | [208] |
| | Bioluminescence ATP-based assay | ATP | Monitoring total microbial count on fresh-cut melon | 0.1–10.0 fg | [209] |
| | Toluene orthomonooxigenase immobilized on fiber optic cable | Toluene | Toluene detection | 3.00 μMol | [210] |
| Immunoassay | Anti-ricin IgG immobilized on fiber optic cable | Ricin | Detection of toxic protein ricin | 100 pg/mL | [211] |
| | Purified polyclonal antibodies | Atrazine | Detection of atrazine | 20 ppt | [212] |
| | Gold-coated sensor chip with phage antibody | *Lysteria monocytoges* | Detection of L. *monocytogenes* | $5 \times 10^5$ CFU/mL | [213] |
| | Fiber optic cable *with B. badius* and phenol red | Cadmium | Cadmium detection in milk | 0.1 μg/L | [214] |
| Nucleic acid | Multi-well cartridge connected with Charge Coupled Device immobilized with Yeast and bacterial cells | Androgens and estrogens | Response to various analytes and drugs | – | [215] |
| Whole-cell | fiber optic cable with recombinant protein | Glycan | – | fMol/L | [216] |
| | Fiber optic cable with Flavoprotein | Glucose | – | mMol | [217] |

metabolites. These techniques, however, are restricted to the lab since they need specialized equipment and personnel. The development of biosensors is prioritized as an effective alternative because of their high sensitivity, low cost, and low detection limit. Numerous biosensors, including optical [222], electrochemical [223], and aptameric [224], have been developed for the detection of various drugs of abuse. Since the last decade, portable biosensors for the detection of drugs of abuse have been gaining interest among the scientific community. Several portable biosensors have been developed for the on-spot and sensitive detection of various drugs of abuse [225–227].

Cocaine is one of the widely abused drugs sold and smuggled illegally through international borders to make a substantial monetary profit. Therefore, on-spot detection of cocaine at airports, international border crossings, seaports, and crime scenes is essential. Sanli et al. proposed a Screen-printed electrode (SPE) based biosensor functionalized with cobalt NPs and single-chain antibody fragments for the detection of cocaine with an LOD of 3.6 ng/mL. This novel biosensor demonstrated intriguing cocaine selectivity and sensitivity when compared to molecules from other addictive drugs. The proposed biosensor showed excellent affinity, is simple to prepare, adaptable, and portable, and has tremendous potential for mobile detection devices [228]. Another study developed a highly sensitive biosensor based on a single nanochannel and DNA aptamers to detect cocaine. The single nanochannel-aptamer-based biosensor showed exceptional sensitivity and selectivity for identifying cocaine molecules. Additionally, the cocaine sensor showed a detection limit as low as 1 nM [229].

Tang et al. developed a two-step structure-switching aptasensor for the detection of cocaine [230]. The proposed sensor was based on an evanescent wave optical biosensing platform. Two specifically designed aptamer probes were employed to build the molecular structure switching in the proposed biosensing platform. In the presence of cocaine, two cocaine aptamer fragments immediately form a three-way junction, and the quencher group of one fragment efficiently quenched the fluorophore group of the other. The cDNA sequences mounted on the optical fiber biosensor hybridized with the tail of a three-way junction. Evanescent waves were employed to

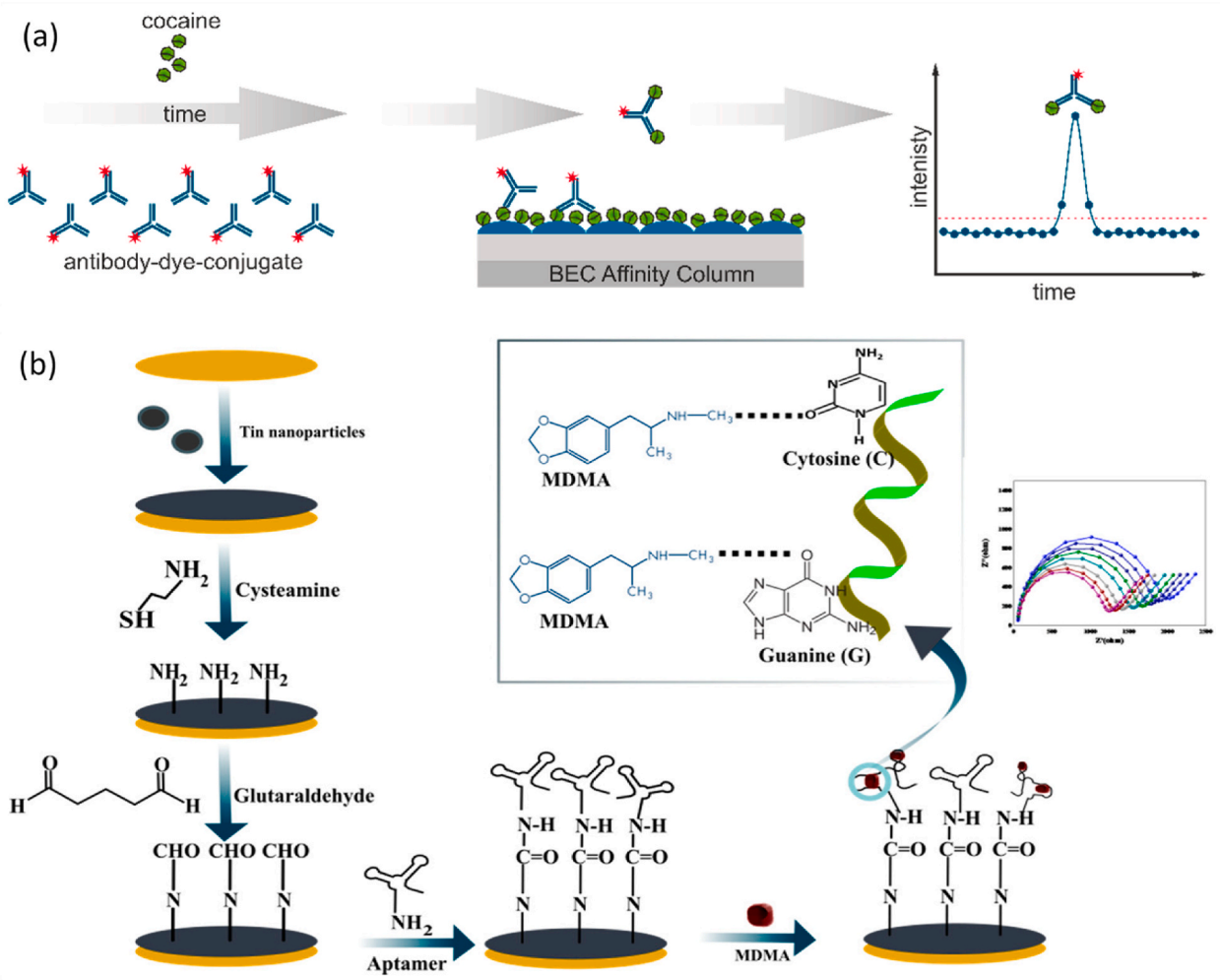


**Fig. 4.** The sample is combined with a fluorescently labeled anti-cocaine antibody and injected into an affinity column covered with a conjugate based on the cocaine derivative benzoylecgonine (BEC). A quick fluorescence signal rise detects unbound antibodies. (a) -Adapted from Ref. [231]. Scheme for Nanomaterial-Modified Impedimetric Aptasensor for 3,4-Methylenedioxymethylamphetamine Detection- (b)- Adapted from [242].

excite the fluorescence; and the fluorescence signal correlated with the concentration of cocaine. With an LOD (LOD) of 165.2 nM, the proposed aptasensor showed good recovery, precision, and accuracy [230]. Paul and his colleagues developed a Laser-Induced Immunofluorometric Biosensor that uses a monolithic affinity column with immobilized hapten to catch fluorescently labeled antibodies when cocaine is not present (Fig. 4a) [231]. The synthesized immunosensor utilizes a specialized column with abundant immobilized hapten to capture fluorescently labeled antibodies in the absence of cocaine. Cocaine presence blocks antibody sites, allowing labeled protein to flow, detectable by laser-induced fluorescence and a CMOS camera. Liquid handling is precise via syringe pumps and microfluidic chips. The biosensor detects cocaine at 7 ppt (23 pM) with a 90-s response time and a sub-3-minute total assay time. It identifies 300 pg of cocaine via surface wipe sampling. This sensor is highly sensitive and swift, offering continuous analyte measurement.

*Cannabis sativa* is an annual flowering plant that produces terpenes, fatty acids, and flavonoids in addition to its main chemical constituents, the cannabinoids. Because cannabinoids are involved in numerous physiological processes in animals and plants, cannabis has been utilized for both therapeutic and recreational purposes over time [232–235]. There are currently more than 100 cannabinoids known. The most popular among them are 9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are the decarboxylated versions of 9-tetrahydrocannabinol acid (THCa) and cannabidiolic acid (CBDa), respectively [236]. Cannabinoids and other performance-enhancing substances (PES) are on a list of banned substances in athletic competitions. Anabolic substances that promote muscle growth and improve oxygen transport are also included in the PES list. Moreover, driving under the influence of cannabinoids often results in fatal road accidents. The American Controlled Substances Act of 1970 places marijuana on its Schedule I list of substances [237]. The need for detecting people who are driving under the influence of marijuana increases, resulting in fatal accidents. Marijuana is often used as a recreational drug because of its stimulant and euphoric effects. The principal psychoactive component of marijuana is tetrahydrocannabinol (THC), which affects the endocannabinoid system of the central nervous system [238,239].

The unstoppable illegal sale and smuggling of such drugs have raised concerns among law enforcement. Researchers have developed several portable biosensors specific to cannabinoids for their on-spot detection and identification. An electrochemical impedance spectroscopy (EIS) based immunosensor was proposed by Durmus et al. for the detection of JWH-018 (the N-4-hydroxyphenyl metabolite-a synthetic cannabinoid) [240]. First, a catechol-attached polypeptide was used to create a functional surface (CtP). A covalent cross-linker was then used to integrate the anti-K2 antibody into the polymer. The increase in Rct that occurs after the target is directly bound to the functionalized surface is the basis for the detection principle. An LOD and linearity for the N-4-hydroxyphenyl metabolite were established to be 10-500 ng/mL and 5.892 ng/mL, respectively. The biosensor's selectivity was tested using a variety of interference compounds (including cocaine, codeine, and (methamphetamine). Finally, in spiked synthetic urine samples, the immunosensor successfully identified JWH-018 (N-4-hydroxyphenyl metabolite). The findings demonstrated that the created platform may be used to accurately and sensitively detect various JWH series [240]. Lu et al. reported a sandwich immunoassay for detection of THC detection [241]. The proposed sensor is based on a double-layer AuNP amplification system placed onto a glassy carbon electrode to absorb thionine (Thi) and horseradish peroxidase (HRP). A conductive layer comprising chitosan, AUNP, HRP, and thionine held the anti-THC between the two layers. When H2O2 was present, immobilized HRP and thionine took part in a series of redox reactions that caused the faradaic current to rise. Due to steric hindrance, the target THC's binding to the immobilized antibody prevented electron transfer. Chronoamperometry was utilized to quantify the amount of THC in phosphate buffer saline (PBS). The results demonstrated a solid linear association between the response current and the THC concentration range of 0.01 to $10^{-3}$ ng/mL with an LOD of 3.3 pg/mL [241].

The central nervous system (CNS) stimulant 3,4-Methylenedioxy Methamphetamine (MDMA), often known as Ecstasy and Molly or Mandy, is most frequently used for recreational purposes. To curb the widespread abuse of MDMA, it is essential to develop rapid, sensitive testing technologies for the drug. Soni et al. designed a nanoarchitecture based on aptamer-modified tin nanoparticles (SnNPs) and used it as an electrochemical sensor (Fig. 4b) [242]. Due to its larger surface area in comparison to the unmodified electrode, the platform displayed improved electron transfer and conductivity. This outcome was attributed to the significantly expanded electroactive surface area of SnNPs@Au, enabling efficient immobilization of 1.0 μM AptMDMA and producing a robust electrochemical reaction to MDMA. The SnNPs@Au platform modified with AptMDMA was utilized as a precise analytical tool to detect MDMA in both artificially introduced biological and water samples. It displayed linear detection within the 0.01–1.0 nM MDMA range ($R^2 = 0.97$), boasting a detection limit of 0.33 nM and a sensitivity of 0.54 Ω/nM. The sensor showed stability, resulting in signal recoveries of 92–96.7 % (with a Relative Standard Deviation, RSD, of 1.1–2.18 %). This groundbreaking aptasensor, which merges SnNPs and aptamers, introduces a dependable platform for identifying recreational drugs [242]. In another study, Tseng et al. proposed a biomolecular layer with extremely specific binding that allows for the immobilization of antibodies to detect low quantities of MDMA [243]. This study used a microcantilever-based biosensor to investigate the interactions between anti-MDMA antibodies and MDMA. A cysteamine-based self-assembled monolayer was used to immobilize affinity monoclonal antibodies for the detection platform. Different amounts of MDMA-conjugated anti-MDMA antibodies were bonded to the sensing surface. Monitoring the simultaneous data, such as the resonant frequency shift of microcantilevers, allowed researchers to observe the intermolecular interaction. This study found that anti-MDMA antibodies may respond precisely to MDMA. The results show that the microcantilever-based biosensor can be employed to evaluate MDMA response profiles of anti-MDMA and to give abundant data for immunoassays [243].

## 7. Biosensors for detection of biological- and chemical-warfare agents

Biosensors for quantifying and detecting biological warfare agents have recently gained significant interest due to their sensitivity,

low cost, ease of use, and portability. Although there are a limited number of commercially available biosensors, their utility has been shown by their use by military and law enforcement agencies for developing effective countermeasures against biological warfare agents [12,244]. Recent studies on the topic have increased the topic's practicality and utility. The necessity for rapid and precise biosensors to detect infectious agents has become more urgent, considering recent biological terrorism concerns and outbreaks of microbial infections [245,246]. Most rapid biosensors for the detection of biowarfare agents are designed to produce detectable signals in response to an interaction between a molecular probe inside the detector and an analyte of interest. Bacterial or fungal cells, viral particles, or certain compounds, such as chemicals or protein toxins, generated by the infectious agent may all serve as analytes. Most biosensors utilize peptides or nucleic acids as probes because of their ability to fold into a wide variety of tertiary structures [12].

Several probes and primers that apply to certain diseases and biowarfare agents have been designed. Recently, several companies have started to commercialize PCR-based kits to detect pathogens. Such kits eliminate the requirement for a complete design of primers and probes and allow for the quick identification and monitoring of biowarfare agents [247]. Immunoassay techniques are frequently used in the medical, pharmaceutical, and food sectors to detect infectious diseases, toxins, and poisons. Various immunoassays for biothreat detection have already been investigated [247].

BioPen, a device created by a team from Ben Gurion University for antigen detection using the commonly used enzyme-linked immunosorbent assay (ELISA) technology, aids frontline soldiers in determining whether they have been exposed to biologically

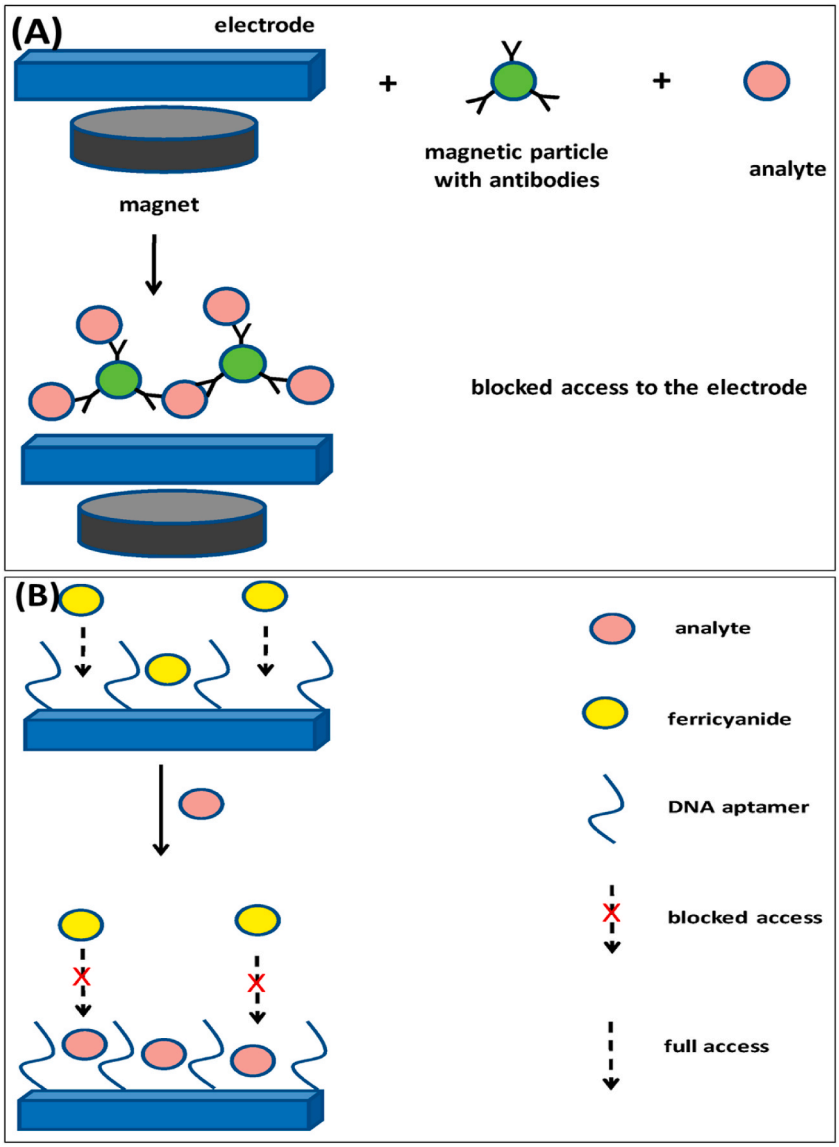


**Fig. 5.** Working principle of the impedimetric sensor with immobilized ssDNA operates on the premise of operating when there is restricted access to the electrode surface for a redox-active substance such as ferricyanide (3-) (A).- Adapted from Ref. [255]. The working principle of magnetic particles preventing access to the surface of an electrode (B)- Adapted from [256].

hazardous chemicals in less than 20 min [248]. This diagnostic system has a compact LCD and is user-friendly, requiring no prior training and being self-sufficient. This may also be used to test drinking water, detect environmental toxins, and diagnose various dangerous diseases, such as hepatitis B and C and even some kinds of cancer, more accurately and effectively. Various countries have established surveillance systems (e.g., the United States BioWatch Programme), laboratories, and various monitoring tools for early detection of a bio-attack. BioWatch is the United States project designed to detect the discharge of airborne pathogens in a biological assault on major American cities. This approach gives investigators a general notion of the origin and time of the bioterror attack. It also gives a tiny bio-agent sample for examination by forensic experts and preserves the chain of custody [249,250]. The security challenges posed by genome editing, which allows the alteration of genes, also pose a security challenge for law enforcement agencies. Various guidelines have been established by regulatory authorities worldwide to keep the development of genome editing technologies in control [251,252].

While biosensors cannot be considered alternatives to costly and conventional laboratory procedures, they can provide a simple and cost-effective tool for on-site tests and initial screening samples to narrow down on a suspect one. Several studies have been conducted to detect biowarfare agents, and various extensive reviews have been published describing biosensors' role in detecting and quantifying biowarfare agents. MingcongRong et al. proposed functionalized manganese-doped carbon dots (FMn-CDs) by coupling pyrolysis-derived Mn-CDs with ethylene diamine, ethylenediamine tetraacetic acid, and Europium [Eu(III)] ions [253]. Intense blue fluorescence was emitted from the FMn-CDs, which also had great photostability, good water-solubility, and a mostly positive biocompatibility characteristic. One of the biomarkers for *Bacillus anthracis (B. anthracis)* spores includes 2, 6-dipicolinic acid (DPA). It acts as a suction light group for antennas and may sensitize the Eu(III) combined on the FMn-CDs to create strong red fluorescence.

A ratiometric biosensor for the detection of DPA was created using the absorbance energy transfer emission impact of DPA on the sensitized Eu(III). The proposed method has a detection limit of 0.1 nM and a linearity range of 0.1–750 nM. With the lowest detection limit of 1 nM, the FMn-CDs test material was developed for visual DPA detection using a smartphone under a portable UV light [253]. *B. anthracis* can develop into biological weapons of mass destruction owing to its virulence factors encoded by plasmid-borne genes. One example of these genes is '*lef*', which stands for "lethal factor". Bailin Zhang et al. developed a rapid and sensitive anthrax DNA biosensor. The biosensor was based on a photonic crystal structure that was configured for complete internal reflection [254]. A single-stranded DNA lef probe was biotinylated and mounted onto the sensor using biotin-streptavidin interactions to detect the *lef* gene with detection sensitivity as low as 0.1 nM. Moreover, there was no observable change in the resonant wavelength after adding the unrelated DNAs. These findings showed that a total-internal-reflection sensor using a photonic crystal structure is a precise and sensitive method for detecting anthrax *lef* [254].

Biological defense and security applications necessitate quick, precise estimation of bacterial infections. A novel qualitative electrochemical detection technique for *B. cereus* and *E. coli* was proposed by Setterington and Alocilja with detection limits of 40 CFU/mL and 6 CFU/mL, respectively [255]. This rapid procedure combines immunomagnetic separation and cyclic voltammetry and takes about an hour to provide findings that are presumed to be positive or negative. Target cells are extracted from the sample solution using an immune-functionalized magnetic/polyaniline core/shell nanoparticle (c/s NP) and then magnetically positioned on a screen-printed carbon electrode (SPCE) sensor. The presence of target cells reduces current flow between electrically active c/s NPs and SPCE to a substantial degree (Fig. 5A). In another study, Mazzaracchio et al. developed a label-free aptasensor for *B. cereus* spores using a gold screen-printed electrode functionalized with an aptamer specific for detecting *B. cereus* spores (Fig. 5B). Testing against *B. cereus* spores revealed successful results under optimized conditions (3-h incubation, no $MgCl_2$). The aptasensor detected spore concentrations from $10^4$ CFU/mL to $5 \times 10^6$ CFU/mL, with a $3 \times 10^3$ CFU/mL detection limit. The aptasensor's specificity for *B. cereus* spores was proven against other strains. This demonstrates its potential for on-site, label-free measurements of *B. anthracis* spore simulants using portable instruments, highlighting its real-world utility [256].

Charles Poitras and Nathalie Tufenkji developed a biosensor for detecting *E. coli* O157:H7 employing a quartz crystal microbalance with dissipation monitoring (QCM-D). The detection platform relied on a cysteamine self-assembled monolayer immobilized on gold-coated QCM-D quartz crystals to identify antigens of interest [257]. For the detection of *E. coli* O157:H7 throughout a large range of cell concentrations from $3 \times 10^5$ to $1 \times 10^9$ cells/mL, a highly log-log linear response in the initial Dslope (slope of the dissipation shift as a

**Table 6**
Biosensors for biological warfare agents.

| Bioagent | Biosensor type | Biosensor composition | Limit of Detection | Reference |
|---|---|---|---|---|
| *Francisella tularensis* and ricin | Optical | Bio-layer interferometry based on fiber optic biosensors and standard 96-well microplates | $10^4$ CFU/mL and 10 pg/mL | [259] |
| *B. anthracis* | Voltammetric | Gold electrode modified with a genetic probe | 5.7 nmol/L | [258] |
| *B. anthracis* | Voltammetric | Gold screen-printed electrode modified with DNA | 10 pmol/L | [260] |
| Botulinum toxin | Potentiometric | Light addressable potentiometric sensor | 10 ng/mL | [261] |
| *Francisella tularensis* | Optical | Long-period fiber gratings | 1 ng | [262] |
| Ricin | Voltammetric | Magnetic beads covered with antibody, silver nanoparticles with an antibody | 34 pmol/L | [263] |
| *B. anthracis* | Optical | Manganese-doped carbon dots with ethylene diamine and ethylenediamine tetraacetic acid with bound $Eu^{III}$ | 0.1 nmol/L | [253] |
| *B. anthracis* | Optical | Photonic crystal sensor with total internal reflection modified with DNA | 0.1 nmol/L | [254] |
| *B. cereus* and *E. coli* | Voltammetric | Polyaniline/magnetic immunoparticles | 40 CFU/mL and 6 CFU/mL | [264] |
| *E. coli* O157:H7 | Piezoelectric | QCM | $3 \times 10^5$ cells/mL | [257] |
| *B. cereus* | Impedimetric | Screen-printed Au electrodes with DNA aptamer | $3 \times 10^3$ CFU/mL | [256] |

function of elapsed time) was obtained. The proposed biosensor also displayed a reasonable level of selectivity when employing Bacillus subtilis and an *E. coli* K12 D21 model organism with a log-log linear range of $10^7$ to $10^9$ cells/mL [257]. In another study, Ziolkowski et al. created an electrochemical biosensor to identify the pagA gene and detect *B. anthracis* [258]. This biosensor has a DNA molecular beacon probe that was folded and connected to gold electrodes. The probe unfolded in the presence of *B. anthracis* and its pagA gene, allowing the electrochemical characteristics of the transformed electrodes to be measured. The biosensor had an LOD of 5.7 nmol/L and a linear range of 22.9–86.0 nmol/L [258]. Some other biosensors for the detection of biowarfare agents are summarized in Table 6.

## 8. Conclusions and Future Directions

This article emphasizes the importance of portable biosensors in analyzing sensitive biological samples, particularly in forensic and crime scene investigations. The application of biosensors serves as essential tools for forensic scientists and criminal investigations because of their rapidity, precision, stability, specificity, and low cost. The use of portable biosensors in forensic toxicological analysis is one critical application addressed in the study. Several biosensors have been developed to detect pollutants, heavy metals, phenols, pesticides, and other toxic substances of forensic interest. The paper also highlights the significance of biosensors in explosive detection, which is critical for counterterrorism, security, and environmental protection. Conventional explosive detection procedures are sometimes challenging, costly, and time-consuming. With their specificity and sensitivity, portable biosensors are an appealing option. To detect explosives such as TNT and TTX, researchers synthesized biosensors that use aptamers, antibodies, and other biomolecules. These biosensors have shown good results in terms of sensitivity, selectivity, and detection speed, making them useful instruments in crime scene investigations and security operations.

The article also dives into the detection of physiological fluids, such as blood, saliva, and sperm, at crime scenes. While not thoroughly studied in the context of forensic investigations, numerous biosensors for detecting these fluids in other applications have been created. Biosensors, for example, have been developed for quick blood analysis, blood type determination, and sperm analysis for fertility testing. Using these biosensing methods in forensic circumstances might possibly speed up the process of identifying and analyzing body fluids, assisting in the resolution of sexual assault or violence cases.

Detecting illicit drugs through portable biosensors is another critical topic addressed in this article. Several biosensors are used for detecting illicit drug compounds because of their great sensitivity, low detection limits, and simplicity of use. Biosensors have been designed to detect cocaine, cannabis, and other illicit substances. The article discusses several ways for sensitive and quick drug detection, such as aptameric biosensors, immunoassays, and nanochannel-based sensors.

Finally, the review delves into the use of portable biosensors in the detection of bio- and chemical-warfare weapons. The need of detecting infectious agents and poisons quickly and accurately is emphasized, particularly in the context of bioterrorism threats and epidemics. Biosensors based on molecular probes, peptides, nucleic acids, and immunoassays are valuable tools for detecting and monitoring biowarfare chemicals. The potential for these biosensors to be used in frontline scenarios, such as for troops exposed to toxic chemicals, emphasizes their relevance in boosting national security.

Although portable biosensors for the detection of sensitive forensic samples show great promise for the future, they also suffer from a number of drawbacks that must be overcome before they can reach their full potential. The following constructive and productive topics of discussion and debates can point the way forward as technology develops and transdisciplinary partnerships get stronger:

Identifying low concentrations of target analyte in the complex forensic samples, current portable biosensors may face difficulty. Research into increasing the sensitivity and specificity of biosensor systems is needed to address this shortcoming. Using cutting-edge nanomaterials, novel bio-recognition components, and signal amplification strategies could significantly improve the biosensor's sensitivity to detect low concentrations of analytes, making them more useful in police investigations. Forensic samples frequently contain various analytes that must be detected simultaneously. In order to expedite the investigation process and preserve precious sample material, the development of portable biosensors with multiplexing capabilities (capable of detecting multiple samples) would be beneficial. Simplifying sample preparation is an essential step because it significantly impacts biosensor performance. Portable biosensors will be more accessible to law enforcement officers in the field if the time and expertise necessary to process samples are reduced through automation and simplification. Accurate and repeatable results can be achieved using microfluidic devices and integrated sample preparation modules by reducing the complexity and room for human mistakes in sample preparation.

The data produced by portable biosensors must be managed and processed effectively before they can be put to use in the real world. For on-the-ground investigations, it will be critical to implement user-friendly software interfaces and data analysis methods. Law enforcement officials may be able to makefaster and well-informed decisions with the help of real-time data interpretation. Protocols for validation and standardization are crucial if portable biosensors are to become widely used in forensic settings. Researchers, forensic scientists, and regulators should work together to develop comprehensive quality assurance and validation protocols. This will guarantee that the data gathered by portable biosensors is trustworthy and may be used as evidence in court.

Portable biosensors used in field applications are frequently exposed to challenging environmental conditions. Improvements in the future could include making the devices more resistant to changes in temperature and humidity as well as possible impacts. The durability and dependability of portable biosensors can be improved with the use of robust materials and protective coatings. As portable biosensors become increasingly commonplace in forensic investigations, keeping privacy and ethics in mind is essential. Finding a happy medium between protecting the public and respecting people's right to privacy is crucial. To keep the public's faith in forensics, rules should be set regarding how information gathered by portable biosensors is to be used, stored, and eventually discarded. The development of portable biosensors for forensic usage necessitates the collaboration of experts from a wide range of disciplines. Forensic scientists, engineers, biologists, chemists, and data analysts working together will generate novel approaches to

present challenges, allowing the profession to advance.

The recent developments in portable biosensors are gaining the scientific community's interest worldwide as these biosensors are rapidly becoming indispensable investigative tools in forensic science. Due to their high specificity, speed, and little sample modification, biosensors have become valuable instruments for quick initial screening and sensitive evaluation of suspicious substances found at crime scenes. These portable biosensors provide accurate and reliable results and minimize human errors that often arise during samples' extraction, purification, and preparation. However, despite such benefits, there are currently very few actual applications of biosensors in forensic examinations and in many cases. Although studies have been conducted extensively to detect toxins and hazardous materials of forensic interest, very few studies have focused on applying sensors in forensics and serology. Currently, biosensors in forensic biology and serology are limited to detecting some body fluids; however, their practical application at the crime scene is still in its initial stage. Therefore, in the near future, significant research efforts should be made to ensure the development of biosensors for their practical application at crime scenes. The evidence found at the crime scene loses its integrity over time; therefore, onsite analysis of such evidence at the crime scene is essential. For such purposes, developing portable biosensors for onsite detection of the forensic samples found at the crime scene could be beneficial. Hence, research and development for such portable biosensors is highly desired.

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This article presents the data generated and analyzed in figures or tables. Additional information on methods or materials used in this study will be made available upon request to the corresponding author.

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## 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.

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