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REVIEW

Aptamer-based rapid diagnosis for point-of-care application

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Abstract

Aptasensors have attracted considerable interest and widespread application in point-of-care testing worldwide. One of the biggest challenges of a point-of-care (POC) is the reduction of treatment time compared to central facilities that diagnose and monitor the applications. Over the past decades, biosensors have been introduced that offer more reliable, cost-effective, and accurate detection methods. Aptamer-based biosensors have unprecedented advantages over biosensors that use natural receptors such as antibodies and enzymes. In the current epidemic, point-of-care testing (POCT) is advantageous because it is easy to use, more accessible, faster to detect, and has high accuracy and sensitivity, reducing the burden of testing on healthcare systems. POCT is beneficial for daily epidemic control as well as early detection and treatment. This review provides detailed information on the various design strategies and virus detection methods using aptamer-based sensors. In addition, we discussed the importance of different aptamers and their detection principles. Aptasensors with higher sensitivity, specificity, and flexibility are critically discussed to establish simple, cost-effective, and rapid detection methods. POC-based aptasensors' diagnostic applications are classified and summarised based on infectious and infectious diseases. Finally, the design factors to be considered are outlined to meet the future of rapid POC-based sensors.

Keywords Aptamer · Point of care · Biosensors · Diagnosis

1 Introduction

The demand for human health management has led to increasing clinical trials. Because of an increasing number of clinical trials need to develop more sensitive, reliable, time-efficient, and cost-effective analytical methods. Traditional techniques (molecular assays and microbial culture-based tests) require high-cost equipment and a long-time, which makes expensive diagnosis methods. On the other hand, biosensor technology provides accurate results with less time, high sensitivity, and inexpensive measurements to detect pathogen pathways (Lazcka et al. 2007). The aptamer comes from the Latin word 'Aptus', which means 'to suit' (Sharma 2014). Nowadays, different types of aptamers used in various applications. For example, the RNA or DNA aptamer used in vitro (SELEX procedure, selective evolution of ligands by exponential enrichment) from many random sequences. Stoltenburg et al. (2007) pioneered the isolation of nucleic acid ligands against T4 DNA polymerase through systematic ligand evolution by exponential enrichment (SELEX). It involved alternating cycles of selection of ligands from sets of variant sequences and amplifying the linked species. In another

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study, Mascini et al. (2012) isolated subpopulations of RNA molecules that can specifically bind to a large number of organic dyes, which were later called "aptamers".

Aptamer-based biosensors are applicable in numerous diagnostic processes such as disease detection, cancer detection, heart disease, etc. Biosensors are widely marketed; however, point-of-care testing is new in the diagnosis process. Aptamers have a long shelf life due to their chemical structure, more stable under harsher chemical conditions (thermal stability, nuclease resistance, and alkaline hydrolysis) (Friedman et al. 2015; Kuai et al. 2017; Wang et al. 2019). Aptamers detect small molecules due to their small size and high binding capacities on the immobilised sensor surface (Stanciu et al. 2021). In addition, aptamers detect small molecules with high specificity and different modes of operation (sandwich, TISS, TID, and competitive mode). These modes make the development of flexible biosensors, with the help of modes of operation, open up a new area of sensors that quickly introduce and detect small molecules (Prante et al. 2020). Aptamers are short single-stranded oligonucleotides (less than 100 nucleotides) that identify specific ligands with great affinity and specificity to various targets, from small ions to large proteins (Zou et al. 2019). Aptamers, often called synthetic antibodies, can be used to mimic antibodies in various situations. Aptamers are chemically stable in buffer conditions ($MgCl_2$) due to their resistance on hazardous chemicals without losing their bioactivity and reversible to thermal denaturation. Amino acids, proteins (enzymes, membrane proteins, viral proteins, cytokines and growth factors, and immunoglobulins), metal ions, other small bio-/organic/inorganic molecules, and cells are aptamers molecular and therapeutic targets that help to detect biomolecules. The tertiary structure of aptamers binds to various targets with high affinity and shows high sensitivity, selectivity, stability, and accuracy in POCT diagnosis (Miao et al. 2014; Zuo et al. 2007).

A patent analysis was performed with the Google Patents search tool, using the keywords, aptasensors OR aptamer-based biosensors AND (microchip OR microfluidic OR LOC), from 2006 to 2022 and analysis data provided in Fig. 1. The top 5 key players in the aptasensors market are The Regents of The University of California (US), Searete Llc, Delaware (US), Massachusetts Institute of Technology (US), President and Fellows of Harvard College (US) and Roche Diagnostics Operations, Inc. (US). Several patents in multiple research papers on various elements of the aptamer biosensor field at numerous phases of development have been published in the past two decades (Narayanamurthy et al. 2020b). The wealth of knowledge gained over the last two decades is an excellent opportunity to review the profession and critically identify novel ideas.

The development of point-of-care (POC) technologies to provide fast, self-supported testing in outpatient or remote settings to complement routine clinical diagnostics is current in medical diagnostics. The widespread availability of low-cost tests and their integration with digital devices for remote data transmission and analysis projected to create a fundamentally new approach for global, near-real-time public health interventions. Aptasensors are one of the most promising possibilities to accelerate the translation of traditional benchtop medical diagnostics into point-of-care tests in the new era of digital and personalised medicine (Prante et al. 2020). The focus of the in vitro diagnostic (IVD) sector has switched to point-of-care diagnostics (POC) in the last decades, as POC tests might theoretically provide a quick sample-to-answer time with minimal human intervention (Dhiman et al. 2017). The World Health Organization (WHO) developed the ASSURED (affordable, sensitive,

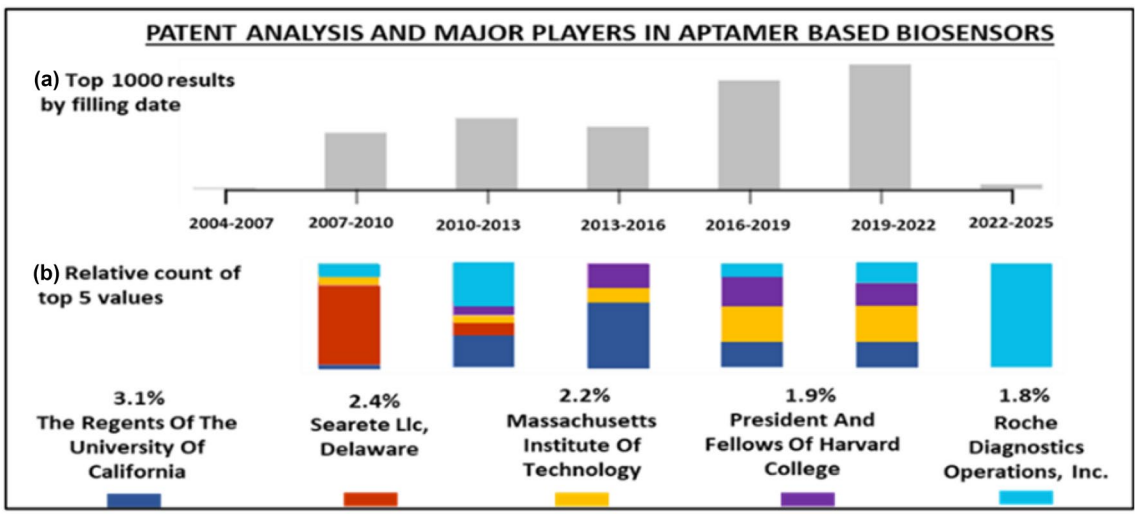

Fig. 1 Patent analysis and significant players in aptamer-based biosensor

specific, user-friendly, robust, equipment-free, and deliverable) criteria for evaluating POC diagnostic tests for resource-limited settings (Drain et al. 2014). In addition, the POC test has evolved with a specified target product profile (TPP) that is helpful at different levels, such as including homes (TPP1), communities (TPP2), clinics (TPP3), and external laboratories (TPP4), and hospitals (TPP5) (Kaur et al. 2019; Pai et al. 2012). Various miniaturised POC diagnostic/biosensing platforms have been introduced in the IVD market, ranging from optical and fluorescence to electrochemical. None of these platforms met the ASSURED criteria except for immunochromatography assays (Drain et al. 2014). Immunochromatography has shifted in the in vitro diagnosis field due to its rapid turnaround time, ease of operation, and exceptional affordability (Wang et al. 2021). The present study overviews recent advancements in aptamer-based biosensors for POC diagnostics and global health. The article begins with the aptamer synthesis method, the SELEX system. SELEX used in the synthesis technique for the production of aptamers. Various aptamer transducing mechanisms such as electrochemical, optical, and mass-sensitive approaches are discussed in detail. Recent efforts to miniaturise aptasensors into point-of-care formats and clinical uses of aptasensors to detect a wide spectrum of infectious and non-infectious disorders are demonstrated. Finally, the future prospects and difficulties for aptamer-based biosensors in global health are highlighted.

2 Design strategies for aptasensors

Miniaturised devices are extensively fabricated and possess good market potential; research are done to improvise the existing design strategies regarding relativity, sensitivity, detection time, and point-of-care diagnosis. Aptamers are essential in ligand–protein binding affinity with respect to their POC application (Narayanamurthy et al. 2021).

2.1 SELEX system

Aptamers are synthesised by a repetitive in vitro selection process called systematic ligand evolution by exponential enrichment (SELEX). SELEX process is divided into two alternate steps. In the first step in Fig. 2, original oligonucleotides are amplified to the desired concentration using a polymerase chain reaction (PCR). The set of single-stranded oligoribonucleotides is generated by in vitro transcription of double-stranded DNA with T7 RNA polymerase. Single-stranded oligodeoxyribonucleotides are generated by separating strands of double-stranded PCR products to select DNA aptamers. In the second stage, the amplified oligonucleotide pool incubated with target molecules, and the interacting oligonucleotides are used

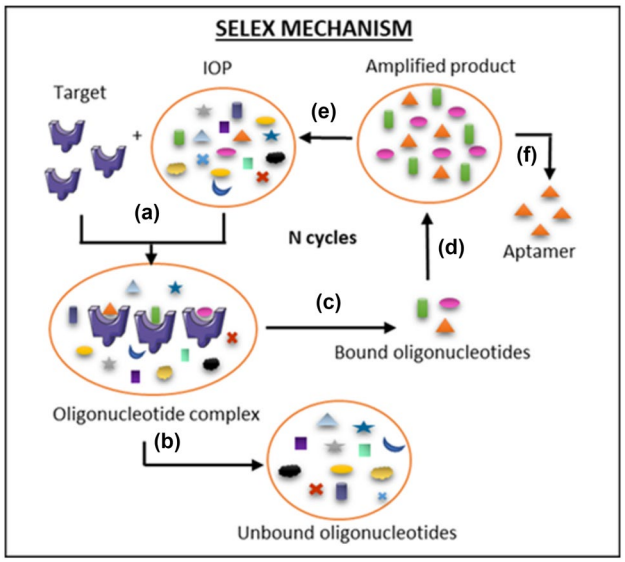

Fig. 2 Scheme of SELEX. **a** The initial oligonucleotide pool (IOP) incubated with a target molecule. **b** Unbound oligonucleotides separated from bound molecules by washing steps. **c** Bound oligonucleotides eluted from the target molecule. **d** Eluted oligonucleotides amplified using the PCR (DNA-SELEX) or RT-PCR (RNA-SELEX) technique. **e** The enriched pool is then subjected to further rounds of selection. **f** After 5–15 rounds, aptamers are cloned and analysed in detail

for the first stage of the next SELEX round (Marimuthu et al. 2012). Separating oligonucleotides with higher affinity for target molecules and removing unbound oligonucleotides were achieved through intense competition for binding sites. The selection of aptamers increases with each SELEX round. Maximum enrichment of the oligonucleotide pool through aptamers with high affinity to the target molecule is achieved after 5–15 rounds (Liu et al. 2011; Mascini et al. 2012). The SELEX method applies to selecting aptamers capable of binding target molecules and selecting oligonucleotides with specific enzymatic activity. In this case, the ability to catalyse the desired chemical reaction was used in the selection criterion (Lakhin et al. 2013). Aptamers show a high ligand–protein affinity for their targets, from the micromolar range to the low picomolar content, comparable to some monoclonal antibodies, sometimes even better (Jenison et al. 1994). A large number of oligonucleotide sequences and their molecular diversity allow the isolation of aptamers with an affinity for the most varied molecules. Aptamers are evolved significantly against multiple targets, including small metal ions and organic molecules, peptides, proteins, viruses, bacteria, whole cells, and even targets within live animals (Lakhin et al. 2013; Zhou and Rossi 2017), (Fu and Xiang 2020), (Tickner et al. 2020), (Hasegawa et al. 2016), (Li et al. 2021).

2.2 Assay configuration

Immunoassays are based on the antigen–antibody interaction used to transmit bio-recognition events. Each aptamer–target combination shows distinct recognition modes frequently used in sensor design (Hermann and Patel, 2000). Many test setups have been created and reported because aptamers have selected to bind many targets, from tiny molecules to macromolecules. Nuclear magnetic resonance (NMR) studies have revealed that tiny molecular targets are frequently buried within the binding pockets of aptamer (Fig. 3a), leaving limited area for a second molecule interaction. Small-molecule targets are hence often tested using the single-site binding arrangement.

On the other hand, complex structured protein targets interact between several discriminating contacts (e.g. stacking, shape complementarity, electrostatic interactions, and hydrogen bonding). As a result, single-site binding (Fig. 3b) and dual-site binding (Fig. 3c) can be used to test protein targets. Dual-site binding requires the presence of two aptamers that bind to distinct areas of the protein. One of the most common test forms is the dual-site binding assay, popularly known as the "sandwich" assay. The analyte sandwiched between two aptamers, including one capture probe and the other reporting probe (Fig. 3c). Capture probes frequently mounted on the surface of solid substrates (such as electrodes, glass chips, nanoparticles, or microparticles).

In general, capture and reporter probes have different nucleic acid sequences; however, some proteins (e.g. dimeric) include two identical binding sites, allowing the sandwich test to be performed with a single aptamer (Song et al. 2008). In contrast, reporter probes were coupled with signalling moieties (such as fluorophores, enzymes, or nanoparticles—NPs). It is also worth noting that when no two aptamers share identical or overlapping binding sites on the target of interest, an antibody can be used as the second aptamer (Fig. 3d). Utilising

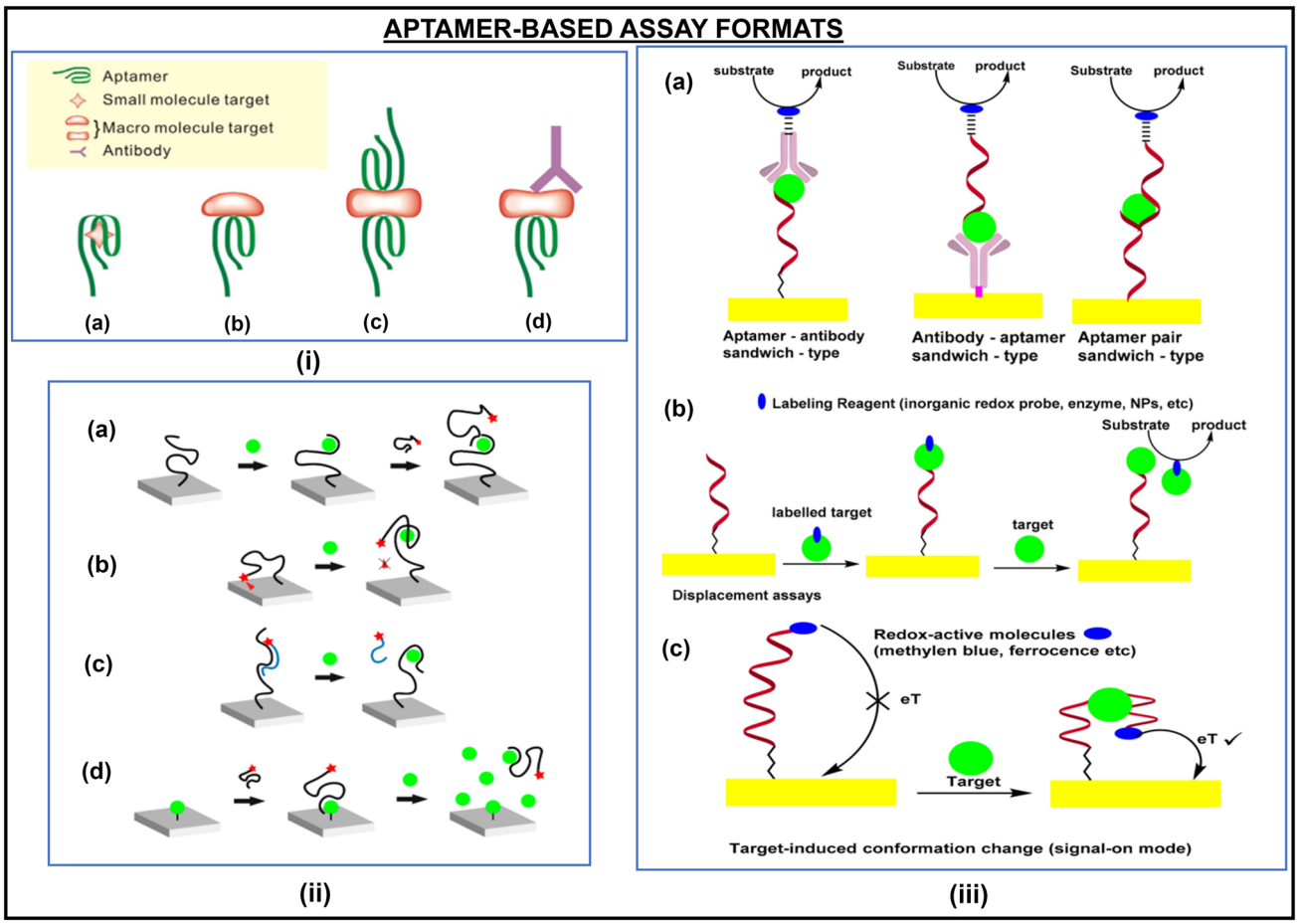

Fig. 3 Aptamer-based assay formats. (i) **a** Small-molecule target buried within the binding pockets of aptamer structures; **b** single-site format; **c** dual-site (sandwich) binding format with two aptamers; and **d** "sandwich" binding format with an aptamer and an antibody (Song et al. 2008). (ii) **a** Sandwich mode; **b** Target-induced structure switching (TISS) mode; **c** Target-induced dissociation (TID) mode; **d** Competitive replacement (CR) mode(Prante et al. 2020). (iii) **a** Sandwich-based aptasensing; **b** Displacement -based aptasensing; **c** Folding -based aptasensing (Radi and Abd-Ellatief 2021)

this phenomenon, many aptamers can combine with a single molecular target.

Aptamers and nucleic acid are usually immobilised on the biosensor's surface. The immobilisation significantly improves the biosensor's handling and simplifies the nucleic acid's regeneration (Wei et al. 2010). Using complementary strands to bind the aptamer makes it possible to develop competitive assays that open new possibilities for biosensing in general and small molecules in particular. Complementary strands and the oligonucleotide nature of aptamers allow the implementation of amplification and increased aptasensor sensitivity. Scientist Han K and his colleagues categorised into four fundamental modes: target-induced structure switching mode, sandwich or sandwich-like mode, target-induced dissociation/displacement mode, and competitive replacement mode. These modes currently represent the dominant design strategies for this class of devices (Fig. 3ii). These design approaches aim to successfully detect ligands by converting the unique binding process between ligands and aptamers into different signal variants. Each designed biosensor shows excellent performance in detecting standard samples. However, few of them have been used for the detection of real samples such as serum or blood. The TID mode is more generic than other approaches because it is less dependent on the conformation of the ligands or aptamers. Before aptamer-based biosensors can be used in practise, there is still much to be done, including improving their stability and reliability, especially in detecting real samples. The aptamer preferentially binds to the free molecule when the target molecule is supplied in excess and is detached from the immobilised target molecule (Prante et al. 2020).

Additionally, scientist Radi A. E et al. demonstrated direct apta assay formats in Fig. 3iii. Molecular recognition of the target molecule using the cognate aptamer adsorbed to the sensor surface is the focus of direct Apta assay formats. The high detection limits and limited selectivity of the sensing layer are the main drawbacks of this method. The biosensing assays could be improved using different configurations, including (a) sandwich, (b) displacement, and (c) convolution aptasensors. This configuration is applied in improvements in electrochemical aptasensors for monitoring target molecules, focusing on efficient strategies for detecting sandwich structures, EIS measurement of the change in charge transfer resistance related to the concentration of the target molecule, and the change in aptamer conformation that turns the electrochemical signal of the electroactive markers on and off (Radi and Abd-Ellatief 2021).

3 POC-based aptasensor detection methods

A biosensor is a relevant POC diagnostic platform and is a portable analyzer for patient monitoring (Liu et al. 2014a, b). Various biomolecules (receptor probes, proteins, enzymes, aptamers, cells, and antibodies as nucleic acids) are applied in biosensors for detection. These biomolecules are immobilised on the surface of the transducer by physical or chemisorption. Biochemical interaction events such as electrochemical, optical and mass sensitive are measured on the surface of the transducer.

A systematic literature search has been performed using google scholar with the following keywords: "aptasensor or aptamer-based biosensor or point of care and electrochemical, optical, mass sensitive" throughout 2006–2022 (Fig. 4) presents a pie chart revealing the aggregate number of articles on POC-based aptamer's detection method from 2006 to 2022. Electrochemical biosensors are gaining more interest from researchers in the last two decades compared to optical and mass-sensitive biosensors. They are measured with different types of transformations (Choi 2020; Cui and Zhou 2020). Three critical components of a biosensor: (I) specific detection of biomarkers, (II) transmission mechanism for interpreting biochemical events as ready signals, (III) detectors for quantification and further analysis (Mayeux 2004). These have been extensively developed and are typically divided into portable diagnostic devices and compact desktop systems (St John and Price 2014).

3.1 Electrochemical aptasensors

Electrochemical biosensors transform biological interactions between samples and analytes into readable electrical signals using electrodes through detection probes (Bhalla et al. 2016). Various electrochemical biosensors were investigated to detect biomarkers like blood glucose, uric acid, ketones, lactic acid, and deoxyribose nucleic acid (DNA) (Wang et al. 2008). Electrochemical aptamers (E.C.) exploit the ability of aptamers to specifically bind to a target and their superior stability compared to other bio-recognition elements (enzymes, antibodies, etc.) and combine these desirable items. Aptamer properties with high sensitivity, portability, miniaturisation ability, and quantitative detection

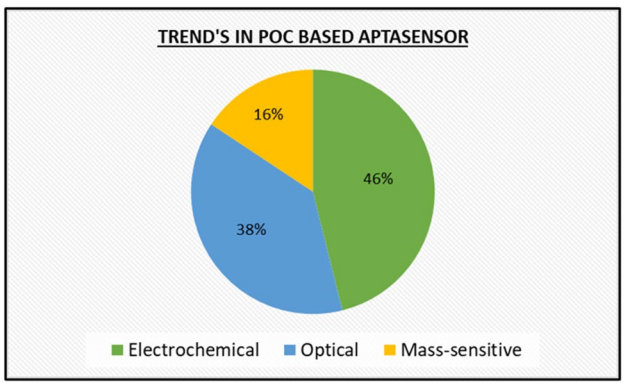

Fig. 4 Trends in POC-based aptasensor

are considered for E.C. systems (Wang et al. 2021). Electrochemistry has maintained a strong presence in chemical and biological sensors. This is because electrochemical readout mechanisms can selectively quantify the interaction between a recognition element and a target analyte (Liu et al. 2014a, b). The transducer, which transforms the recognition event caused by the contact of the analyte with the recognition element into a quantifiable indication, is one of the components of the biosensor. Amperometry, voltammetry, potentiometry and electrochemical impedance spectroscopy are the most effective electroanalytical methods (EIS). The reaction that involves the transfer of electrons is connected to the electrochemical transducer. As a result, only redox labels that can be affixed to the target, recognition elements, or soluble redox mediators that spread onto the electrode surface to be reduced or oxidised by heterogeneous electron transfer can be used to quantify electrochemical reactions. (Kawde et al. 2005).

3.1.1 Amperometry

Amperometric biosensors function at a specific applied potential between the working and reference electrodes. Then, a current signal is generated due to the oxidation or reduction process, which is as extensive as the analyte concentration (Thévenot et al. 2001). These biosensors have response times, dynamic ranges, and sensitivities comparable to potentiometric biosensors. Based on DNA nanotetrahedron (NTH) coupled with Au nanoparticles (NPs) and enzymatic signal amplification, a well-designed electrochemical aptasensor for profiling cancerous exosomal proteins was created. This assay's recognition and capture unit were aptamer-modified DNA NTHs, and signal amplification was achieved using Au NPs–DNA conjugates coupled with horseradish peroxidase. This aptasensor detects HepG2 liver cancer exosomes at a detection limit of 1.66 104 particles/mL.(Jiang et al. 2020). SPEs are the most commonly used electrochemical sensors in developing POC devices. SPEs can be manufactured commercially or by hand using a variety of materials. SPEs are typically integrated systems. On an insulating substrate, typically plastics or ceramics, combine working (usually carbon or gold), counter (usually carbon or gold), and reference electrodes (silver or Ag/AgCl). SPEs are low-cost electrodes that can be easily integrated with simple electronic devices in compact configurations to create user-friendly handheld systems that provide sensitive diagnostic tests with faster response times, promoting early disease diagnosis. Carbon SPEs (SPCE) and gold SPEs (SPAuE) are widely used to fabricate electrochemical aptasensors. The transduction element of a novel amperometric aptasensor for the specific detection of cardiac troponin I (cTnI) was screen-printed carbon electrodes coated with a carboxyethylsilanetriol-modified graphene oxide derivative. The aptasensor was used to detect the cardiac biomarker in the 1.0–1.0 g/mL range, with a detection limit of 0.6 pg/mL. (Villalonga et al. 2022). Using zirconium-carbon loaded with Au (Au/Zr–C) as electrode-modified material and snowflake-like PtCuNi catalyst as label material, a sensitive sandwich-type cTnI electrochemical aptasensor was developed. This amperometric cTnI aptasensor performed admirably, with a wide linear range of 100–0.01 pg mL1 and a detection limit of 1.24 103 pg mL1 (S/N = 3), good selectivity, satisfying reproducibility, exceptional stability, and good recovery(Chen et al. 2022). (Yunus et al. 2022) used amperometric aptasensor based on diazonium grafted screen-printed carbon electrode for detecting cfp10 and mpt64 biomarkers for early tuberculosis diagnosis with a detection limit of 1.68 ng mL^{-1} and 1.82 ng mL^{-1} for CFP10 and MPT64 antigens, respectively. Petroni et al. developed a simple method for the amperometric detection of nitrite and ascorbate using a ME device with screen-printed electrodes (Petroni et al. 2017) [100], whereas a systematic study of the prolonged amperometric detection of oxygen in ILs was achieved by using mechanical polishing to activate platinum screen-printed electrodes (Pt-SPEs) (Lee et al. 2016).

3.1.2 Voltammetry

Voltammetry is a fascinating and adaptable technique that can be applied to biosensors. It combines electric current and potential difference, allowing for reasonable system response and significant applications as multicomponent detectors (Thévenot et al. 2001). Using micropatterned electrodes to track the production of the cytokine's tumour necrosis factor and interferon directly from a small number of immune cells, Liu et al. provide another illustration of real-time detection (Fig. 4 i). This study designed two electrodes that encircle a cell capture area. A tumour necrosis factor-binding aptamer was added to one of the electrodes, while an interferon aptamer was added to the other. Liu et al. showed the real-time detection of these two cytokines as they were released from immune cells following mitogenic activation using live cells in the capture area. Liu et al. defined the cytokine release rates and quantified the release of the cytokines, and secreted IFN-g and TNF-a molecules were monitored by performing square wave voltammetry (SWV) (Liu et al. 2012a) (Fig. 5i). To detect Lys, a unique dual-signalling electrochemical aptasensor was developed using "signal on/off" and "labelling/label-free" techniques (Fig. 5iv). Researchers used square wave voltammetry to quantify dual signal changes. The biosensor showed remarkable sensitivity with a LOD of 0.8 pm due to the superposition of the dual signal changes (IRu + IFc) (Cao et al. 2017). Some researchers described the creation of an electrochemical DNA aptamer-based biosensor for interferon (IFN) detection. A DNA hairpin containing

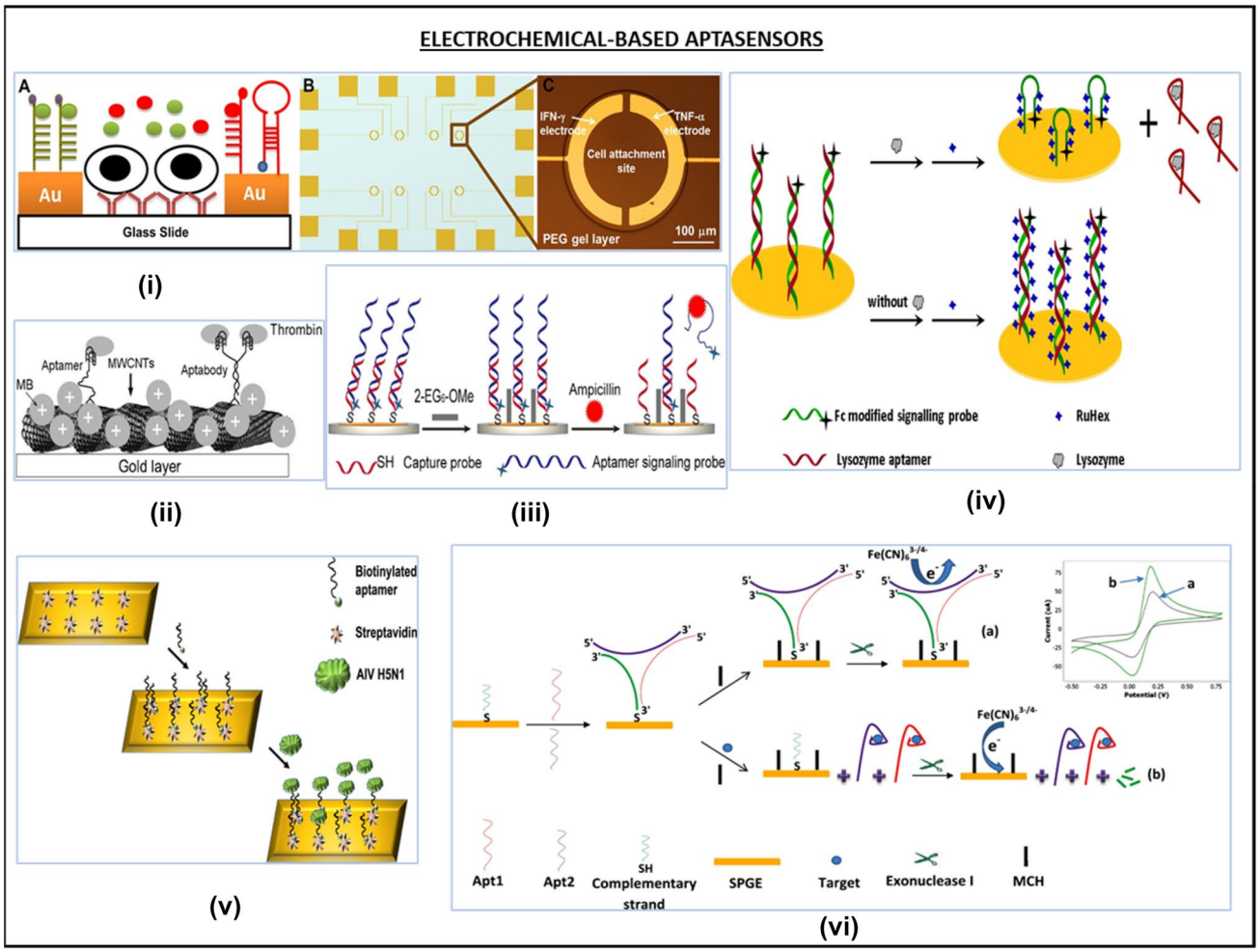

Fig. 5 Electrochemical-based aptasensor (i) **A** Schematic illustration depicting a selective modification of gold electrodes with different cytokine-binding aptamers. A pair of half-ring-shaped Au electrodes fabricated on glass slides are embedded inside one PEG hydrogel and incubated with antibodies for immune cell capture. Upon injection of cells, T cells and human monocytes are bound on Ab-modified glass regions. Two cytokine-binding aptamers are respectively modified on individually addressable electrodes for detecting cytokine release in real-time **B** Electrode layout, where the overall device size is half of a glass slide (25 mm 37.5 mm) **C** 300 mm diameter of PEG wells are used to capture approximately 400 cells inside one well (Liu et al. 2012a), (ii) The immobilisation of aptamer and aptabody at a layer formed by electro polymerization of a mixture of multi-walled carbon nanotubes (MWCNTs) with methylene blue (MB) (Hianik and Wang 2009), (iii) SD-EASs for the detection of Ampi A (Yang et al. 2017), iv) The fabrication of dual-signalling electrochemical aptasensor (Cao et al. 2017), (v) Immobilisation of Streptavidin by physical absorption onto the gold surface (Citartan and Tang 2019), (vi) Myoglobin detection with an electrochemical aptasensor with Y-shaped DNA architecture. Apt aptamer, MCH 6-mercapto-1-hexanol, SPGE screen-printed gold electrode (Taghdisi et al. 2016)

an IFN-binding aptamer was thiolated, conjugated with a methylene blue (MB) redox tag, and self-assembled on a gold electrode. When IFN- was bound, the aptamer hairpin unfolded, pushing MB redox molecules away from the electrode and decreasing electron-transfer efficiency. Square wave voltammetry (SWV) was used to measure the change in redox current, which was highly sensitive to IFN- concentration. The optimised biosensor had a detection limit of 0.06 nM and a linear response range of 10 nM (Liu et al. 2010). Sanghavi et al. recently developed another voltammetric aptasensor with a linear detection range of 30 pg/mL–10 g/mL for the detection of cortisol in biological media (serum and saliva) on a microfluidics platform for point-of-care (POC) applications (Sanghavi et al. 2016). The operating principle entails the displacement of triamcinolone (a skin treatment drug) that was previously bound to cortisol aptamers immobilised on gold nanoparticles. The displaced triamcinolone was electrochemically reduced at a graphene-coated glassy carbon electrode, producing a current proportional to the cortisol concentration. This sensing method requires sample volumes of less than one microliter and is resistant to interferences from other glucocorticoids in the sample, making it promising for real-time sensing applications. (Bagheri et al. 2015) used a modified fluorine-doped

tin oxide (FTO) as the substrate of a novel aptasensor for the electrochemical determination of digoxin. For this purpose, a selective thiolated digoxin aptamer was immobilised onto the gold nanoparticles-deposited FTO (GNPs/FTO) surface. Differential pulse voltammetry can detect digoxin in a linear concentration range of 0.02–0.2 g/L. The proposed aptasensor had a detection limit of 0.01 g/L. In addition, the aptasensor was successfully used to detect digoxin in urine and blood plasma samples. Furthermore, the high sensitivity and specificity, low detection limit, and rapid response allow the determination of trace amounts of digoxin for routine clinical analysis. A novel electrochemical aptasensor based on gold nanoparticles decorated with boron nitride nanosheets deposited on a fluorine-doped tin oxide (FTO) electrode for the sensitive and selective detection of myoglobin (Mb) is reported by (Adeel et al. 2019). DPV and EIS were performed with a detection limit of 34.6 ng/mL and a dynamic response range of 0.1–100 g/mL. The multilayered sensor has a high signal response for Mb. It appears to be a promising candidate for point-of-care diagnosis in real-world samples. This strategy could pave the way for using other 2D materials with large bandgaps to develop biosensors. A generic approach to multianalyte sensing platforms for cardiac biomarkers was reported by (Grabowska et al. 2018), with the development of aptamer-based voltametric sensors for brain natriuretic peptide (BNP-32) and cardiac troponin I. (cTnI). In the case of BNP-32, the developed sensor has a linear response from 1 pg mL1 to 1 g mL1 in serum; for cTnI, linearity is observed from 1 pg mL1 to 10 ng mL1 as required for early-stage heart failure diagnosis.Scientists developed electrochemical aptasensor assisted by Au nanoparticle-modified sensing platform for high-sensitivity determination of circulating tumour cells. They used alternating current voltammetry (ACV) for determining performance of electrochemical aptasensor. The LOD of the aptasensor was 23 cells mL^{-1} with a linear range from 1×102 to 1×106 cells $mL-1$(Wang et al. 2020). They describe a simple electrochemical immunoassay for detecting HIV antibodies that locates capture and detection reagents near a microelectrode. Covalently attached antigenic peptides from HIV-1 gp41 or HIV-2 gp36 to a SU-8 substrate that also served as a template for the deposition of three-dimensional microelectrodes. The detection limit for HIV-1 and HIV-2 is 1 ng ml-1 (6.7 pM). Taghdisi et al. reported the construction of a Y-shaped DNA architecture made up of two aptamers and a complementary strand that was put together on screen-printed gold electrodes for the ultrasensitive detection of myoglobin. The Y-shaped ensemble is resistant to exonuclease I treatment, as depicted in Fig. 5vi, which prevents the redox probe from diffusing to the electrode surface. When myoglobin is present, the aptamer–target complexes disassemble the Y-shaped structure at the sensor interface and encourage the exonuclease I-mediated destruction of the DNA strand still present at the electrode surface. Due to the unrestricted passage of the redox probe to the transducer, a robust electrochemical signal is consequently recorded, enabling the detection of myoglobin concentrations as low as 27 pM measured by dpv and cyclic voltammetry (Taghdisi et al. 2016).

During the last few years, novel electrode configurations have been designed and manufactured to improve the properties of previous conventional electrodes. Paper-based sensors and biosensors are microfluidic analytical devices representing a new generation of POC diagnostics based on developing disposable electrodes as part of POC devices. These devices combine the multiplex capabilities of relatively mature microfluidics with the flexibility and ease of use of lateral flow test strip technology. Paper is a biocompatible cellulose fibre network with a large porous structure and surface area that allows for many attachment points for nanoassemblies, amplifying the detection signal. Paper is also easily formable and foldable, making it an ideal candidate for the fabrication of aptamer-based electrochemical POC devices. However, in the last five years, few authors have developed electrochemical aptasensors using paper as a substrate (Villalonga et al. 2022). Paper-based electrochemical aptasensors have received much attention due to their excellent characteristics, such as low power consumption, portability, selectivity, and sensitivity. Electrochemical aptasensors have a higher potential for POC diagnosis than optical aptasensors because of their ability to detect targets quantitatively (Su et al. 2015). Much effort has been put into developing a paper-based DPV electrochemical aptasensor for detecting human acute promyelocytic leukaemia cells (Ming et al. 2020).

The basic idea is as follows: To capture HL-60, the three-dimensional macro-porous Au-paper electrode is modified with aptamers. The detection range of this device is 5.0 102–7.5 107 cells mL1, with a detection limit of 350 cells mL1. Another example of aptamer-based electrochemical sensors is the integration of aptamer detection strategies in paper-based origami microfluidics (μPAD), which is widely used in countless examples of chemicals and biosensors (Narayanamurthy et al. 2017). Scientists created a novel electrochemical femtomolar aptasensing APT-ERGO/GCE interface by covalently immobilising 38-mer amine-functionalised (NH2-APT) 17-estradiol (E2) DNA aptamers on a graphene amplifying platform with a limit of detection (LOD) of 0.5×10–15 mol L-1. Electrochemical aptasensors based on GCE, AuE, and FTO electrodes have been widely used for disease detection. However, these types of working electrodes do not have a disposable use, and their configuration entails the integration of additional external electrodes, such as a counter and reference electrode, typically platinum and Ag/AgCl, and their placement in an electrochemical cell. As a result, using GCE, AuE, and FTO necessitates

using non-disposable devices, large sample volumes, and trained personnel. Despite the drawbacks of these electrodes, many authors have reported their use for electrochemical aptasensors, demonstrating their practical applicability and expanding the possibilities for miniaturisation, multiplexing, design, and fabrication of point-of-care devices. Scientists describe a simple electrochemical ELISA to detect HIV in clinical samples with a detection limit of 1 ng ml-1 (6.7 pM) for both HIV-1 and HIV-2 (Bhimji et al. 2013). They used CV and DPV for electrochemical analysis.

Despite the impressive sensitivity of the electrochemical sensor in the absence of any amplification strategy, the sensor was not tested in real samples, where the matrix's complexity would most likely result in unspecific adsorption and signal suppression (false positive)(Chaibun et al. 2021). (Negahdary et al. 2017) demonstrated a study of early detection of myocardial infarction. DPVs were recorded for all the samples. ELISA and the aptasensor determined the quantitative results for the TnI levels in all the samples. The results indicated that in the 89 samples, there were 4 false-positive results with no false-negative ones. Therefore, the aptasensor had a diagnostic sensitivity of 100% and a diagnostic specificity of 85%. Electrochemical devices have recently gained a lot of interest in the transduction of aptamer interactions. Electrochemical transduction offers significant benefits compared to optical, piezoelectric, or thermal sensing. High sensitivity and selectivity, compatibility with novel microfabrication technologies, intrinsic compactness, cheap cost, disposability, minimal simple-to-operate, resilient power requirements, and sample turbidity independence are all advantages of electrochemical detection (Wang 2005). A few electrochemical-based aptamer targets are listed in Table 1.

3.1.3 Potentiometry

A potentiometric biosensor operates on the potential difference between working and reference electrodes. Unlike the amperometric biosensor, the measured species are not consumed. Comparing its activity to the reference electrode, its response is proportional to the analyte concentration. When a highly stable and accurate reference electrode is used, potentiometric biosensors have a significant advantage in terms of sensitivity and selectivity (Thévenot et al. 2001). Jia et al. [82] developed a phage-modified light-addressable potentiometric sensor for label-free cancer cell detection. Phage probes were covalently immobilised onto a silane-modified Si3N4 surface via glutaraldehyde to form the sensor surface. This sensor could detect human phosphatase of regenerating liver 3 in concentrations ranging from 0.04 to 400 nM, as well as mammary adenocarcinoma cells ranging from 0 to 105 mL. (Liu et al. 2012b). Scientists recently demonstrated the feasibility of using a nanostructured hybrid material (based on carbon nanotubes, CNTs) that incorporates thrombin-binding aptamers (TBAs) to potentiometrically detect large analytes such as proteins (Düzgün et al. 2010). (Düzgün et al. 2013) performed a comparing study of the performance characteristics and surface characterisation of two different solid-contact selective potentiometric thrombin aptasensors, one based on a network of single-walled carbon nanotubes (SWCNTs) and the other on polyaniline (PANI). The sensitivity of the PANI and SWCNTs aptasensors is calculated to be 2.97 mV/decade and 8.03 mV/decade, respectively. Rius' group created carbon nanotube-based potentiometric aptasensors that used aptamer-functionalised carbon nanotubes as probes to detect and identify a specific strain of bacteria cells. Carbon nanotubes were functionalised with aptamers either through non-covalent adsorption via stacking interactions or through covalent binding between amine-modified aptamers and carboxylated carbon nanotubes (Zelada-Guillén et al. 2013, 2012). The target-recognition-induced conformational changes in the linked aptamers can switch the surface charge on the SWCNT layer and the potential responses of the electrode in the presence of the target bacterial cells. Similarly, the same group proposed a graphene-based aptasensor whose ultrasensitive performance outperforms the results obtained with carbon nanotubes as the transduction layer (Hernández et al. 2014). However, aptamer labelling and immobilisation are typically required for this technique. These processes not only take more time and money, but they also affect the binding affinities of bacteria and aptamers. Qin's team created a label-free potentiometric aptasensing strategy for rapid, sensitive, and selective bacterial detection (Ding et al. 2014).

3.1.4 Impedometry

The electrochemical impedance spectroscopy (EIS) technique measures the change in resistance/impedance caused by the interruption of electron flow caused by biomolecule binding, which is promising for label-free electrochemical assays using an extraneous redox probe (e.g. ferri/ferrocyanide redox couple). (Chakraborty et al. 2021) reported an electrochemical aptasensor for detecting CEA using polyethylene terephthalate (PET) as electrode support. The aptasensors in this work were integrated with a smartphone interfaced domestically developed potentiostat, allowing for portable and on-site measurement. This sensor used electrochemical impedance spectroscopy in small sample volumes (around 50 L) and was validated against a commercially available ELISA kit for human serum analysis, achieving a satisfactory coefficient of variation (6.5%) in real samples. As a result, this work proposed a complete POC system for CEA detection that demonstrated high affordability, sensitivity, mass production capability, and portability for analysing multiple targets. Scientists developed an impedance aptasensor for detecting H5N1, using a microfluidic

Table 1 Electrochemical-based aptasensor

Material	Type of aptamer	Target	Read out method	Limit of detection	Sensitivity	Reference
Gold coated electrode	ssDNA	Oxytetracycline	CV & SWV	1–100 nM	Low	(Kim et al. 2009a, b)
Au/TBA modified electrode	DNA	Thrombin	EIS and CV	2 nM	Low	(Radi et al. 2005)
MGP-modified gold electrode	ssDNA	ATP	SWV	0.1 nM	High	(Tang et al. 2011)
Gold coated electrode	DNA	Cocaine	CV	10 mM	Low	(Baker et al. 2006)
Graphene coated electrode	α-thrombin aptamer	Thrombin	CV	0.03 nM	High	(Wang et al. 2011)
Gold coated electrode	ssDNA	ATP	CV & SWV	11.0 CFU/ml	Low	(Zuo et al. 2007)
Gold coated electrode	ssDNA	ATP	EIS and CV	0.1 nM (ATP)	High	(Du et al. 2008)
Gold coated electrode	Ferrocene coated aptamer	Adenosine	EIS	5 nM	High	(Wang et al. 2010)
Gold nanoparticles coated glassy carbon electrode	ssDNA	Thrombin	DPV	0.55 fM	Ultrasensitive	(Ding et al. 2010)
Gold nanostructured graphite screen-printed electrodes	Thiolated DNA aptamer	VEGF	DPV	30 nM	High	(Ravalli et al. 2015)
GCE, SCE, Platinum wired electrode	Hairpin oligonucleotide (HO) aptamer	Mucin 1 protein (MUC1)	EIS and CV	2.2 nM	Ultrasensitive	(Hu et al. 2014)
Au electrode	Thiolated aptamer	Cardiac troponin I (cTnI)	SWV	1 – 10,000 pM	Higher	(Jo et al. 2015)
Screen-printed gold electrodes (SPGEs)	Y-shape structure of dual-aptamer (DApt)	Myoglobin	DPV	100 pM–40 nM	Ultrasensitive	(Taghdisi et al. 2016)
Au electrode	Lysine aptamer	Lysine	Swv,	1.0×10^{-11}–1.0×10^{-7}	High	(Cao et al. 2017)
CG-TH-Au NPs electrode	ssDNA	tau 381	EIS, CV and DPV	0.70 pM	High	(Tao et al. 2019)
Au electrode	Thiolated & MB modified DNA hairpin aptamer	IFN-γ	SWV	0.06	High	(Liu et al. 2010)
AuNPs/Au electrode	MB–aptamer	CTCs K562 cell	EIS and CV	23 cells mL^{-1}	High	(Wang et al. 2020)
Ag/Agcl, glass carbon electrode	Aptamer modified magnetic beads MBs	CTCs MCF-7	DPV	50 cells	High	(Xia et al. 2021)

chip made of polydimethylsiloxane (PDMS) and a gold interdigitated screen-printed microelectrode incorporated (Fig. 5v). Streptavidin was coupled with biotinylated aptamers against H5N1 and physically fixed on the gold surface. With a detection time of under 30 min and an impedance-based test, a limit of detection of 0.0128 hemagglutinin units (HAU) was attained. Without label amplification or sample preparation, this study's authors achieved a detection limit for H5N1 previously obtained in the impedance-based immunosensor with shorter detection times (Citartan and Tang 2019). Daprà et al. described an all-polymer electrochemical device with electrodes formed by a conductive polymer bilayer (Daprà et al. 2013). By electrochemical impedance spectroscopy (EIS), the electrode was functionalised with aptamer probes to detect ampicillin and kanamycin A. Shin et al. used an aptamer-based impedimetric immunosensor to identify a cardiac injury biomarker that was essentially the creatine kinase-MB in a heart-on-a-chip (Shin et al. 2016). Direct electron transfer was used to measure the impedometric detection of the redox active cardiac biomarker myoglobin (Mb) using aptamer-functionalised black phosphorus nanostructured electrodes. Few layer black

phosphorus nanosheets were synthesised and functionalised with poly-L-lysine (PLL) to facilitate binding with anti-Mb DNA aptamers generated on nanostructured electrodes. This aptasensor platform has a record-low detection limit (0.524 pg mL^{-1}) and sensitivity (36 A pg-1 mL cm^{-2}) for Mb in serum samples, with a dynamic response range of 1–16 g mL^{-1}. (Kumar et al. 2016). (Hianik and Wang 2009) Combined two thrombin-binding aptamers by hybridising their complementary supporting components (Fig. 5ii). A so-called aptabody was created as a result, which has two thrombin-binding sites. They used impedance spectroscopy for electrochemical analysis. Schlecht et al. (2006) reported an impedimetric nanogap aptasensor with a 75 nm electrode separation. High sensitivity of thrombin detection was obtained using microwave frequency impedance for both RNA aptamers and antibody-based biosensors. Compared to conventional aptamers, the aptasensor created by immobilising these aptabodies onto the surface of multi-walled carbon nanotubes demonstrated approximately three times more sensitivity.

We can conclude from these demonstrations that aptasensors offer promising prospects for use in miniaturised and portable electrochemical systems for various applications. The use of SELEX also allows for the selection of multiple aptamers with high affinity for the analyte, and this synergy should be investigated further in future work. However, due to the recent introduction of aptasensors, compiling, sorting, and comparing data for affinity and kinetic parameters remain necessary. Nonetheless, aptamers are quite appealing as bio-recognition elements for POC electrochemical biosensing due to their simplicity, low cost of production, the possibility of numerous targets, chemical stability, and specificity, even when used in turbid samples such as biological fluids.

3.2 Optical aptasensor

Optical biosensors are interpreted with light emigration, luminescence, immersion, and the visual dimension of the analyte (Gowri et al. 2021). Optical biosensors develop to detect biomarkers such as proteins and metal ions associated with the presence of cancer cells (Zahra et al. 2021). These biosensors are based on light absorption and changes in luminescence due to interaction with the target. These aptasensors incorporate easy labelling, tiny reagents, and quick and inexpensive procedures. The optical biosensor shows another system for safe, easy-to-use, cost-effective technologies, including the elimination of nucleic acid modification. As far as we know, only a sprinkle of light biosensors is in the market to defeat the pandemic. Optical biosensing can combine detection and imaging, which may provide a deeper understanding of a pathogen and detect it in biological samples (Yao 2014). Optical bioimaging combines advanced optical methods with pathogen-specific tracers, allowing targeting and detection of abnormalities during a disease pathway at the molecular stage. A number of the benefits of optical bioimaging over conventional imaging methods like MRI, CT, and PET include femtomolar sensitivity, high spatial resolution, non-invasive and non-ionising imaging, low equipment/personnel cost, simple mobilisation, quantitative results and short time interval (Arranz and Ripoll 2015; Dzik-Jurasz 2003). Direct imaging without sample preparation has many challenges: dense tissues in biological samples introduce a loss of sunshine directionality that leads to a better degree of scattering (Maddali et al. 2021).

3.2.1 Fluorescence-based biosensor

Fluorescence-based sensing and imaging offer unique advantages like good sensitivity, high temporal resolution, biocompatible imaging agents, and non-invasive characteristics relevant to research and clinical settings (Shin et al. 2010). Fluorescence is an optical approach widely used to build APA sensors due to its low cost, high sensitivity, ease of use, and high efficiency (Musumeci et al. 2017). The high sensitivity and quantification capacity of fluorescence-based sensors successfully detect cancer biomarkers (Borghei et al. 2017). These aptasensors have fluorophore and quencher markings at the end of active centre where the bio-recognition process occurs, influencing the fluorescence reaction. However, this labelling method can cause problems in aptamer performance and could cause a weak fluorescence response. In addition, the extinguisher should not hinder the fluorescence emission, and a high background could be obtained (Borghei et al. 2017). Despite the problems mentioned above, fluorescence aptasensors are still used and can be divided into two essential types: labelled fluorescence aptasensors (Li et al. 2017) and unlabelled fluorescence aptasensors (Bose et al. 2016; Sun et al. 2015). Streptavidin-triggered amplified fluorescence polarisation (SAFP) has recently been suggested by (Musumeci et al. 2017) for the detection of angiogenin. Alexa Fluor 488 has been used to label angiogenin fluorescently, and the angiogenin aptamer has had biotin attached to its 5′ terminus. When streptavidin is present, the interaction of the biotinylated aptamer and the fluorescently labelled protein results in a significantly enhanced fluorescent polarisation signal, allowing the detection of angiogenin with a limit of 6.3 nM (Fig. 6i). Scientists recently created a fluorescent aptasensor based on competitive binding to detect HNE (Musumeci et al. 2017). The HNE aptamer, a molecular beacon conjugated with fluorescein and dabcyl at its 5′ and 3′ ends, and a brief DNA sequence complementary to a portion of the aptamer sequence and the loop of the molecular beacon are the three oligonucleotides employed in this assay (Fig. 6ii). The short

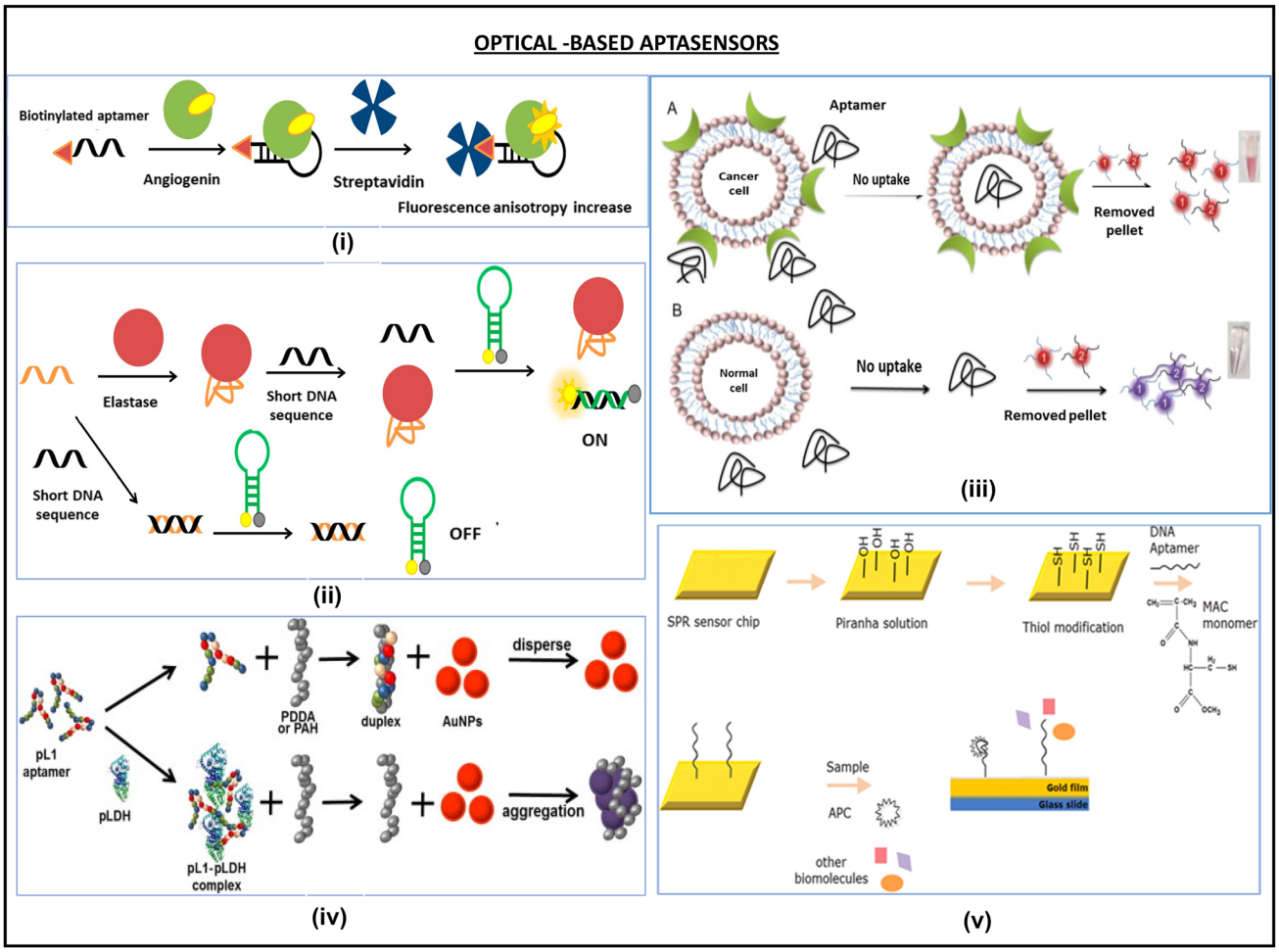

Fig. 6 Optical-based aptasensor: (i) Angiogenin detection strategy based on streptavidin-triggered amplified fluorescence polarisation (Musumeci et al. 2017), (ii) Elastase detection strategy based on competitive binding involving the elastase aptamer, a molecular beacon and a short DNA sequence (Musumeci et al. 2017), (iii) Selective colorimetric method for detection of cancer cells by employing DNA probe 1,2–functionalised gold nanoparticles and AS1411 aptamer (Borghei et al. 2017), (iv) The illustration of the aptasensor for pLDH detection (Jeon et al. 2013), (v) Selective label-free surface plasmon resonance (SPR) preparation for the specific detection of human-activated protein C-APC (Koyun et al. 2019)

DNA is initially incubated with the aptamer before adding the molecular beacon. As a result, because the short DNA is already attached to the aptameric sequence, the molecular beacon is unable to engage with it in the absence of the target. Because there is more space between the fluorescent and the quencher when HNE is present, the aptamer binds the protein rather than the short DNA, allowing it to hybridise with the molecular beacon and produce a strong fluorescent signal. This method's predicted detection limit is 47 pM (Musumeci et al. 2017). A paper-based analytical apparatus was proposed by scientists for the sensitive, focused, and precise detection of total immunoglobulin E (IgE) in human serum (Fig. 5v). The assay's foundation was the resonance energy transfer between UCNPs and the organic dye tetramethylrhodamine (TAMRA), and the identifying probe was an IgE aptamer with a stem-loop structure. IgE's presence alters IgE aptamer structure, increases the gap between the donor and acceptor, and prevents the energy transfer process. As a result, the luminescence of UCNPs recovered in a way that was independent of IgE concentration. With a detection limit of 0.13 IU/mL, a linear calibration was achieved in the range of 0.5e50 IU/mL (He et al. 2021).

Fluorescent biosensors have various parameters like intensity, energy transfer, lifetime, and quantum yield, which will be exploited for virus detection in Fig. 4b (Sharma et al. 2018). A phenomenon in which the light emitted by a substance is not due to heat is called luminescence and can be divided into electrochemiluminescence (ECL) and chemiluminescence (CL) according to the energy sources (triggers). Both are often used to develop aptamer-based sensors to detect cancer biomarkers (Kou et al. 2020). Several CL aptasensors have already been introduced for early cancer

detection (Eivazzadeh-Keihan et al. 2017). The excellent results are considered the most sensitive optical approach (Park et al. 2013). Jie and Jie (2016) described a quantum dot (Q.D.) -based ECL signal probe with great potential for early cancer detection in clinical samples. Wang et al. (2016) designed a radiometric dual-signalling electro-chemiluminescent aptasensor with good reproducibility, high selectivity, and stability toward its target among non-target cancer cells. (Khang et al. 2017) developed a simple, inexpensive, easy-to-use, and portable medical platform in hospitals and homes for early breast cancer diagnosis.

3.2.2 Colorimetric aptasensors

Colourimetric biosensors use a colour shift that can be seen with the naked eye or a simple optical detector to detect the presence of specific substances (Song et al. 2011). Colourimetric biosensors are great candidates for POC diagnostics due to their ease of use and the fact that they do not require expensive analytical equipment (Stewart et al. 2008). Colorimetric biosensors are regularly acclimated to find a chosen analyte by shading changes that might be seen with the naked eye. They'll be utilised as explicit moveable optical identifiers for quantitative estimating. Thus, point-of-care recognitions of hazardous infections are particularly engaging for forestalling future pandemic episodes because antiviral treatment ought to be conveyed rapidly. Scientists created a straightforward colorimetric technique based on aptamer–cell interaction to identify cancer cells (Fig. 6 iii). Through an affinity relationship between AS 1411 and the overexpressed nucleolin receptors in cancer cells, nucleolin aptamers (AS 1411) were able to capture cancer cells. The elimination of aptamers from the solution was sparked by the particular binding of AS 1411 to the target cells. The colour of the solution is red because no aptamer was left in it to hybridise with complementary ssDNA–AuNP probes. ssDNA–AuNP probes and aptamers coexisted in solution in the absence of target cells or in the presence of normal cells, and the aptamers' assembly of DNA–AuNPs resulted in a purple solution. This hybridization-based technique showed selective colorimetric responses to the presence or absence of target cells, which could be seen with the naked eye, according to UV–vis spectrometry. With a detection limit of 10 cells, the linear response for MCF-7 cells in the concentration range of 10–105 cells was obtained. The suggested approach demonstrated potential uses in early cancer diagnosis and the extension of the system to detect other cells (Borghei et al. 2016). The scientists have presented Plasmodium lactate dehydrogenase (pLDH), a biomarker for malaria, and pL1 aptamer against Plasmodium vivax lactate dehydrogenase (PvLDH) and Plasmodium falciparum lactate dehydrogenase (PfLDH) are the basis of the strategy (Fig. 6 iv). Additionally, the cationic polymers poly (diallyl dimethyl ammonium chloride, or PDDA, and poly (allylamine hydrochloride, or PAH), agglomerate gold nanoparticles (AuNPs), which should allow for the observation of the red to blue colour change that is dependent on pLDH concentration. They came to the conclusion that the aptasensor that was created to detect pLDH can provide an accurate and sensitive diagnosis of malaria (Jeon et al. 2013).

Assah et al. 2018 demonstrated that nanoparticles might be employed as colorimetric probes to construct multifunctional biosensors for viral detection. This is primarily based on the unique optical properties of the specific nanoparticles, which can generate noticeable colour shifts that can be detected with the naked eye or quantified using a simple optical detector. The primary basis for plasmonic nanoparticles changing colours is based on the plasmonic effect, as seen in Fig. 6v. When nanocomposites (AuNPs) are surrounded by dsDNA or viruses, the nanoparticles are disseminated in the solutions, even when added to salt.

3.2.3 Surface plasmon resonance-based biosensor

SPR sensors can detect mass changes at the surface by measuring the accompanying change in the refractive index. This technology is based on the constants of aptamers, and their targets are frequently employed in the SELEX procedure and perform well, swiftly, and precisely. One gold nanoparticle functionalised with biotin is used to scatter light as part of a method for biomolecular recognition. The addition of streptavidin and subsequent specific binding interactions change the nanoparticle's dielectric environment, which causes the particle plasmon resonance to shift in frequency. Using single nanoparticles with a uniform scattering spectrum allows the detection of spectral shifts as tiny as 2 meV (Raschke et al. 2003). For the precise detection of human-activated protein C, scientists presented an empathetic and selective label-free surface plasmon resonance (SPR) aptasensor preparation (APC) (Fig. 6v). Bovine serum albumin, haemoglobin, and myoglobin were used in selectivity tests of SPR aptasensor. The limit of detection (LOD) and limit of quantification (LOQ) values of the DNA-Apt SPR aptasensor were found to be 1.5 ng/mL and 5.2 ng/mL, respectively (Koyun et al. 2019). Researchers created a technique to identify the SARS-CoV-2 S1 spike protein. To immobilise biotinylated aptamers, the biotin-streptavidin platform was paired with the portable Localised Surface Plasmon Resonance apparatus, which is outfitted with a two-channel system. The aptasensor selectively and specifically recognised S1 spike protein in real-time rather than S2 spike protein, RBD spike protein, or bovine serum albumin using aptamer-protein bio affinity interactions. The aptasensor dynamic range and detection limit were 1 nM–100 nM and 0.26 nM, respectively (Lewis et al. 2021). The most common commercially available type of SPR imaging is

intensity-based SPR imaging, which firms use like Biosensing Instrument and Carter to identify antibodies, single cells, viruses, proteins, and drug molecules. To detect norovirus, Ashiba et al. used a dual antibody trapping approach that involved attaching antibody-functionalised Q.D.s to a biosensor that had been treated with virus antibodies (Ashiba et al. 2017).

A few optical-based aptasensor targets are mentioned in Table 2.

3.3 Mass-sensitive aptasensor

A mass-sensitive biosensor is a device that measures a property that scales proportionally to mass associated with or bound to its sensitive surface assembled with capture probes. Mass-sensitive aptasensors are differentiated into two parts. One is quartz crystal microbalance and another is microcantilever-based assays. Because of the heaviness or thickness of the thin film, they are commonly referred to as "mass-sensitive" approaches (Song et al. 2008).

3.3.1 QCM-based biosensor

The quartz crystal microbalance-based biosensor is a second exciting technology for making aptasensor. The quartz is placed between two electrodes that immobilise biomolecules. The system's frequency may be checked in real time. While it is running, time and bio interaction can be monitored. As a result of binding, there is an increase in mass, and the resonance frequency is reduced as a result of this (Lim et al. 2020). In QCM-based biosensors, DNA probes are the most often used nucleic acid detection receptors. Target recognition in QCM-based biosensors is based on sequence complementarity between two DNA strands. Single-stranded DNA (ssDNA) probes complementary to the infectious agent's target gene can be immobilised through Au–S or avidin/streptavidin–biotin linkages onto the crystal surface (Afzal et al. 2017). When an infectious agent sample is introduced to the mix, The pathogen's target sequences are hybridised into the biosensor. Complementary base pairing occurs in ssDNA probes (Fig. 7iv). Due to the binding event, a mass loading occurs at the crystal surface, resulting in a frequency response. As a result, the recognition method is very specialised. Only complementary sequences will attach to the DNA probes. Nucleic acid biosensors, for example, can detect single-base changes in DNA.

The change in the crystal's oscillation frequency owing to receptor–target binding is the basis for microgravimetric procedures using piezoelectric quartz crystals. The signal that is noticed is a change in oscillation frequency. The target can be detected without the need for labels using this method. However, using "weight labels"—such as aptamer-functionalised Au nanoparticles—to amplify the binding reaction on the QCM surface appears beneficial (Pavlov et al. 2004). Streptavidin was immobilised when gold layers were applied to quartz crystals. The receptor layer was subsequently applied, which consisted of biotinylated aptamers. IgE was detected using DNA aptamers with a detection limit of 100 g/L and a linear detection range of 0–10 mg/L. RNA aptamers were used as receptors to detect HIV-1 Tat protein. 0.25 ppm detection limits and 0.65 ppm were attained, with linear detection ranges of 0–1.25 ppm and 0–2.5 ppm, respectively (Minunni et al. 2004; Tombelli et al. 2005). In vitro, the QCM method selected RNA aptamers against the arginine-rich motif Rev peptide, implicated in HIV-1 infection. In a label-free mode, the authors were able to track the selection process from a random RNA pool as mass change and evaluate the kinetic characteristics of the interaction (Fukusho et al. 2002). Scientists created a QCM-based aptasensor to find S. Typhimurium (Fig. 7v). In less than an hour, this aptasensor found S. Typhimurium at 103 CFU/mL. This research showed that QCM-based selection of aptamers might be more efficient, and QCM-based aptasensor may be more sensitive in detecting S. Typhimurium (R. Wang et al. 2017a, b). Thrombin binding aptamer immobilised QCM-aptasensor was used by (Bayramoglu et al. 2019a) to detect thrombin from solution and diluted serum or fibrinogen-precipitated plasma samples. The Sauerbrey equation carries out the quantitative analysis of QCM chip. A few mass-sensitive-based aptasensors targets are mentioned below in Table 3.

3.3.2 Microcantilever-based biosensor

In biophysics and biochemistry, the nanomechanical and micromechanical cantilever has played an important role. Cantilever array sensors' small size and scalability may be advantageous for diagnostic screening applications, disease monitoring, genomics, or proteomics. Because some of the cantilevers can be used as sensor cantilevers for detection and others as passivated reference cantilevers that do not show affinity to the molecules to be detected, using microcantilever arrays allows simultaneous detection of several analytes and solves the inherent problem of thermal drifts that is often present when using single microcantilever sensors (Lang et al. 2017). (Hwang et al. 2007) reported micromechanical sensing using resonating cantilevers was used to detect hepatitis C virus (HCV) With a sensitivity of 100 pg/mL. This method took advantage of immobilised aptamers on the top surface of the cantilever and their steric crowding when bound to bulkier targets. The latter caused surface stress, which was detected by changing the resonant frequency of the microcantilevers. The microcantilevers' small size made high-throughput multiplex screening possible, which was advantageous for the POCT of multiple viruses. However, because of their susceptibility to environmental

Table 2 Optical-based aptasensor

Material	Type of aptamer	Target	Read out method	Limit of detection	Sensitivity	Reference
Carboxyfluorescein	Thrombin binding aptamer	Hg^{2+}	FRET	5 nM	High	(Liu et al. 2009)
Fluorescein isothiocyanate	Quantum dot-aptamer	Carcinoembryonic antigen	FTIR	5 pg/ml	High	(Zhou et al. 2014)
2-amino-5,6,7-trimethyl-1,8-naphthyridine (ATMND)	DNA aptmer	Pb^{2+}	Fluorescence spectra	4 nM	High	(Xiang et al. 2009)
Streptavidin-coated QDs	DNA aptmer	Adenosine	Luminescence-based detection	50 mM	Very high	(Liu et al. 2007)
Quantum dots & AuNPs	ssDNA aptamers	K^+	FRET	100 mM (K^+)	Medium	(Kim and Jurng 2011)
2-amino-5,6,7-trimethyl-1,8-naphthyridine (ATMND)	DNA aptmer	Cocaine	Fluorescence spectra	1 mM	High	(Xu et al. 2009)
N,N-dimethyl-2,7-diazapyrenium dication (DMDAP)	α-thrombin-binding aptamer	PDGF	Fluorescence spectra	8 pM	High	(Huang et al. 2007)
Carboxyfluorescein, Graphene oxide	DNA aptmer	ATP	Flow cytometry	0.019 mM	High	(Z. Liu et al. 2014a, b)
Fluorophore-doped silica NPs	DNA aptmer	Cancer cells	Fluorescence spectra	250 cells	High	(Smith et al. 2007)
Carboxyfluorescein,Graphene oxide sheets	Carboxyfluorescein OTC aptamer	Oxytetracycline	FRET	10 nM	High	(Zhao et al. 2013)
Carboxyfluorescein	Lys aptamer	Lysozyme	Fluorescence spectra	0.08 µg/ml	Medium	(Chen et al. 2012)
FAM-labelled probes	Thiolated aptamer	PDGF	Colorimetric	6 nM	High	(Chang et al. 2013)
Tetramethylbenzidine (TMB)	DNA aptamer	VEGF165	Colorimetric	0.3 pM	High	(Dong et al. 2020)
Gold nanoparticles	Thiolated aptamer	CCRF-CEM	Colorimetric	2 nM	Low	(Medley et al. 2008)
Gold nanorods (Au NRs)	DNA aptamer	CD63	Colorimetric	160 exosome/mL	High	(Yingzhi Zhang et al. 2019a, b)
Gold nanoparticles	Thiolated aptamer	Adenosine	UV/Vis spectrometer	20 mM	High	(Liu et al. 2006)
Magnetic nanoparticles	DNA aptamer	MUC1	Colorimetric	0.09 µg/mL	High	(Liu et al. 2018)
Streptavidin-coated magnetic beads	DNA aptamer	HNE	Colorimetric	0.4 pM	High	(Cheng and Zhao 2013)
Gold nanoparticles	DNA aptmer	Oxytetracycline	UV/Vis spectrometer	25 nM	High	(Kim et al. 2010)
Gold nanoparticles,	DNA aptmer	Cocaine	UV/Vis spectrometer	2 mM	High	(Zhang et al. 2008)
Gold nanoparticles, QDs	DNA aptmer	Ibuprofen	UV/Vis spectrometer	5 mM	High	(Kim and Jurng 2011)
Gold capped magnetic nanoparticles (GMPs)	DNA aptamer	Thrombin	SPR	0.1 nM	High	(Chen et al. 2015)
Graphene oxide sheets	DNA aptamer	Nampt	SPR	ND	Low	(Park et al. 2012)
Gold chip	RNA aptamer	C-reactive protein	SPR	0.005 ppm	High	(Bini et al. 2008)
Gold chip	DNA aptamer	Human IgE	SPR	141 ng/ml	Low	(Y. H. Kim et al. 2009a, b)
Gold chip	DNA aptamer	Retinol binding protein 4 (RBP4)	SPR	1.58 mg/ml	Low	(Lee et al. 2008)

Table 2 (continued)

Material	Type of aptamer	Target	Read out method	Limit of detection	Sensitivity	Reference
Gold film	RNA aptamer	Thrombin VEGF	SPR	1 pM (thrombin) 500 FM (VEGF)	High	(Li et al. 2007)
AuNPs	Thiolated aptamer	Human IgE	SPR	1 ng/ml	Ultrasensitive	(Wang et al. 2009a, b)
AuNPs	Thiolated hairpin DNA aptamer	Adenosine	SPR	0.21 pM	High	(Yao et al. 2015)
Gold chip	Thiolated aptamer	Vaspin	SPR	3.5 ng/ml	High	(Ahmad Raston and Gu 2015)
AuNPs	DNA aptamer	BVDV type 1 virus	SPR	800 copies/ml	Ultrasensitive	(Park et al. 2014)
Gold film	Hairpin-shaped aptamer	IFN-γ	SPR	10 pM	High	(Chuang et al. 2014)

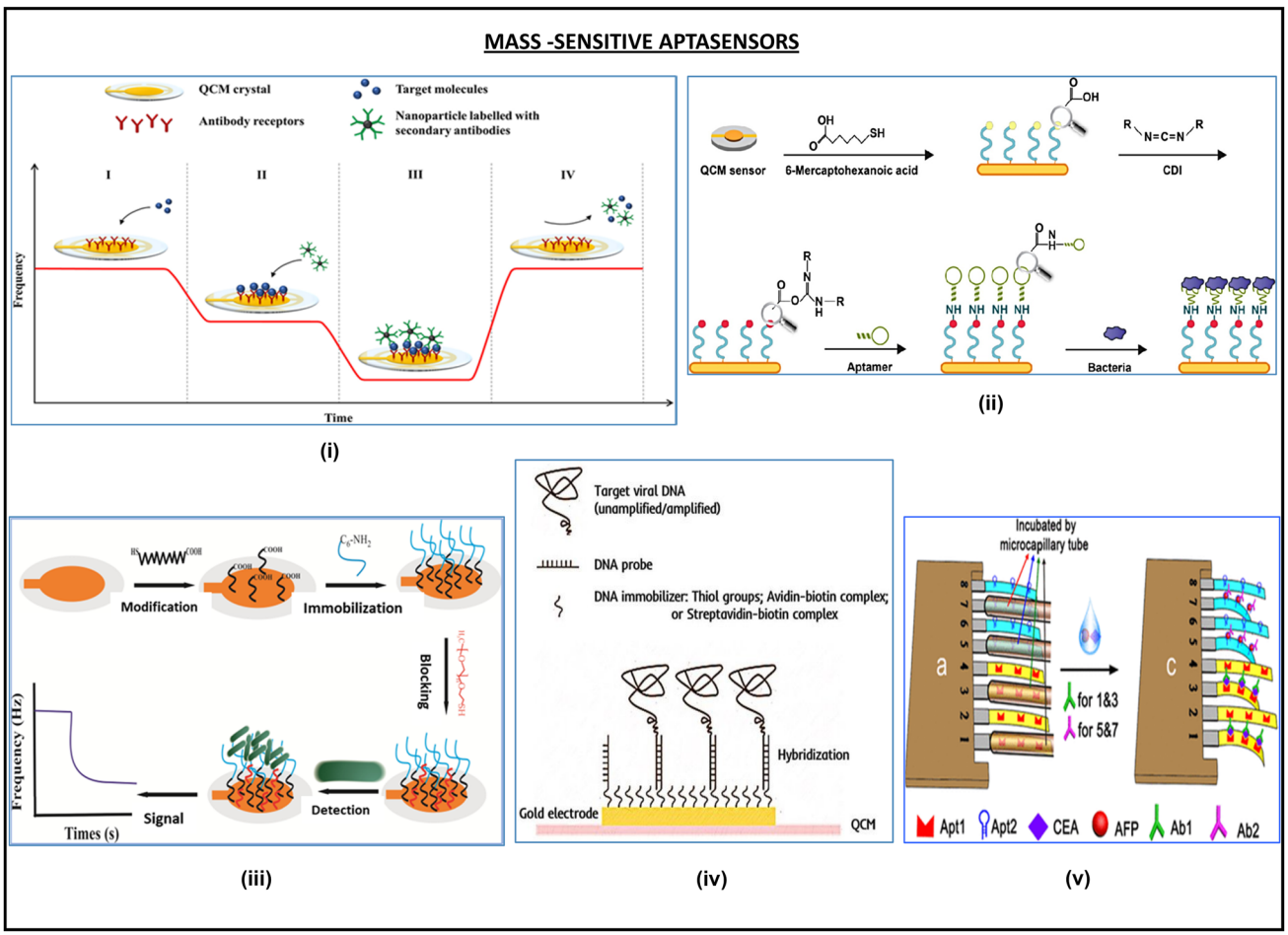

Fig. 7 Mass-sensitive-based aptasensors: (i) QCM-based biosensors are promising tools for the rapid detection of infections (Lim et al. 2020), (ii) Aptamer-based QCM biosensor for salmonella detection (Ozalp et al. 2015) (iii) The schematic process of the QCM-based aptasensor for detection of *S. Typhimurium* (R. Wang et al. 2017a, b). (iv) schematic representation of the DNA-QCM virus sensor (Afzal et al. 2017), (v) Microcantilever Array Biosensor for Simultaneous Detection of Carcinoembryonic Antigens and α-Fetoprotein (Li et al. 2019)

Table 3 Mass-sensitive aptasensors

Material	Type of aptamer	Target	Read out method	Limit of detection	Sensitivity	Reference
Nanoporus gold film	DNA aptamer	H5N1 virus	QCM	1.25 HAU mL^{-1}	High	(Wang et al. 2017a, b)
AT-cut quartz crystals with Au electrodes	S1 (DNA)	E. coli O157:H7	QCM	1.46×10^3 CFU/ml	High	(Yu et al. 2018)
AT-cut quartz crystals with Au electrodes	Surface protein-specific aptamer (DNA)	AIV H5N1	QCM	0.0128 HAU (HA unit)	Highest	(Wang and Li 2013)
AT-cut quartz crystals with Au electrodes	S8-7 (DNA)	Salmonella	QCM	100 $CFUmL^{-1}$	High	(Ozalp et al. 2015)
AT-cut quartz crystals with Au electrodes	Brucella melitensis-binding aptamer (DNA)	Brucella melitensis	QCM	10^3 $CFUmL^{-1}$	Low	(Bayramoglu et al. 2019b)
PDA coated MCT beads and QCM chip	Lysozyme-specific aptamer (DNA)	Lysozyme	QCM	17.9 ± 0.6 ng/mL	High	(Shan et al. 2014)
AT-cut quartz crystals coated with gold	15-Mer thrombin aptamer (DNA)	Thrombin	QCM	7.7 pM	High	(Xi et al. 2021)
AT-cut quartz crystals with Au electrodes	B5 (DNA)	S. typhimurium	QCM	10^3 CFU/mL	High	(L. Wang et al. 2017a, b)
Gold layer	RNA Aptamer	Helicase	Microcantilever	100 pg/mL	High	(Hwang et al. 2007)

conditions, the measurements on the microcantilever are carried out entirely in a temperature and relative humidity-controlled chamber, limiting their use for POCT (Fig. 7v). (Li et al. 2019) developed a microcantilever array aptasensor based on a sandwich structure forli simultaneously measuring two biomarkers carcinoembryonic antigen (CEA) and α-fetoprotein (AFP) via an optical readout technique—real-time monitoring of the cantilever profile. This aptasensor's detection sensitivity for CEA was 1.3 ng/mL and 0.6 ng/mL for AFP, respectively. This study demonstrated the ability to measure two biomarkers simultaneously using a microcantilever array biosensor, which has great potential for further application in detecting multiple targets simultaneously for early clinical diagnosis. (Vinchurkar et al. 2016) Described the label-free aptasensor, a potential point-of-care device that detects as low as 800 Circulating Tumour Cells (CTCs). It consists of a cost-effective, batch-fabricable polymeric microcantilevers based sensor with a simple, stable, and efficient biofunctionalization process.

Few mass-sensitive-based aptasensors targets are mentioned below in Table 3

3.4 POC-based aptasensor's diagnostic application

Biosensors with high sensitivity and specificity are needed to address the significant healthcare problems that are constantly increasing. The ability of aptasensors to accurately detect and discriminate pathogens without knowledge of their membrane components or structural genes is critical. This article discusses numerous initiatives for the use of aptasensors in the control of harmful bacteria and viruses. Here we briefly describe a few examples of the use of aptasensors in detecting infectious and non-infectious microorganisms (Table 4).

3.5 Infectious diseases

Infectious diseases are the most widespread, caused by various infectious agents. Infectious diseases commonly spread through the direct transfer of bacteria, viruses, fungi and parasites from one person to another. This can happen when an individual with the bacterium or virus touches, coughs or sneezes on someone who is not infected.

3.5.1 Detection of bacteria

Bacteria are microscopic single-celled organisms found in various habitats, both within and outside of other animals. While some germs are hazardous, others are beneficial. Pathogenic bacteria are bacteria that cause bacterial illnesses and disorders. Pathogenic bacteria enter the body, reproduce, crowd out good bacteria, or replicate in typically sterile tissues, resulting in bacterial diseases. Harmful bacteria can produce toxic toxins. Bacteria can be extracted using a centrifuge, and most aptamers against bacteria can be picked using whole-cell-based SELEX. Rapid diagnosis

Table 4 Comparative analysis of sensing strategies

POC Aptasensors	Advantages	Disadvantages	Reference
Electrochemical	Method diversification High sensitivity Rapid selection of aptamers	Poor stability of electrode	da Silva (2017) Campuzano (2021) Kim(2009)
Optical	Highly sensitive assays, easy operation, fast response Can be used in a homogenous format (Bind and detect, no target immobilisation and washing)	Use of fluorophore makes the assay is a bit expensive A short lifetime of the fluorophore Need an instrument to read the output	Sassolas(2011) Feng(2014) Lim(2010)
Mass-sensitive	Faster, easy to use, cheaper, {Citation} Visual detection Sensitive Real-time response Highly sensitive Rapid	Signal-to-noise ratio is high Less sensitive Time-consuming Expensive A short lifetime of quartz crystal	Song(2008) Arugula(2014) Gooch(2017)

and treatment of this infectious pathogen are critical from a clinical standpoint. Based on optical, piezoelectric, and electrochemical transduction systems, a range of DNA (Zhou et al. 2011), RNA, and PNA (Prabhakar et al. 2008) biosensors against tuberculosis biomarkers have been created. IS6110, a T.B. biomarker, was detected using a QCM-based piezoelectric biosensor (Kaewphinit et al. 2010)., A dextrin-coated GNP conjugated electrochemical DNA biosensor was created To diagnose M. tuberculosis. The hybridisation of AuNPs, magnetic particles (M.P.s), each functionalised with DNA probes, and a tuberculosis-specific DNA fragment inside the IS6110 gene is used in this biosensor as shown in Fig. 8 (10) (Torres-Chavolla and Alocilja 2011). Another work (Das et al. 2010) revealed using a ZrO2-based electrochemical DNA biosensor for the rapid, early, and sensitive detection of M. tuberculosis. Using thiolated DNA and PNA probes bound on the gold electrode surface, the SPR method was used to detect tuberculosis. In M. tuberculosis-infected clinical samples, PNA probes had higher sensitivity and a lower detection limit than DNA probes (Prabhakar et al. 2008). Apart from DNA, PNA, and RNA-based biosensors, aptamer-based biosensors are becoming more popular as faster, more sensitive, and selective tuberculosis diagnostic tools (Min et al. 2008). A new aptamer-based biosensor chip (Wang et al. 2013) has been created to integrate Aptamer with CNTs for early MTB diagnosis.

Food-born infections are the most prevalent infectious disorders caused by pathogens like E. coli and S. Typhimurium, Vibrio cholera, Listeria monocytogenes, and Vibrio parahaemolyticus, among others. Salmonellosis is a disease caused by Salmonella sp. that is found worldwide. Diarrhoea is a bacterial infection caused by pathogenic bacteria such as E. coli O157:H7, Salmonella typhimurium, and Salmonella paratyphimurium. Using unaltered gold nanoparticles and a colorimetric assay, an aptamer-based biosensor was reported to detect these bacteria (Wu et al. 2012). Another foodborne disease is cholera, which is caused by Vibrio cholera. A DNA biosensor was created to detect Vibrio cholera PCR amplicons (Chua et al., 2011). The application of DNA biosensors to detect the invA gene of Salmonella utilising the SPR detection method has recently been reported (Zhang et al. 2012, p. 201).

3.5.2 Detection of virus

Viruses are obligatory intracellular parasites that measure 20–300 nm in diameter. A DNA or RNA genome and a genome-protective protein coat make up viral particles (virions) (capsid). Despite their simple structure, Viruses can cause a wide range of diseases in animals and plants. Viruses produce over 15 pandemic or epidemic diseases, according to the World Health Organization (WHO), including the current COVID-19 pandemic. Early diagnosis is

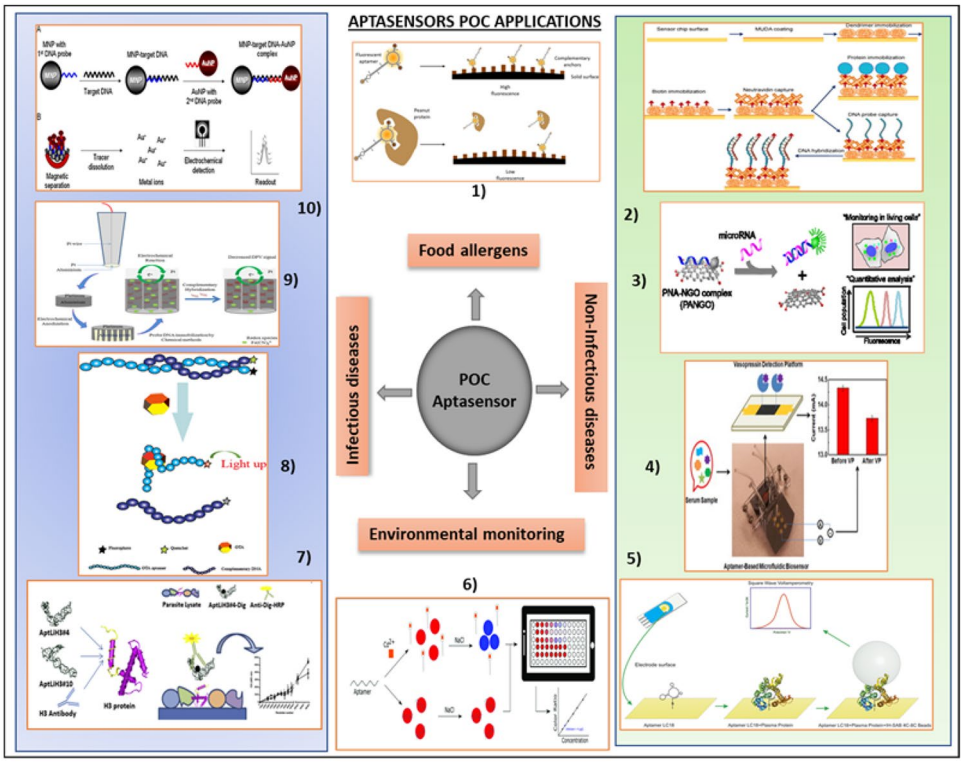

Fig. 8 Aptasensor POC applications. (1) Aptamer-based detection of food allergen peanut protein (Stidham et al. 2022), (2) SPR-based biosensor for lung cancer detection using dendrimers as surface enhancement polymers (Altintas and Tothill 2013), (3) miRNA sensor-based peptide nucleic acid and nanographene oxide (PANGO) (Ryoo et al. 2013), (4) Label-free electrochemical monitoring of vasopressin in aptamer-based microfluidic biosensors (He et al. 2013), (5) Aptamer-based sensor for plasma protein detection(Zamay et al. 2016), (6) Aptamer detection of cadmium from water sample for environmental monitoring (McConnell et al. 2020), (7) DNA aptamers targeting Leishmania infantum H_3 protein (Frezza et al. 2020), (8) The fluorescent aptasensor for OTA determination based on the conformational change of aptamer (Guo et al. 2020), (9) Electrochemical nanoporous membrane-based detection of dengue(Rai et al. 2012), (10) DNA-based electrochemical biosensing platforms (Torres-Chavolla and Alocilja 2011)

critical in epidemic management because it allows speedy implementation of containment measures to limit the likelihood of amplification and international transmission. (Cucinotta et al. 2020). Several electrochemical methods based on aptamers have been successfully used to detect SARS-CoV-2 viral particles or proteins in clinical specimens. Aptamers that bind to the S protein are the most commonly used, and they are frequently conjugated to gold-coated electrodes in electrochemical aptasensors. For example, the RBD-targeting aptamer CoV2-RBD-1C was immobilised on screen-printed carbon electrodes coated with gold nanoparticles for electrochemical detection of SARS-CoV-2 S protein with a limit of detection (LOD) of 1.30 pM (66 pg/ml). The aptasensor detects S proteins from SARS-CoV and SARS-CoV-2 but not MERS-CoV (Abrego-Martinez et al. 2022). In particular, CoV2-RBD-4C labelled with rhodamine 6G dye was attached to gold nanostars for fluorescence detection of S protein and viral particles by distance-dependent nanoparticle surface energy transfer spectroscopy, achieving a LOD as low as 130 fg/ml for S protein and 8 particles/ml for virus (Pramanik et al. 2021). The aptamer CoV2-RBD-1C was immobilised on a short PEG interface on gold nanofilm deposited on a D-shaped plastic optical fibre probe, and S protein binding was monitored using the very sensitive SPR phenomenon, yielding a LOD of 37 nM for S protein (Cennamo et al. 2021).

Hepatitis is an infectious inflammatory health condition caused by different strains of the hepatitis virus (HAV, HBV, HCV, HDV, HEV, HFV, and HGV). A recently demonstrated gold nanoparticle-based DNA biosensor monitors hepatitis B virus DNA with a detection limit of 15 pmol/L (Lu et al. 2013). In another investigation, a biotinylated RNA probe-based biosensor was used to detect non-structural viral protein 3 (NS3) with a detection limit of 500 pg/ml (Roh et al. 2012).

Dengue fever is an infectious and endemic disease that is spread by mosquitos and is caused by Dengue viruses (DENV1-4). Because of its high surface area, dengue fever has been diagnosed using nanoporous alumina membrane-based nucleic acid. A nanoporous alumina membrane-based electrochemical DNA biosensor that can detect the cDNA sequence in Dengue virus has been created and shown in

Fig. 8 (10) (Rai et al. 2012). Electrochemical DNA sensing technology was recently used to identify the Dengue virus's 31-mer oligonucleotide sequence. It used cross-linking of DNA probes on the surface of a nanoporous alumina membrane, followed by measurements of impedance changes during probe-target DNA hybridisation (Deng and Toh 2013). Humans and other primates are infected with the Ebola virus, which causes a severe, often deadly sickness known as Ebola virus disease or Ebola haemorrhagic fever. A 2′-fluoropyrimidine-modified RNA aptamer with a Kd of 54 nM (Shubham et al. 2018) was discovered to bind an Ebola virus soluble glycoprotein preferentially. Hong et al. recently developed a magnetism-controlled chip-based aptamer selection platform (Hong et al. 2019). They generated many DNA aptamers with strong binding affinities against the Ebola virus glycoproteins and nucleoproteins. They have developed an Ebola virus detection method with a 4.2 ng/mL detection limit based on the binding of these aptamers to glycoproteins. These findings will be helpful in future Ebola virus detection applications.

3.5.3 Detection of fungi

Only a few hundred fungus species can cause human sickness out of millions. Fungal infections can be found all over the natural world. When an invasive fungus takes over an area of the body and overwhelms the immune system, it is called a fungal infection. Compared to viral and bacterial diseases, fungal infections are rare and rarely fatal. The CDC classifies fungi into four categories: (1) fungal nail infections, vaginal candidiasis, ringworm, and Candida infections of the mouth, throat, and oesophagus are all prevalent fungal disorders; (2) fungal diseases that affect people who live in or travel to specific areas, such as blastomycosis, coccidioidomycosis or valley fever, Cryptococcus gattii infection, histoplasmosis, and Para coccidioidomycosis; (3) fungal diseases that affect people with weakened immune systems, such as aspergillosis, Cryptococcus neoformans infection, Candida Auris infection, mucormycotic, Pneumocystis pneumonia, and Talar mycosis; and (4) other fungal diseases, including fungal eye infection, mycetoma, and sporotrichosis. (Wan et al. 2021).

Public health depends on the detection of mycotoxin pollutants and dangerous fungi. Aptamers have primarily been created against mycotoxins, poisonous secondary metabolites produced by fungi, to detect fungal infections. Many potential aptasensors for detecting different mycotoxins have been developed using these aptamers mentioned in Fig. 8 (9) (Guo et al. 2020; Wang et al. 2019; Xia et al., 2020). In addition, nucleotide aptamers that target infectious fungus have been produced. Using SELEX, Tang et al. generated two high-affinity DNA aptamers that bind (13)-D-glucans from Candida Albicans cell wall. These two aptamers were used to develop an ELONA test to detect (1 → 3)-β-D-glucans in serum samples (Tang et al. 2016).

3.5.4 Detection of parasite

Parasites are parasites that survive by feeding on other species (hosts). Parasitic illnesses are caused by parasites that make their victims unwell. Parasitic diseases are widespread in tropical and subtropical areas (Jacobs 2015). Trichomonas vaginalis is a parasitic anaerobic, flagellated protozoan that causes trichomoniasis. Using SELEX, Espiritu and coworkers identified a DNA aptamer against the T. vaginalis adhesion protein AP65. They developed an enzyme-linked aptamer test with 8300 cells/mL detection limit to identify T. vaginalis (Espiritu et al. 2018). The parasite Leishmania infantum causes infantile visceral leishmaniasis. Organisations created aptamers against L. infantum (Ospina-Villa et al. 2018). Frezza et al. isolated two DNA aptamers against the L. infantum H3 (LiH3) protein previously discovered in an ssDNA library. They employed an HRP-labelled anti-digoxigenin antibody to detect LiH3 binding after labelling one of the two aptamers with digoxigenin. According to their findings, these two DNA aptamers are promising biosensing compounds for leishmaniasis detection (Frezza et al. 2020). Cryptosporidium is a tiny parasite that causes cryptosporidiosis, a diarrheal condition. Iqbal et al. produced 14 DNA aptamers with a strong affinity for Cryptosporidium parvum. They designed an electrochemical aptasensor to detect C. parvum oocysts in fresh fruit and natural lake and river water samples, with detection limits of 100 and 50 oocysts, respectively (Iqbal et al. 2019, 2015).

3.6 Non-infectious diseases

Metabolic disorders, which can be inborn or hereditary, are caused by abnormalities in the body's normal metabolic responses, leading to various diseases, as outlined below.

3.6.1 Cancer

According to the World Health Organization, cancer spreads worldwide, with rates expected to increase by 50% to 15 million cases by 2020. In the United States, cancer-related deaths are expected to increase by 580,350 points in 2013. One of the most pressing challenges in clinical practice is the early detection and diagnosis of this disease. Various sensitive, cost-effective, and quick cancer detection technologies are being developed to solve this problem. Using a wide range of DNA and RNA probes as the most valuable diagnostic tools has significant potential in the cost-effective monitoring of various types of cancer by early detection of the amount of expression of numerous cancer biomarkers utilising NAB technology (Mousa 2010).

Biosensor technology based on RNA is still in its early stages of development. However, its specificity and accessibility have sparked interest in cancer diagnosis and prognosis. miRNA-based biosensors based on nanoparticles are currently being investigated as potential cancer diagnostic tools (Catuogno et al. 2011; Hong et al. 2013). Biosensors that use aptamers as probes have also shown promise in the diagnosis of cancers such as lung cancer (Zhang et al. 2013), ovarian cancer (Lin et al. 2013), and a variety of other diseases (Wu et al. 2012; Yeong Won et al. 2013). Lung cancer is the most common cancer around the globe, and it can now be detected with various NABs. Biosensors are being developed to identify genes and biomarkers linked to lung cancer, such as TP53 and k-ras. A recently developed DNA biosensor for detecting single nucleotide polymorphisms (SNPs) in the TP53 gene in Fig. 8(2). This technique used a synthetic DNA probe that could hybridise with its mutant TP53 gene counterpart and be identified via SPR and QCM analysis (Altintas and Tothill 2013). Several studies have identified different indicators for bladder cancer detection utilising NABs (Proctor et al. 2010). Using a silicon resonator as an optical sensor, a susceptible nucleic acid (DNA) biosensor was developed for the early detection of biomarkers for bladder cancer such as FGFR3 (fibroblast protein receptor 3) and HRAS (Harvey RAS) in urine samples. The DNA probes had a particular contact with their mutant FGFR3 and HRAS targets in this biosensor (Shin et al. 2013).

Breast cancer is a severe and crucial cancer that is more common in women (almost 23% of all malignancies occur in women) and has a bad prognosis (Boyle et al. 2008). The malfunctioning of several hormones (HER2, E.R., PR, ki-67, mucin 1, i.e. MUC1) and abnormalities in the signal cascade (p53 pathway, RAS pathway, etc.) cause this type of cancer (Yeong Won et al. 2013). Using a fluorescent assay, a PNA-based biosensor has recently emerged as a promising tool for detecting and quantifying the expression of the HER2 oncogene. This PNA-based biosensor can distinguish between the wild-type and mutant targets with excellent specificity and sensitivity (Metaferia et al. 2013). The detection of breast cancer cells overexpressing MUC1 proteins has been reported using a novel electrochemical aptamer-based biosensor. The sandwich formation was used in this approach between MUC1-specific aptamer-cell-aptamer assays (Zhu et al. 2013). The human papillomavirus causes cervical cancer, another prevalent cancer among women (HPV). For the first time, a leaky surface acoustic wave (LSAW) PNA biosensor with high sensitivity and selectivity was created to detect HPV genomic DNA in clinical samples (Wang et al. 2009a, b). The development of NABs with multimarket detection should yield promising results for cancer diagnosis that is both quick and inexpensive.

Leukaemia is one of the most well-known, researched, and deadly cancers. It begins in blood-forming tissues, such as the bone marrow, resulting in vast aberrant blood cells entering the bloodstream (Snyder 2012). A sensitive and accurate diagnosis is required for efficient therapy of this disease. Flow cytometry, polymerase chain reaction, and fluorescence measurement are some of the current methods for detecting leukaemia cells (Shan et al. 2014). As a result, a sensitive and quantitative biosensor with POC features has been presented for use in diagnosis and treatment (Liu et al. 2009). Compared to conventional molecular probes, the device combines the optical capabilities of gold nanoparticles with the advantages of aptamers (single-stranded oligonucleotides that attach to a specific target molecule), including stability and ease of manufacture, and high specificity (Kong and Byun 2013). Ramos cells (lymphoma cells) reacted with aptamers coated with gold nanoparticles, enabling low-cost qualitative and quantitative detection of cancer cells in the bloodstream; in the future, other aptamers could be used to identify many types of cancer cells. When all of the benefits are considered, aptamers appear to have promising therapeutic potential in cancer treatment. Aptamers can be used in cancer therapy to block or stimulate immune receptors in lymphocytes to relieve immune suppression or boost the immune response against cancer (Pandiyan 2019; Pastor et al. 2018; Tan et al. 2011; Zhu and Chen 2018). Aptamers can also be used to guide and deliver anticancer agents such as chemotherapeutics or siRNAs into cancer cells.

3.6.2 Diabetes mellitus

Diabetes mellitus is the most prevalent metabolic condition characterised by elevated blood glucose levels. The correct diagnosis and control of diabetes necessitate detecting and maintaining blood glucose levels. The development of glucose detection biosensor technology has accounted for nearly 85% of the global biosensor market (Yoo and Lee 2010). Only a few NABs for detecting biomarkers and miRNA levels linked to diabetes have been published. Personal glucose meters (PGMs) based on DNA have been reported for blood glucose monitoring. Instead of PCR, PGM uses enzymatic turnovers to detect 40 pM DNA. The quantification is based on cDNA-invertase coupled with the analyte DNA binding to a specific target (Xiang and Lu 2012). Diabetes has also been linked to a change in the level of miRNA expression. This technique utilises nano-sized graphene oxide, which works as a quencher and quenches the fluorescence of PNA probes as shown in Fig. 8 (3). Following PNA and target miRNA binding, the fluorescence is regained (Ryoo et al. 2013). Type 2 diabetes is a common metabolic condition that causes insulin resistance due to biomarkers over RBP4. An aptamer-based biosensor was created to quickly detect Retinol binding protein 4 (RBP4) levels in serum samples. The biosensor was developed by immobilising RBP4-specific

aptamers on an Au chip and then detecting them using the SPR detection method (Lee et al. 2008). The development of simple, rapid, inexpensive, and extremely sensitive nucleic acid-based biosensors for diabetes diagnosis is gaining traction.

3.6.3 Cardiovascular diseases (CVD)

Cardiovascular disease is another frequent disease with rising occurrences; hence detecting cardiovascular biomarkers is critical from a clinical standpoint. The charge distribution phenomena displayed by the synthesised aptamer–CRP complex on the gold interdigitated (GID) capacitor under an electric field was used in a study to develop an RNA-based aptasensor. It has a detection limit of 100–500 pg/ml for C-reactive protein (CRP), the most prevalent biomarker for CVD (Qureshi et al. 2010). A tiny and portable aptamer-based electrochemical biosensor was recently created for detecting vasopressin, a biomarker for traumatic injuries. The conductivity of carbon nanotubes (CNTs) immobilised by aptamers was measured after selective aptamer-vasopressin conjugation, shown in Fig. 8 (4) (He et al. 2013). Pegaptanib (Pfizer/Eyetech), an aptamer that binds to human vascular endothelial growth factor (VEGF), has been approved by the Food and Drug Administration (FDA) for clinical use in treating age-related macular degeneration (AMD) in the last two decades since aptamers were first selected through SELEX (Ng et al. 2006). Various aptamers can be turned into diagnostics and therapies to detect and manage patients with or at risk of cardiovascular problems in cardiovascular illnesses. Aptamers, for example, can be employed as anti-thrombotic and anticoagulants, as discussed elsewhere (Keefe and Schaub 2008; White et al. 2000).

3.6.4 Chronic respiratory diseases

Chronic illnesses (C.D.s), which are defined as a lengthy period of infection with persistent symptoms, are one of the leading causes of death worldwide (World Health Organization 2014), accounting for 70% of all healthcare spending (Anderson and Squires 2010). According to World Health Organization statistics, C.D.s are a severe health danger to the elderly and the young, and C.D.s have a higher risk of causing death in patients in resource-limited areas (WHO) (Tunstall-Pedoe 2006). Treatment can enhance CD care and prevent development (Korhonen et al. 2003). However, the appealing concept of early CD diagnosis is frequently thwarted by the existing clinical practice's slow and expensive diagnostic processes. Furthermore, the time it takes to get CD diagnosis results is a significant impediment to optimal healthcare resource allocation and coordination, resulting in a substantial increase in financial burden (Bleakley and Lange 2009). Zamay G S et al. developed an aptamer-based electrochemical sensor for lung cancer detection using crude blood plasma samples mentioned in Fig. 8 (5). They enhanced the detection limit of the LC-18 aptasensor using beads to 0.023 ng/mL (Zamay et al. 2016). For DNA quantification of Mycobacterium tuberculosis from clinical samples, Zribi et al. developed a label-free LoC electrochemical sensor based on carbon nanotubes/ferrocene (Zribi et al. 2016). The use of a rapid flow creates a thin depletion layer on the sensor surface, which improves the rate of DNA capture. As a result, the LOD was increased from picomolar (pM) to femtomolar (F.M.), with a dynamic range of 0.1 FM–1 pM, compared to 1 pM–100 nM with standard microelectrodes. This is critical since pathogenic analytes vary dramatically in clinical samples. The direct genomic pathogenic detection method eliminates amplification and provides an accurate pathogenic quantification method. Adding a sample processing module that allows for raw sample analysis will make the POC test more appealing.

Non-infectious diseases account for 71% of global deaths each year and necessitate diagnosis for treatment and disease prevention and management. The most important ASSURED criteria for non-infectious disease diagnosis are ease of operation, rapidity, and affordability. Non-infectious disease diagnosis, in particular, is based on biochemical (e.g. biomarkers, glucose, haemoglobin, etc.) or biological (e.g. electrical, neural, muscular, etc.) analysis, which necessitates laboratory infrastructure and large equipment that is difficult to set up in low-resource settings. Furthermore, a distant laboratory, poor sample transport, sample quality maintenance, and financial burden may all be issues that impede the process of diagnosing non-infectious diseases. Given this issue, we are shifting in how we diagnose non-infectious diseases. In the last decade, there has been a strong emphasis on point-of-care (POC) diagnosis over centralised laboratory-based investigations, such as in the case of diabetes diagnosis and management, where we have made significant progress by developing a handheld glucometer device (POCT device/biosensor) from urine acid hydrolysis and test strips. Furthermore, this POCT device has changed how doctors diagnose patients by increasing the patient's desire for testing.

3.7 Other applications

The Aptasensing platform provides a wide range of point-of-care applications in the medical field, such as therapeutic drug monitoring(Chung et al. 2022), sweat analysis(Dalirirad and Steckl 2019), detection of complex fluid(Berto et al. 2018) and pregnancy test (Yu Zhang et al. 2019a, b).

Currently, allergen detection in foods is done using time-consuming and complicated procedures that prevent consistent sampling for allergens that could cause anaphylactic

shock in consumers due to cross-contamination. Scientists in a consumer device have successfully used aptamer technology to identify peanut antigens in food. The new aptamer-based protein detection method is reliable in a wide range of food matrices and responds to peanut protein at concentrations as low as 12.5 ppm (37.5 g of peanut protein in the sample) (Stidham et al. 2022). Integrating the test into a sensitive, reliable, and user-friendly portable device will allow consumers to quickly and easily determine if foods contain peanut allergens before consuming them. The technology discussed here has tremendous potential to improve the lives of children and families, as many food reactions occur outside the home. The fluorescently labelled aptamer is incubated with the sample. When it binds its target, it cannot bind its complementary anchor on the solid surface, resulting in low fluorescence. In another study, Tah A and et al., conjugated aptamers with gold nanoparticles (AuNP) and then used the specific absorption properties of graphene oxide (GO) for single-stranded DNA (ssDNA) with a paper device, to create a simple colorimetric sensor for the detection of food allergens present down to the nanogram range (allergens were detected in the range of 25 nM to 1000 nM with a LOD of 7.8 nM, 12.4 nM, and 6.2 nM for peanut, milk and crab allergens, respectively)(Tah et al. 2018).

Aptamers, due to their greater synthetic and chemical simplicity compared to antibodies, offer better stability and usefulness for detecting environmental contaminants and for environmental monitoring. In addition, hazardous targets can be selected for nucleic acid aptamers, which can complicate the production of antibodies. Aptamers have been selected and used to develop biosensors for environmental pollutants such as heavy metals, small-molecule agricultural toxins, and bacterial infections from water, which is particularly relevant. Industrial wastes and liquid effluents are significant sources of contamination to natural water systems, including rivers and groundwater (Yadav et al., 2020). Contamination of water sources with arsenic, cadmium, lead, silver, and mercury can harm aquatic life and human health (Yadav et al., 2020). The propensity of heavy metals to bioaccumulate in living systems exacerbates these problems (Malik et al. 2019. Electrochemical methods are one of the most commonly used methods for heavy metal detection (Malik et al. 2019; Mishra et al. 2018; Rapini and Marrazza 2017). However, optical and mechanical methods have also been described (Khoshbin et al. 2018; Kudłak and Wieczerzak 2020; Zhang et al. 2018). Aptasensors have enormous potential, and this exciting and challenging field is on the verge of exponential growth. The ability to develop affinity-based detection systems based on tailored characteristics such as size, toxicity, and matrix effects allows the field of biosensing to explore previously unexplored horizons in sensor development.

4 Critical discussion

The production of the desired aptamer is required by the aptasensor technology to be faster, more efficient, and with high throughput. These needs refining the initial library for selection and performing parallel microarray characterisation or microfluidic SELEX with next-generation sequencing (NGS), resulting in more specific aptamers with high affinity in less time. Similarly, the binding affinity of aptamers can be improved and optimised by molecular docking modelling. In addition, the buffer's pH and ionic strength affect the aptamers' three-dimensional structure. Any small change in composition alters the shape of the aptamer, which affects the binding affinity to the target. Therefore, experimental settings must remain consistent throughout the analysis. Modified bases can also be used to increase the affinity of the aptamer. This technique has been used for many years to increase RNA stability and binding affinity to specific chemical groups (Li et al. 2008). The scope of analytical work is still limited due to expensive probe synthesis and challenging labelling procedures. Despite this rapid development, aptamer-based bioassays are still in their infancy compared with immunoassays, reflecting some extent the low availability of aptamer species and the limited understanding of aptamer surface immobilisation technologies.

While fluorescence methods are considered the most popular signal transduction options, colorimetric methods are the simplest sensing approach that the naked eye can perceive. Few optical sensors can be used in biological samples due to the low concentration of diverse analytes and the complexity of the biological environment that interferes with detection methods. Electrochemical methods are widely used for the detection and quantification of pathogens due to their special characteristics, such as rapid response and low-cost detection. They offer the possibility of developing regenerable biosensors with low detection limits, a wide linear response range, good stability, and the ability to be easily scaled down. In addition, electrochemical aptasensors require fewer analytes for detection than optical sensors. According to the reported detection limits, electrochemical techniques were more sensitive than optical aptasensors (LOD of 1 cfu/ml) (Shahdordizadeh et al. 2017).

Similarly, the sensitivity and selectivity of QCM- and SPR-based biosensors for the study of HIV-1 protein. Both are reagent-free and one-step analytical methods, making them attractive to many scientists (Tombelli et al. 2005). Both basic research and biological diagnostics have benefited from the widespread development and use of aptamer-based sensors, which have eventually evolved into tools that can solve the problems of today's antibody-based technology. Various nanomedicines with active targeting have been investigated, and clinical data show that carrier materials

with a size of 5–200 nm, such as antibodies, can significantly increase the therapeutic index of low molecular weight drugs. A number of aptamer-based applications are enabled by aptamers' superior specificity and discriminatory ability to replace antibodies. These "miniaturised molecules" will become mainstream and find their way into nanotechnology applications (Lammers et al. 2010). In addition, nanomaterials such as gold nanoparticles coupled with aptamers are increasingly used for diagnosing and treating diseases than the "traditional" drug targeting systems such as antibodies, liposomes, polymers and micelles (Li et al. 2010).

The very stable QDs often take the role of traditional fluorescent dyes (Naresh and Lee 2021). Optical and electrochemical aptasensors often use metal nanoparticles (Kim and Jurng 2011), magnetic nanoparticles (Xia et al. 2021), and other nanomaterials for signal amplification. Because of their exceptional performance, nanomaterials play an increasingly important role in the field of aptasensors. Current aptasensor methods are not sensitive enough to detect infectious and non-infectious diseases. We have listed some of the considerations that must be taken into account when developing a rapid aptasensor-based POCT.

- Biosensor design: the design must be miniaturised, simple, user-friendly, inexpensive, portable, and should provide a long shelf life with accuracy. In addition, cross-contamination and evaporation must be reduced.
- Integration: the designed aptasensor should be such that it can be integrated with other thermal sensors, optical detectors, mass-sensitive and cloud analytics 4.0 approaches for effortless qualitative and quantitative detection of the target.
- Sensitivity: The biosensors must have a lower LOD to reduce the recurrence of infection after treatment.

5 Conclusions and future prospective

Aptasensors have experienced considerable growth in the present decades, and their advantages over conventional methods have been extensively researched and documented. The potential of aptamer-based biosensors or testing methods for POC diagnosis or global health has been rapidly explored in recent years. Their unique properties, such as stability as dry reagents, negligible batch-to-batch variability, cost-effectiveness, and high detection sensitivity and specificity are desirable for use in the field or in poorly equipped environments. The suitability of aptamers as detection elements for analytical applications ranging from separation methods to biosensors is discussed in this paper. A new approach for the preparation of aptamers against target molecules was demonstrated. A number of transducers (e.g. electrochemical, optical, and mass sensitive) have been used in aptasensors.

Aptamer research is still in its infancy, and better knowledge of aptamer-target interactions and pharmacokinetics is needed before they can be used in clinical trials or commercialised. All these technologies are inexpensive, fast and pioneering in nanotechnology. Therefore, they are one of the best ways to focus on developing point-of-care devices. The disease spreads daily; therefore, cheaper technologies are needed for first-line treatment. The development of successful cures is slow, but it never stops, and the best results are yet to come. Aptamers have the advantage of little or no immunogenicity in cancer treatment. Their lower molecular weight allows them to penetrate solid tumour tissue relatively quickly, and their in vitro production makes them less expensive than Abs.

Despite the remaining challenges, the recent development of biosensors based on POC-compatible aptamers has shown tremendous potential to improve personalised diagnosis and global health on a large scale. Thus, integrating aptamer biosensors into emerging wearable technologies could provide an alternative method for long-term health monitoring and disease management in the context of digital precision medicine. Despite the seemingly endless opportunities to improve sensor technology, the ultimate goal is to develop an accurate, rapid, economic, and easy-to-use detection system suitable for POCT that can become the standard for diagnostics (Narayanamurthy et al. 2020). Comparative studies with different aptasensor targeting similar viruses or bacteria in different matrices are required to achieve this goal. This review summarises existing diagnostic tools for various diseases in public health and emergency settings. More diagnostic methods are urgently needed as cases rapidly increase worldwide until appropriate drugs/vaccines are available. Reliability, performance, ease of use for field use, and data acquisition and processing are essential considerations. As a detection method, additive manufacturing of these aptasensor has not been fully explored. We believe that developing such techniques will contribute to the growth and advancement of improved aptasensor in the future, and will produce novel, user-friendly wearable sensors that non-professionals can use to achieve the goals of low-cost monitoring applications in the field or at home. In many aspects of life, including health and finance, the pandemic is life-threatening in all parts of the world. The new POC biosensor with comprehensive features can quickly detect epidemics, guide appropriate medical care and play an essential role in outbreak management.

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Conceptualization, Visualization, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Data Availability The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

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