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**Review Article**

# Applications of aptamer-gold nanoparticle conjugates in biosensors for point-of-care diagnostics

Nur Syamimi Mohamad[1], Lee Yook Heng[2] and Eda Yuhana Ariffin[3*]

[1]Southeast Asia Disaster Prevention Research Initiative (SEADPRI), Institute for Environment and Development (LESTARI), Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor Darul Ehsan, Malaysia
[2]Department of Chemical Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, 43600 UKM Bangi, Selangor Darul Ehsan, Malaysia
[3]Department of Chemical Sciences, School of Distance Education, Universiti Sains Malaysia, E39, Minden Heights, 11800 Gelugor, Pulau Pinang

*Corresponding author: edayuhana@usm.my

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**Abstract**
The rapid, sensitive and selective detection of biomolecules made possible by biological sensing technology has completely changed the field of diagnostics. Recent advancements include the implementation of aptamer-gold nanoparticle (AuNP) conjugate-based biosensors, which represent a novel category of clinical diagnostic tools. This thorough study consolidates recent advancements while critically assessing the diagnostic capabilities, technological constraints, and translational preparedness of aptamer-AuNP biosensors. By systematically analysing 28 peer-reviewed studies published from 2014 to 2023, utilizing data from Web of Science and PubMed, this review highlights issues, such as instability, inadequate specificity, restricted reproducibility, and difficulties in incorporating biosensors into user-friendly diagnostic platforms. The results also demonstrate a significant increase in research activities over the past five years, with optical and electrochemical platforms identified as the predominant modalities of study. Analytical evaluations demonstrated exceptional sensitivity (as low as 0.02 pg $mL^{-1}$) and significant stability (up to 35 days) in actual biological specimens, including serum, urine, saliva, and food matrices. However, major gaps remain in long-term reproducibility, integration into user-friendly formats, and specificity in complex matrices. This analysis outlines the limitations and suggests alternatives to improve sensor design and implementation for practical diagnostic applications, particularly in personalized medicine and point-of-care diagnostics.

**Keywords:** Aptamer, gold-nanoparticles, biosensor, optical, electrochemical

## Introduction

Conventional diagnostic methods, including enzyme-linked immunosorbent assays (ELISA), polymerase chain reaction (PCR), and high-performance liquid chromatography (HPLC) are extensively utilized in clinical and laboratory environments owing to their sensitivity and precision. These methods frequently necessitate costly equipment, labour-intensive procedures, skilled personnel, and centralized laboratory facilities, thereby constraining their suitability for rapid, on-site diagnostics. Additionally, extended turnaround times and restricted portability impede their application in point-of-care or resource-constrained settings. The identified limitations have prompted the advancement of biosensor technologies as alternative platforms that can effectively address these challenges via rapid, cost-efficient, and miniaturized detection systems. Biological sensing technologies have revolutionized diagnostics by allowing for quick, sensitive, and selective detection of biomolecules. In this domain, the two most common transduction modalities are optical and electrochemical, with each presenting distinct advantages and purposes. Optical biosensors utilize the interaction of light with biological recognition components to generate an identifiable signal. This interaction can emerge as a variety of phenomena, including absorbance, fluorescence, chemiluminescence, and surface plasmon resonance [1]. Absorbance-based measurement evaluates the total amount of light absorbed by a sample at certain wavelengths. This method is widely used due to its simplicity and the wide variety of ready-made detectors available, with variations in absorbance indicating the presence and quantity of the target analyte [2].

Meanwhile, fluorescence-based detection takes advantage of the emission of light by fluorophores upon excitation, providing excellent sensitivity and the capacity to identify low-abundance targets [3]. These sensors are often used to quantify nucleic acids, proteins, and tiny molecules [4]. Chemiluminescence is light emission caused by a chemical reaction. It is known for its great sensitivity and is widely used in clinical diagnostics to detect enzyme activity and nucleic acids [5]. In surface plasmon resonance (SPR)-based biosensing, alterations at the interface, such as the binding of biological recognition elements with analytes, cause changes in the local refractive index. These modifications, in turn, affect the excitation of surface plasmon resonance. This methodology provides a label-free, real-time way for monitoring biomolecular interactions, making it extremely useful. As a result, SPR is widely used for assessing binding kinetics and affinities, as thoroughly detailed by Zeng and co-workers [6].

Diagnostic methods incorporate electrochemical biosensors, which will practically transform a biological recognition event into an electrical signal and are distinguished by their great sensitivity, simplicity, low cost, and potential for downsizing, making them ideal for point-of-care diagnosis [7]. Electrochemical sensors are categorized into various categories, including amperometric, potentiometric, impedimetric, photoelectrochemical, and electro generated chemiluminescence [8]. For example, amperometric detection measures the current produced by the redox reaction of an analyte at an electrode surface, with the current being proportional to the analyte concentration, allowing quantitative analysis. This approach is commonly used for glucose monitoring and other metabolic assays [9].

Potentiometric detection measures voltage changes due to selective interaction of the analyte with an ion-selective electrode, useful for detecting ions and small molecules in applications such as blood gas and electrolyte analysis [10]. Impedimetric detection measures changes in the impedance of an electrode interface upon binding of the target analyte, advantageous for detecting large biomolecules like proteins and cells due to sensitivity to changes in the electrical properties of the sensing surface [11]. Aside from advancements in the integration of optical and electrochemical modalities to enhance sensitivity, selectivity, and functionality of biosensor technology, most researchers also focus on the developing nanomaterials matrix as surface of sensor's fabrication [12,13].

This is due to modification on surface of a biosensor increases the surface area available for biorecognition events and thereby boosting the biosensor's sensitivity and detection limit. Aptamer-gold nanoparticle conjugates are frequently employed in both optical and electrochemical biosensors, benefiting from the unique optical properties and excellent electrical conductivity of AuNPs [14-16]. The unique properties of AuNPs, combined with the high specificity and affinity of aptamers, make these biosensors highly effective for detecting a wide range of analytes at very low concentrations [17-19]. Thus, integration of these technologies holds great promise for developing advanced point-of-care diagnostic tools that are both highly effective and accessible.

While significant progress has been made in leveraging the unique properties of aptamers and gold nanoparticles (AuNPs) for biosensing applications, challenges remain, particularly in terms of stability, specificity, reproducibility, and integration into practical diagnostic devices. Previous studies have demonstrated the potential of these biosensors for ultra-sensitive detection, yet issues such as cross-reactivity in complex biological matrices, standardization of preparation methods, and the translation of laboratory successes into robust, user-friendly point-of-care systems have not yet been fully addressed. This review seeks to consolidate advancements in aptamer-AuNP biosensor development over the past decade while critically analysing their diagnostic impact, technical limitations, and readiness for clinical implementation. This review systematically evaluates recent studies to identify key areas of innovation, highlight performance bottlenecks, and outline future directions that may bridge the gap between research and practical deployment in point-of-care settings.

## Systematic methodology

### Search strategy, database sources, and study selection

Comprehensive search conducted across major scientific databases including PubMed and Web of Science (WOS). Keywords searching contained within "gold nanoparticles", "biosensors", "optical and electrochemical techniques", "aptamer" and related terms. Thus, prompt basically was ( ( "gold nanoparticles" OR "gold colloids" OR "gold nanostructures" OR "gold nanomaterials" OR "Au nanoparticles" OR "Au colloids" OR "Au nanostructures" OR "Au nanomaterials" ) AND ( "biosensors" OR "biochemical sensors" OR "biological sensors" OR "analytical devices" OR "sensor arrays" OR "biosensing platforms" OR "biomolecular sensors" ) AND ( "optical" OR "optical devices" OR "optical phenomena" OR "optical systems" OR "electrochemical" OR "electrochemical sensors" OR "electrochemical reactions" OR "electrochemical analysis" ) AND ( "aptamer" OR "aptamers" OR "chemical antibodies" OR "antibody mimics" ) ). The search was restricted to English-language and original research articles, looking at title, abstract and keywords and for the choice of strings, the criteria followed were: (i) identification of keywords considering the research question; (ii) synonyms based on relevant keywords; and (iii) use of Boolean operators "AND", "OR" and "*". Studies published within the given timeframe (ten years, 2014–2023) were included in the filters, as the database search was conducted on 28 March 2024. Since several 2024 articles were not yet properly indexed at that time, they were disregarded to maintain the analysis's uniformity and completeness. Then, this review focused on original research articles, excluding revisions, theses, and brief communications. The selection of documents for this assessment was based on searches using platform-specific structured query strings in the Web of Science (WoS) and PubMed databases. (**Table 1**).

**Criteria eligibility**

We carried out an independent identification of the abstracts, keywords, and documents' content for the preliminary selection overview. Articles that did not examine biosensors, were not aptamer-based, did not use AuNPs materials, did not target biological samples, or did not use actual samples were eliminated at this point.

**Table 1.** Searched strings in each database (WoS and PubMed) for documents selection in this systematic literature review

| Search Engine Database | Screening | Search Strings |
|---|---|---|
| WOS (https://www.webofscience.com) | (i) Topic<br>(ii) Years: 2014-2023<br>(iii) English language<br>(iv) Article | (("gold nanoparticles" OR "gold colloids" OR "gold nanostructures" OR "gold nanomaterials" OR "Au nanoparticles" OR "Au colloids" OR "Au nanostructures" OR "Au nanomaterials") AND ("biosensors" OR "biochemical sensors" OR "biological sensors" OR "analytical devices" OR "sensor arrays" OR "biosensing platforms" OR "biomolecular sensors") AND ("optical" OR "optical devices" OR "optical phenomena" OR "optical systems" OR "electrochemical" OR "electrochemical sensors" OR "electrochemical reactions" OR "electrochemical analysis") AND ("aptamer" OR "aptamers" OR "chemical antibodies" OR "antibody mimics")) |
| PubMed (pubmed.ncbi.nlm.nih.gov) | (i) All fields<br>(ii) Years: 2014-2023<br>(iii) English language<br>(iv) Article | (("gold nanoparticles" OR "gold colloids" OR "gold nanostructures" OR "gold nanomaterials" OR "Au nanoparticles" OR "Au colloids" OR "Au nanostructures" OR "Au nanomaterials") AND ("biosensors" OR "biochemical sensors" OR "biological sensors" OR "analytical devices" OR "sensor arrays" OR "biosensing platforms" OR "biomolecular sensors") AND ("optical" OR "optical devices" OR "optical phenomena" OR "optical systems" OR "electrochemical" OR "electrochemical sensors" OR "electrochemical reactions" OR "electrochemical analysis") AND ("aptamer" OR "aptamers" OR "chemical antibodies" OR "antibody mimics")) |

**Study selection**

A total of 411 records were identified, comprising 348 from WOS and 63 from PubMed. The initial screening based on the English language criterion excluded six documents, lead to 409 documents (WOS: 343, PubMed: 62). The subsequent screening phase, non-research papers were filtered out, brought the total down to 169 documents. 43 duplicate papers were then eliminated as a result. Following this, 43 duplicate records were identified and removed using Mendeley Reference Manager, resulting in the final dataset used for analysis. As a result, 126 documents had their eligibility requirements evaluated. To minimize the risk of overlooking relevant studies that may not have exactly matched the selected keywords, a manual screening process was performed following the initial keyword-based search. Titles, abstracts, and, where necessary, full-text articles were carefully reviewed to assess their relevance based on the predefined inclusion criteria. This process served as a verification step to identify relevant studies that may have been missed during the screening final relevant articles. A preliminary selection overview was then conducted, excluding studies that deviated from the inclusion criteria. Ultimately, 28 studies met the inclusion criteria and were included in the systematic review for in-depth examination. **Figure. 1** illustrates the search approach in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines.

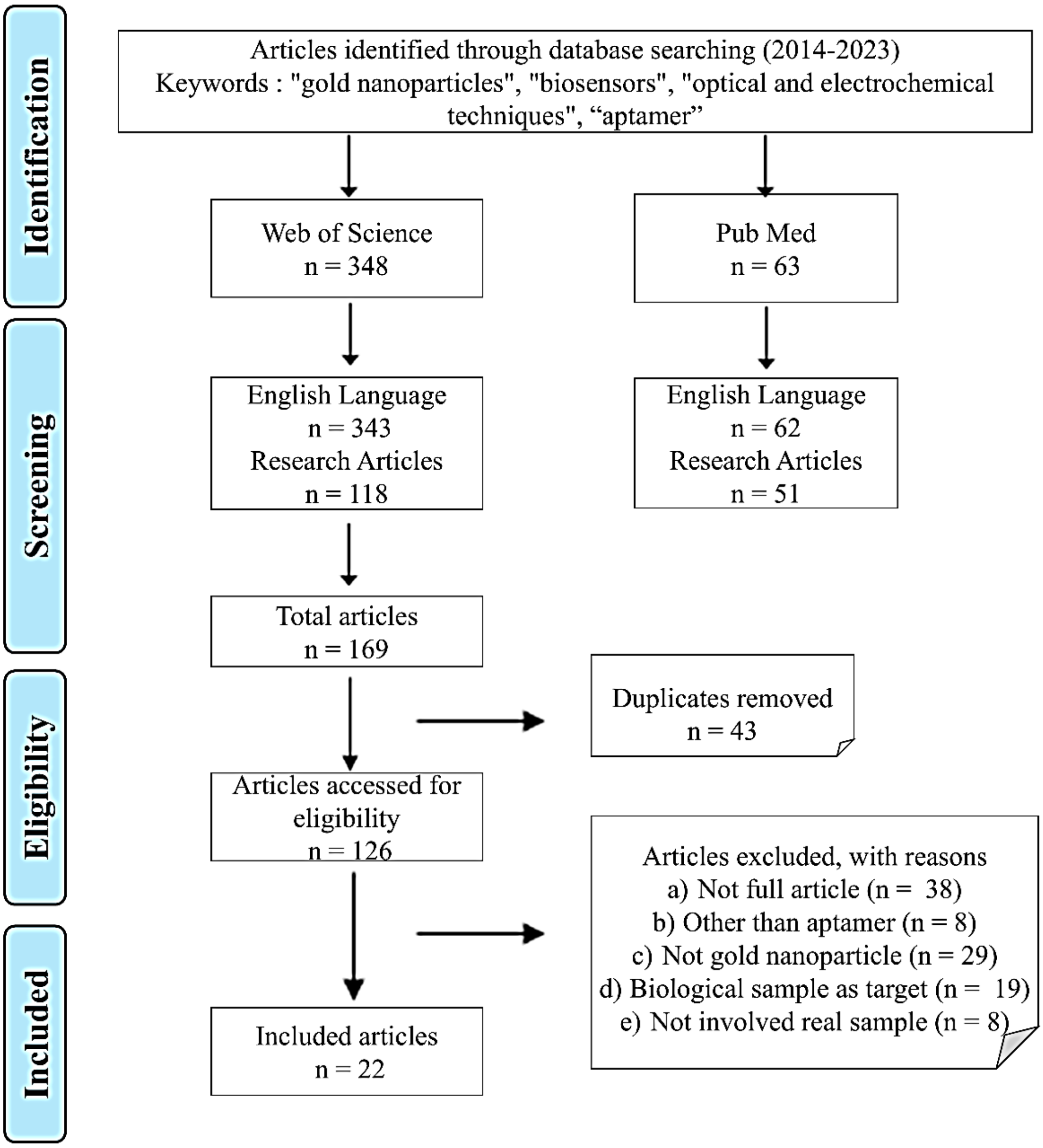


**Figure 1**. Flow chart showing the PRISMA-compliant screening approach and search results

## Discussion

### Overview of gold nanoparticles

### Synthesis of gold nanoparticle

There are several methods to synthesized gold nanoparticles. It can be classified into two main categories: wet chemical methods and physical methods. Generally, wet chemical methods are suitable for gold nanoparticles with specific surface properties, while physical methods are preferred for applications that demand high-purity particles.

Wet chemical methods involve chemical reaction in solution to reduce a gold precursor to form nanoparticles. Wet chemical methods are commonly used by the researchers because these methods can control the shape, size, and stability of nanoparticles. There are several techniques that are categorized as wet chemical methods. The most common and earliest method is citrate reduction method or Turkevich method. This method includes nucleation and growth process in the synthesis of colloidal gold. Citrate acts as a reducing and stabilizing agent. Turkevich method can produce spherical gold nanoparticles with diameter around 10 – 20 nm. This Turkevich method has been improved by Frens [20]. Frens has found the way to control the nucleation for the regulation of the particle size and monodisperse gold suspensions. The improvement of Turkevich method shows that gold nanoparticle size is dependent on the concentration of citrate.

Green synthesis is a wet chemical method. In this method, plant extracts or other natural substances can be used as a reducing agent and offering an eco-friendly approach. Shankar et al. [21] carried out a study that focus on green synthesis using neem leaf extract as a reducing agent, presenting a sustainable method for gold nanoparticles synthesis. Reducing agents like sodium borohydride, ascorbic acid and polyols are used to synthesis gold nanoparticles. These reducing agents can produce small and uniform particles or different shape of gold nanoparticles [22]. There were few other wet chemical methods that can modify and functionalize the surface of gold nanoparticles [23], control size and shape by controlling the temperature [24], and enhance the stability of gold nanoparticles [25].

Physical methods for synthesizing gold nanoparticles rely on breaking down or evaporating bulk gold material into small scale particles. These types of methods, normally require high energy and specialized equipment. These physical methods are costly but will produce high purity of gold nanoparticles. Laser ablation is one of the physical methods in synthesizing gold nanoparticles. This method involves the use of a high-powered laser to irradiate a bulk gold target submerged in a liquid medium. When the laser hit the gold surface, it causes rapid heating and vaporization of gold atoms, forming a plasma that subsequently cools and condenses into nanoparticles. This method is simple and can produce pure gold nanoparticles without any chemical contaminations. Mafune et al. [26], demonstrated laser ablation in liquid medium with a surfactant to synthesize a stable gold nanoparticle. The addition of surfactant could improve particle stability by preventing agglomeration.

Laser-induced synthesis is another technique for physical methods. In this technique, laser is used to interact with pre-existing colloidal particles in a solution. It will cause fragmentation, reshaping or aggregation of nanoparticles. Unlike laser ablation, laser-induced synthesis modified gold nanoparticles that already present in the solution. Mafune et al. [27] investigated laser-induced aggregation and fermentation in gold colloids. The laser irradiation can lead to controlled restructuring and formation of fractal-like aggregates. There are few other methods or techniques that categorized under physical methods. Some of this method for example pulsed laser deposition can create thin film or form gold nanoparticles coatings on a substrate [28]. Khaleeq-ur-Rahman et al. [28] studied the energy and pulse length of the laser that can influence gold nanoparticles morphology and size.

### Characteristics of gold nanoparticles employed for amplifying signals

Gold nanoparticles have their own characteristics that make them able to amplify signals in biosensor. There are three types of signal amplification: biological signal amplification [29], electrochemical amplification [30] and optical signal amplification [31]. One of the main characteristics that contributes to signals amplifying in the biological signal amplification are the high ratio of the surface area to volume [32]. High surface area of gold nanoparticles will increase the volume of aptamer to immobilize onto the gold nanoparticles surfaces. It will enhance the sensitivity of the biosensor, subsequently leading to an amplified detection signal. Gold nanoparticles are chemically inert and biocompatible [33-35]. This allows gold nanoparticles to interact with aptamer in the complex biological samples such as serum and blood without affecting the biological activity which is important for signal integrity and amplification in biosensor. Moreover, gold nanoparticles can be easily functionalized with various biomolecules, including antibodies, aptamers, peptides, and nucleic acids due to their strong affinity for thiol (-SH) and amine (-$NH_2$) groups [34-35]. Functionalized gold nanoparticles can specifically bind to target molecules and enhance the signal amplification.

In term of conductivity, gold nanoparticles have making them highly conductive [33,36]. In electrochemical biosensors, gold nanoparticles can be used as an electron mediator and signals amplifier by promoting more efficient electron transfer between the electrode and the biological recognition elements such as aptamer.

Gold nanoparticles have been shown to exhibit catalytic properties and contribute in amplifying the optical signals [31,37]. It can catalyse reactions that produce colour changes or other detectable outputs, enhancing the signals of the assay. For example, gold nanoparticles are commonly used in enzyme-free assays, where their catalytic action leads to signal amplification without using enzymes labels. Other than that, gold nanoparticles can scatter and absorb light strongly especially in the visible and near infrared region. This property can be used as photothermal biosensing and the photothermal effect can enhance the signal by converting light energy into heat and amplifying the signals. Gold nanoparticles have optical properties that are strongly-sized dependent [38-40]. Small size gold nanoparticles (size ranging between 10 to 30 nm) tend to show different scattering and absorption behaviours compared to larger size of gold nanoparticles [37]. By tuning the size, it can enhance the sensitivity and specificity of the detection of optical biosensors and provide signal amplifications. Gold nanoparticles have colorimetric properties. They change colour based on their size, shape, and aggregation state [31,36,39,41]. The visual signal can be amplified when gold nanoparticles change colour from red to purple due to aggregation in response to a target analyte.

**Advantages and limitations**

Based on the characteristics of gold nanoparticles, these nanoparticles have many advantages in biosensor development. High surface area of gold nanoparticles will increase the number of biomolecules immobilization onto it and enhance the biosensors' sensitivity and selectivity [32,37]. Gold nanoparticles have an excellent conductivity [33,36]. It can improve the signal transduction in electrochemical biosensor and enhance the detection capability. Furthermore, golds are biocompatible and can be easily functionalized with ligands, antibodies or enzymes [40]. These properties allow them to specifically bind to a wide range of target analytes. Gold nanoparticles can amplify the optical detection signals due to their optical properties. Furthermore, gold nanoparticles are stable under a wide range of physical and chemical conditions and enhance the robustness of biosensors.

Despite their advantages, gold nanoparticles also have their own limitations. Gold is an expensive metal. This exhibited excellence electron transfer properties,

highly cost material can limit the scalability and widespread use of gold nanoparticles-based biosensors in low-cost applications. Gold nanoparticles can easily aggregate especially in biological samples or under improper storage conditions. Aggregation can reduce the biosensor performance and can altered their optical properties [29]. Gold nanoparticles may interact or promote non-specific adsorption with other biomolecules or cells and this will lead to false positives or they will not be selective in the detection [40]. The surface of gold nanoparticles needs to be modified to ensure the selective and stable biomolecules binding [36]. The surface modification process can be complex, time-consuming and require precise control over the surface chemistry. Some gold nanoparticles-based biosensors may have a short-term stability. The stability reduces over time due to the changes in the gold nanoparticles properties or the degradation of functionalized biomolecules [40].

**Principles of aptamer-gold nanoparticles conjugates-based biosensors**

Aptamers are small, single-stranded nucleic acids having a high affinity and specificity for certain targets, much like antibodies but with several benefits [11]. They are selected by the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) technique, which draws from substantial nucleic acid libraries [42]. In biosensing applications, these aptamers are adaptable recognition elements because they may be designed to bind a wide range of targets, such as proteins, small molecules, and even entire cells. [43,44]. Gold nanoparticles have unique optical and electrical characteristics that are very helpful in biosensing. Their high surface-to-volume ratio makes it possible for several aptamers to attach, which increases the biosensor's sensitivity and binding capacity. [45]. Furthermore, AuNPs exhibit strong plasmon resonance characteristics that make them useful for a variety of optical detection techniques, including surface-enhanced Raman scattering (SERS), fluorescence, and colorimetry [46,47].

Aptamer-gold nanoparticles conjugates biosensors combine the selectivity and sensitivity of aptamers with the unique properties of gold nanoparticles to detect the specific target. Aptamer is a molecular recognition element for target such as protein, small molecules or ions, which will be immobilized onto gold nanoparticles surfaces. Then, the aptamer-gold nanoparticles conjugates-based biosensor is exposed to the sample containing target analyte. Upon binding the analyte to the aptamer, the aptamer may undergo a conformational shift that can alter the electron transfer or optical properties of the gold nanoparticles. These changes can be measured using either electrochemical sensing or optical sensing. Several detection methods can be used depending on the design of the biosensor.

**Factors influencing biosensors performance**

Several factors influence the performance of biosensors. These factors affect their sensitivity, selectivity and effectiveness in detecting target molecules. Aptamer design and selection is one of the main factors that influence the performance of biosensor [29]. The affinity and the selectivity of the aptamer towards its target depends on its three-dimensional structure and nucleotide sequences. Aptamer must fold correctly according to the target structure and their active conformation. The affinity between aptamer and target will affect the sensitivity and the selectivity of the biosensor. Modifying aptamer by adding the functional group can enhance the biosensor performance such as stability, binding and shelf-life especially for use in complex biological samples. Furthermore, stabilizing the aptamer with chemical modification such as thiol or amine group can improve the biosensors' stability. Blocking agents can be used to reduce non-specific adsorption.

Aptamer immobilization methods affect the sensors performance [48]. A poor immobilization method will reduce binding efficiency and stability. The surface of the immobilization matrix must be functionalized to ensure proper orientation and functionality of immobilized aptamers. Non-specific binding or steric hindrance should be minimized to improve the signal.

The gold nanoparticles' size significantly influences the performance of the biosensors [32]. Smaller gold nanoparticles have a higher surface area-to-volume ratio, which provides more surface for attaching the aptamers. This enhances the binding capacity of the biosensor and can increase the biosensors' sensitivity, as more aptamers can be immobilized on the gold nanoparticles surfaces. Larger gold nanoparticles may provide less surface area for immobilization site but can interact more strongly with the sensing medium, affecting the overall signal intensity.

The size of gold nanoparticles can determine the strength of the generated signals in biosensor. In optical biosensors, smaller gold nanoparticles usually result in sharper and more sensitive localized surface plasmon peaks improving the detection limits [39-40]. In electrochemical biosensors, smaller gold nanoparticles improve electron transfer between the target molecules and the electrode surface and enhance the sensitivity and response time [33].

The size and the concentration of the target molecules may influence the interaction between the aptamer and the target and the resulting signal. Smaller targets or low concentration targets may require higher affinity aptamers or signal amplification methods. Temperature, pH, and ionic strength affect the target-aptamer interaction. Aptamer binding may be sensitive to these conditions and impacting the performance.

**Significance of aptamer-gold nanoparticle conjugate biosensors for ultra-sensitive detection**

Aptamers and AuNPs together therefore improve sensitivity and specificity in a synergistic way. To ensure that the biosensor can differentiate the target analyte from other chemicals in complicated biological samples, aptamers provide the requisite selectivity. The signal produced by target binding is amplified by AuNPs, which is essential for the detection of low-abundance analytes. As an illustration of their potential for early disease identification, aptamer-AuNP conjugates have been employed to identify cancer biomarkers at picomolar concentrations [49]. Aptamer-gold nanoparticle conjugates-based biosensors have been effectively integrated into various detection systems, including optical and electrochemical sensors. The distinct optical characteristics of AuNPs allow colorimetric detection in optical biosensing, in which the presence of the target analyte is indicated by a discernible colour shift. This is especially helpful for point-of-care diagnostics, where it is necessary to get results quickly and concisely [50]. Meanwhile, AuNPs improve the transport of electrons between the analyte and the electrode in electrochemical biosensing, hence enhancing sensitivity and reducing detection limit [51].

The high specificity of aptamers and the signal amplification performance of AuNPs results in the ability to detect very low concentrations of analytes and directly make them indispensable tools in biomedical research and environmental monitoring [52]. These aptamer-modified AuNP biosensors are also particularly pronounced in the development of point-of-care diagnostic devices due to their design to be portable, easy to use, and capable of providing rapid results. The integration of aptamer-AuNP conjugates have demonstrated remarkable potential in point-of-care applications for the detection of infectious illnesses, chronic condition monitoring, and even customized medicine, where prompt and precise biomarker identification can have a substantial impact on patient outcomes [53]. Therefore, further development and application of these technologies could transform point-of-care diagnostics and enhance global health outcomes.

**Trends and key findings across studies**

The selected articles of the scientific breakthroughs on aptamer-gold nanoparticle conjugates will be reviewed in this section, with a focus on the titles, year of publication, author origin, journal name, journal rank, and keywords used in the reported documents (Table 2). Aptamer-gold nanoparticle conjugates have been the subject of a growing number of publications in recent years, especially in 2022 (eight articles) and 2023 (six articles). This trend can be linked to variables related to scientific and technical advancements. Technological developments in the synthesis and functionalization of gold nanoparticles have simplified the process of manufacturing uniform, high-quality AuNPs and enabling highly sensitive interaction monitoring. Thus, significant scientific interest has been generated by these advancements as well as the various uses of AuNPs in targeted medication administration, medical diagnostics, and biosensing. Additionally, the multidisciplinary character of the discipline, which includes biology, chemistry, materials science, and nanotechnology, has also encouraged creative and innovative thinking in research, which has accelerated the rate of publication growth.

Due to substantial government funding and support, a strong emphasis on collaborative efforts between academia, industry, and research institutions and a robust research infrastructure, China has made a significant contribution (ten publications) to the research on aptamer-gold nanoparticle conjugates. Iran has made a significant contribution (eight articles) in the field of biotechnology and nanotechnology because of its strategic focus on these areas, government actions that support policy and provide financing and the establishment of robust academic programs in these areas. Global trends that have contributed to the overall growth in publications include the advent of open-access journals and increased international collaboration, which have made it easier to disseminate research findings more frequently and widely. In general, several important findings involving the deployment of AuNPs in biosensors using optical and/or electrochemical transducers might be drawn from the articles selected based on the keywords listed in **Table 2**. These results illustrate the variety and inventiveness of methods utilized to improve biosensor performance for different diagnostic applications.

The dual-signal output of the ratiometric aptasensors constructed by Shan and co-workers improves detection accuracy to target pathogens like Staphylococcus aureus. The use of DNAzymes in combination with MXene@Au NPs complexes can enhance sensitivity by catalytic signal amplification. MXene@Au NPs composites can serve as effective platforms for electrochemiluminescence (ECL)/ electrochemical aptasensors due to their excellent electrical conductivity and large surface area [54]. Next, an innovative, label-free electrochemi luminescence (ECL) aptasensor has been developed to accurately identify the allergen β-lactoglobulin (β-LG), which is present in milk proteins. The sensor generates signals by modifying a nanocomposite material and placing it onto a printed platform. This nanocomposite is made up of gold nanoparticles (AuNPs), graphene nanoplatelets (GNPs), and ruthenium complex $Rubpy_3^{2+}$ embedded in a Nafion matrix. As the luminophore, the Ru-AuNP combination emits ECL when it is electrically stimulated. The ECL intensity is modulated by the specific binding between the aptamer on the sensor surface and β-LG in the sample solution. This method provides a sensitive and possibly economical way to identify β-LG, which could be helpful in milk product quality control or in the diagnosis of food allergies [55].

As for article "Selection of specific aptamer against rivaroxaban and utilization for label-free electrochemical aptasensing using gold nanoparticles: First announcement and application for clinical sample analysis", it presents a novel label-free electrochemical aptasensor for the targeted detection of the blood thinner rivaroxaban [56]. The creation of a novel aptamer, a molecule with a strong affinity for rivaroxaban, is the primary innovation. Gold nanoparticles (AuNPs) are then combined with this aptamer to provide an extremely sensitive biosensor. When rivaroxaban binds to the AuNPs, the electrical signal is amplified, making low amounts of the drug detectable. This method offers a potentially useful tool for clinical monitoring of rivaroxaban therapy in human plasma and even breath condensate samples, marking a substantial advancement in drug bioanalysis. In biotechnology, the application of aptamers and sophisticated nanoparticles such as AuNPs opens the door to more sensitive and targeted biosensing technologies.

Kurnia Sari and co-workers successfully described the optimization of an electrochemical aptasensor for the detection of the SARS-CoV-2 Receptor Binding Domain (RBD) protein S, a possible COVID-19 biomarker. The developed sensor boosts its sensitivity by using a screen-printed carbon electrode that has been altered with gold nanoparticles (AuNPs). Three crucial factors were optimized by the researchers using a statistical method called Box-Behnken design: the concentration of the aptamer that binds RBD, the duration of aptamer incubation on the electrode, and the duration of RBD protein incubation. The aptamer on the electrode surface was rendered immobile by the linker molecule 3-mercaptopropionic acid. To gauge the sensor's response, they used differential pulse voltammetry, an electrochemical method. This enhanced aptasensor is a promising instrument for quick and on-site COVID-19 detection because of its benefits including portability and quick reaction [57].

In addition, a novel electrochemical AuNPs-aptasensor design for very sensitive HBV detection is shown. The platform makes use of a unique combination of materials: gold nanoparticles (AuNPs) functionalized onto reduced graphene oxide (rGO) prepared via Hummer's method. Strong gold-sulphur bonds allow AuNPs to promote aptamer attachment and give exceptional biocompatibility, while rGO functions as a conductive scaffold with a large surface area. The recognition element is the aptamer, a single-stranded DNA molecule with a high affinity for HBV antigens. The interaction between the aptamer and HBV is what drives the sensing mechanism. When the virus is not present, the sensor displays a robust electrochemical signal. Nevertheless, a conformational shift brought about by HBV binding to the aptamer results in a drop in signal. This method offers a favourable strategy for highly sensitive and specific revealing of HBV, potentially aiding in initial diagnosis and improved patient management [58].

The development of a label-free electrochemical aptasensor tailored to the detection of Tau381, a protein biomarker linked to Alzheimer's disease (AD) has been reported [59]. The sensor is based on a novel composite material consisting of gold nanoparticles, mediator thionin, and carboxyl graphene. The electrical signal is strengthened by this combination, which also offers a means of immobilizing the Tau381 aptamer. The signal from the differential pulse voltammetry (DVP) changes when Tau381 from the sample binds to the aptamer. This method provides a label-free and sensitive way to identify Tau381. The sensor's capacity to differentiate serum samples from AD and non-AD patients was proved by the researchers, who also attained an exceptionally low limit of detection. This raises up the way to a potentially effective tool for AD diagnosis in its early stages [59].

An innovative label-free colorimetric aptasensor for identifying immunoglobulin E (IgE), a biomarker implicated in allergic reactions, is described in a report published in the Analyst Journal. This sensor provides a more straightforward and possibly less expensive option than conventional techniques. A DNA pseudoknot probe is used as the primary means of recognition. The probe takes on a particular folded form that removes a capture probe from gold nanoparticles when IgE is not present. The pseudoknot, however, unfolds when IgE attaches to the aptamer probe, allowing the capture probe to hybridize with the aptamer. A noticeable shift in hue is the outcome of the agglomeration of gold nanoparticles caused by this hybridization. IgE can be detected with precision and sensitivity using this colorimetric reaction, even in biologically complex materials such as vaginal secretions. The approach holds promise for a more convenient and potentially point-of-care diagnostic tool for allergy assessment [60].

**Table 2**. A summary on the development of aptamer-modified AuNP biosensor of the included studies

| No. | Title | Year | Author's country | Journal Name | Rank JCR | Keywords | Ref. |
|---|---|---|---|---|---|---|---|
| 1. | A dual-mode ratiometric aptasensor for accurate detection of pathogenic bacteria based on recycling of DNAzyme activation | 2023 | China | Food Chemistry | Q1 | • Ratiometric aptasensor<br>• *Staphylococcus aureus*<br>• Electrochemiluminescence/electrochemical<br>• DNAzyme<br>• MXene@Au NPs | [54] |
| 2. | A label-free electrochemical aptasensor based on screen printed carbon electrodes with gold nanoparticles-polypyrrole composite for detection of cardiac troponin I | 2023 | Malaysia | IEEE Sensors Journal | Q1 | • Aptamer<br>• Cardiac troponin I (cTnI)<br>• Gold nanoparticle (AuNP)<br>• Label-free<br>• Polypyrrole (PPy) | [61] |
| 3. | Dual synthetic receptor-based sandwich electrochemical sensor for highly selective and ultrasensitive detection of pathogenic bacteria at the single-cell level | 2023 | China | Analytical Chemistry | Q1 | N/A | [62] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4. | Visual electrochemiluminescence biosensor chip based on distance readout for deoxynivalenol detection | 2023 | China | Analytical Chemistry | Q1 | N/A | [63] |
| 5. | A solid-state electrochemiluminescence aptasensor for β-lactoglobulin using Ru-AuNP/GNP/Naf nanocomposite-modified printed sensor | 2022 | Brunei | Microchimica Acta | Q1 | • Label-free ECL aptasensor<br>• β-Lactoglobulin (β-LG)<br>• Milk protein<br>• $Rubpy_3^{2+}$<br>• Graphene nanoplatelets · AuNP | [55] |
| 6. | Selection of specific aptamer against rivaroxaban and utilization for label-free electrochemical aptasensing using gold nanoparticles: First announcement and application for clinical sample analysis | 2022 | Iran | Biosensors (Basel) | Q1 | • Rivaroxaban<br>• Aptamer<br>• Aptasensor<br>• Bioanalysis of drugs<br>• Biotechnology advanced nanomaterial | [56] |
| 7. | Electrochemical aptasensor based on anisotropically modified (Janus-type) gold nanoparticles for determination of C-reactive protein | 2022 | Spain | Microchimica Acta | Q1 | • Aptasensor<br>• Amperometry<br>• Janus nanoparticles<br>• C-reactive protein<br>• Au nanoparticles<br>• Dendrimer | [64] |
| 8. | Gold nanostructures integrated on hollow carbon N-doped nanocapsules as a novel high-performance aptasensing platform for *Helicobacter pylori* detection | 2022 | Iran | Journal of Materials Science | Q2 | N/A | [65] |
| 9. | A new electrochemical aptasensor based on gold/nitrogen-doped carbon nano-onions for the detection of *Staphylococcus aureus* | 2022 | Iran | Electrochimica Acta | Q2 | • *Staphylococcus aureus*<br>• Electrochemical aptasensor<br>• Carbon nano-onion<br>• Gold nanoparticle | [66] |
| 10. | The optimization of an electrochemical aptasensor to detect RBD protein S SARS-CoV-2 as a biomarker of COVID-19 using screen-printed carbon electrode/AuNP | 2022 | Indonesia | Journal of Electrochemical Science and Engineering | Q3 | • Box-Behnken design<br>• 3-mercaptopropionic acid<br>• Differential pulse voltammetry<br>• Portability<br>• fast response | [57] |
| 11. | An innovative dual recognition aptasensor for specific detection of *Staphylococcus aureus* based on $Au/Fe_3O_4$ binary hybrid | 2022 | Egypt | Scientific Reports | Q2 | N/A | [67] |
| 12. | Label-free electrochemical aptasensor for the detection of the 3-O-$C_{12}$-HSL quorum-sensing molecule in *Pseudomonas aeruginosa* | 2022 | Romania | Biosensors (Basel) | Q1 | • Quorum sensing<br>• *Pseudomonas aeruginosa*<br>• Aptamer<br>• Electrochemical aptasensor<br>• Electrochemical<br>• Detection<br>• 3-O-$C_{12}$-HSL | [68] |

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| 13. | Gold nanoparticles anchored onto covalent poly deep eutectic solvent functionalized graphene: An electrochemical aptasensor for the detection of C-reactive protein | 2021 | Iran | Materials Chemistry and Physics | Q2 | • Deep eutectic solvents<br>• Gold nanoparticles<br>• Graphene oxide<br>• Polymerization<br>• Aptasensor C-reactive protein (CRP) | [69] |
| 14. | Design of aptamer-based sensing platform using gold nanoparticles functionalized reduced graphene oxide for ultrasensitive detection of Hepatitis B virus | 2021 | Iran | Chemical Papers | Q3 | • Hepatitis B virus<br>• Aptamer<br>• Electrochemical aptasensor<br>• Hummer's method | [58] |
| 15. | Amperometric aptasensor for carcinoembryonic antigen based on a reduced graphene oxide/gold nanoparticles modified electrode | 2020 | Spain | Journal of Electroanalytical Chemistry | Q1 | • Biosensor<br>• Carcinoembryonic antigen<br>• Graphene<br>• Gold nanoparticles<br>• Aptamer | [70] |
| 16. | A novel label free electrochemiluminescent aptasensor for the detection of lysozyme | 2019 | China | Materials Science and Engineering C-Materials for Biological Applications | Q1 | • Nitrogen-doped graphene quantum dots<br>• Electrochemiluminescence<br>• Aptamer<br>• Lysozyme<br>• Gold nanoparticle<br>• Electrochemical behaviour | [71] |
| 17. | Lateral flow aptasensor for simultaneous detection of platelet-derived growth factor-bb (PDGF-BB) and thrombin | 2019 | USA | Molecules | Q2 | • Lateral flow<br>• Aptamer<br>• Aptasensor<br>• PDGF-BB<br>• Thrombin | [72] |
| 18. | Aptasensor for quantifying pancreatic polypeptide | 2019 | Spain | ACS Omega | Q2 | • Aggregation<br>• Genetics<br>• Metal nanoparticles<br>• Peptides and proteins<br>• Serum | [73] |
| 19. | "Development of a label-free electrochemical aptasensor for the detection of Tau381 and its preliminary application in AD and non-AD patients' Sera" | 2019 | China | Biosensors (Basel) | Q1 | • Aptasensor<br>• Tau381<br>• Carboxyl graphene/thionin/gold nanoparticles<br>• Human serum<br>• Alzheimer's disease | [59] |
| 20. | Design and fabrication of an electrochemical aptasensor using Au nanoparticles/carbon nanoparticles/cellulose nanofibers nanocomposite for rapid and sensitive detection of *Staphylococcus aureus* | 2018 | Iran | Bioelectrochemistry | Q1 | • Au nanoparticles<br>• Carbon nanoparticles<br>• Cellulose nanofibers<br>• Nanocomposite<br>• Electrochemical aptasensor<br>• Staphylococcus aureus | [74] |
| 21. | Sandwich electrochemical thrombin assay using a glassy carbon electrode modified with nitrogen- and sulfur-doped graphene oxide and gold nanoparticles | 2018 | China | Microchimica Acta | Q1 | • Carbon materials<br>• Protein<br>• Aptamer<br>Signal amplification | [75] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 22. | Label-free colorimetric aptasensor for IgE using DNA pseudoknot probe | 2014 | China | Analyst | Q1 | N/A | [60] |

**The analytical performance of biosensors based on aptamer-gold nanoparticle conjugates matrices**

The techniques enumerated in **Table 3** demonstrate a broad range of capabilities with respect to stability, sensitivity, and applicability to different kinds of samples. The criteria of the application, such as the sample's composition, the required sensitivity, and the stability required throughout the analysis period, will determine which approach is best. Together, these elements support the creation of sensitive, accurate, and dependable detection systems in a variety of study and diagnostic domains. Every technique, from environmental monitoring to clinical diagnostics and food safety, has been customized to fulfil requirements. Stability, which denotes a detection method's ability to sustain performance and accuracy over time, is an essential characteristic of analytical procedures. The reliability of data over long periods of time can have a substantial impact on the interpretation and outcome of investigations, which makes this characteristic especially crucial in both research and clinical contexts. The practical utility of detection technology is directly impacted by its stability in routine diagnostic applications.

Extended stability techniques, for instance, guarantee that reagents and calibration standards do not need to be changed frequently in clinical laboratories where assays are performed on a regular basis. This lowers operating costs and minimizes downtime. This is particularly helpful in high-throughput settings where successfully managing massive numbers of samples depends on consistent performance. As an example, the techniques outlined in references: Eshlaghi and co-workers, Villalonga and co-workers, and Khonsari and Sun demonstrated stability for as long as 35, 32, and 34 days, in that order [61,64,71]. Extended durations of stability are suggestive of strong analytical methods capable of producing reliable deterioration, which makes it appropriate for quality control in the dairy processing industry.

The detection method in Hao and co-workers' research has a stability period of two weeks and a range of 1 to 300 ng $mL^{-1}$ with a LOD of 0.33 ng $mL^{-1}$ [63]. When used on peanut butter samples, this technique is essential for identifying allergens, which in sensitive people can result in severe allergic reactions. The identification of minute quantities of allergens in food items guarantees adherence to food safety guidelines and furnishes customers with precise details, thus promoting safer food selections. The technique used in research by Kurup and co-workers outcomes with minimal performance loss. When repeated measurements are made over lengthy periods of time, such as in longitudinal studies, this level of stability is quite helpful. For these investigations to properly monitor changes in the analyte concentration over time, performance consistency is essential. Any appreciable deviation in the precision of the procedure could provide incorrect conclusions and compromise the validity of the investigation.

Here, we go more deeply into these techniques' scientific underpinnings and ramifications. The detection method in Shan and co-workers' research has a very low limit of detection (LOD) of 1 CFU $mL^{-1}$ and covers a wide range from 0 to 108 CFU $mL^{-1}$ [54]. The stability of this approach, which can continue to work for up to 12 days, makes it ideal for applications involving food safety. The approach has been validated on actual samples, including milk, spinach, and frozen chicken, highlighting its usefulness in keeping an eye out for bacterial contamination in food items. The low limit of detection and wide detection range are very helpful in guaranteeing that even minute amounts of bacterial presence may be identified early on, averting possible foodborne disease outbreaks and maintaining public health. With a stability of 17 days and a detection range of 10 to 105 CFU $mL^{-1}$, the single bacterial cell analysis used in Lin and co-workers' study has a limit of detection of 10 CFU $mL^{-1}$ [62]. The dairy business, where bacterial contamination needs to be closely monitored to maintain product safety, is one of the settings in which this method's applicability is demonstrated using milk samples. Techniques that can separate and count individual bacterial cells, such as flow cytometry and fluorescence microscopy, enable the detection of low concentrations of bacteria. Due to its extended stability, samples can be examined over a lengthy period without experiencing appreciable has a very low limit of detection (LOD) of 0.02 pg $mL^{-1}$ and a very wide detection range (0.1 to 1000 pg $mL^{-1}$) with a 20-day stability [55]. Many milk-free products, such as Milo, green tea, milk-free biscuits, chocolates, fish crackers, milk-free cakes, and oats, have been screened using this method for β-lactoglobulin. This method's wide range and great sensitivity are essential for guaranteeing that items labelled as "milk-free" are devoid of milk proteins, accommodating those who have a lactose intolerance or allergy, and assuring product labelling compliance.

Analytes with LODs of 14.08 and 6.03 nM were studied by Ebrahimi and co-workers in relation to human plasma and exhaled breath condensate (EBC) [56]. The method's usage in medical diagnostics is obvious, even though precise detection range details are not given. These LODs' sensitivity is essential for finding biomarkers in physiological fluids, which helps with illness monitoring and early diagnosis. By providing a non-invasive diagnostic tool, the ability to evaluate exhaled breath condensate improves patient compliance and comfort. These techniques' sensitivity makes it possible to identify biomarkers early on, which is crucial for prompt illness diagnosis and treatment.

We compared the analytical performance of biosensors based on aptamer-gold nanoparticles with those employing non-aptamer approaches. Numerous studies have utilized non-aptamer approaches such as enzymes or antibodies as the biorecognition element for biosensor development. For example, Mansor et al. [76] used a tri-enzyme system for sepsis detection with a LOD of $5 \times 10^{-3}$ ng/mL, and Li et al. [77] used antibodies for cancer detection with a LOD less than 21.74 fM. In contrast, Tseng et al. [78] used an aptamer-based for sepsis detection with a LOD of 50 fg/mL, and Lim et al. [79] employed aptamer-based approach for cancer detection with a LOD of 0.1 ng/mL.

From these examples, we can conclude that biomolecules such as enzymes, antibodies, and aptamers demonstrate comparable levels of sensitivity and specificity in biosensor performance. However, enzymes and antibodies have certain limitations in terms of stability, cost, modification, and target range because proteins, enzymes and antibodies can lose activity or denature under harsh conditions such as high temperature, extreme pH, or prolonged storage. In contrast, aptamers which are synthetic nucleic acid molecules, are significantly more stable and maintain their functionality across a broader range of environmental conditions. Furthermore, the production of antibodies and enzymes typically relies on biological systems such as cell cultures or animals, which is time-consuming, costly, and susceptible to conduct. This definition is based on the criteria set by the World Health Organization. These criteria are summarized by the acronym "ASSURED," which batch-to-batch variability. Aptamers, however, are produced through chemical synthesis, allowing for rapid, scalable, and cost-effective manufacturing with high purity. In addition, chemical modification of antibodies and enzymes is often complex and limited, whereas aptamers can be easily and precisely functionalized with various groups for immobilization or signal generation, thus enhancing biosensor design flexibility. Finally, while antibodies and enzymes may have limited ability to detect small molecules, ions, or certain toxic substances, aptamers can be selected in vitro to bind a wide variety of targets, including those that are difficult for traditional protein-based recognition elements to address. These advantages make aptamers an increasingly attractive alternative in biosensor development.

**Current applications and limitations of biosensors based on aptamer-gold nanoparticles**

Aptamer-gold nanoparticles conjugate-based biosensors have gained significant attention across various fields for their sensitivity and selectivity in diverse detection applications including small molecules, toxins, and pathogens, with success in areas impacting public health and safety. By pairing aptamer with gold nanoparticles, these biosensors enable robust and versatile detection mechanisms. These conjugations will amplify the biosensor's signal and offer a highly sensitive and selective platform for detecting a wide range of analytes, from small molecules to complex pathogens. **Figure 2** visually represents the stepwise development of knowledge translation in aptamer-based biosensor technologies, from aptamer-gold nanoparticle conjugation to point-of-care diagnostic application. This schematic illustrates the integration of nanoscale molecular recognition systems with signal transduction platforms, emphasizing the shift from laboratory research to practical clinical diagnostics.

Point-of-care testing (POCT) is defined as medical diagnostic testing conducted at or near the time and place of patient care and must be completed within a day. POCT is low-cost analytical tools and easy to stands for Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free or minimal, and Deliverable to those with the greatest need [80].

**Table 3**. The analytical performance of biosensors based on aptamer-gold nanoparticle conjugates matrices reported

| Sample | Ref. | Detection Range | LOD | Stability |
|---|---|---|---|---|
| Frozen chicken, spinach, and milk sample | [54] | 5 to $10^8$ CFU mL$^{-1}$ | 1 CFU mL$^{-1}$ | 12 days |
| Human serum | [61] | 50 to 500 pg mL$^{-1}$ | 25 pg mL$^{-1}$ | 5 weeks |
| Milk and single bacterial cell | [62] | 10 to $10^5$ CFU mL$^{-1}$ | 10 CFU mL$^{-1}$ | 17 days |
| Peanut butter sample | [63] | 1 to 300 ng mL$^{-1}$ | 0.33 ng mL$^{-1}$ | 2 weeks |
| Milk products and milk-free products | [55] | 0.1 to 1000 pg mL$^{-1}$ | 0.02 pg mL$^{-1}$ | 20 days |
| Human plasma and exhaled breath condensate (EBC) | [56] | 10 to 500 nM | 14.08 and 6.03 nM | 10 consecutive cycles (in same day) |

| | | | | |
|---|---|---|---|---|
| Human serum | [64] | 10 pg mL$^{-1}$ to 1.0 ng mL$^{-1}$ | 3.1 pg mL$^{-1}$ | 32 days |
| Blood serum | [66] | 10 to 10$^{8}$ CFU mL$^{-1}$ | 3 CFU mL$^{-1}$ | 100 consecutive cycles (in same day) |
| Saliva | [57] | 10 to 50 ng mL$^{-1}$ | 2.63 ng mL$^{-1}$ | 30 days |
| Urine samples, microbiological growth media and microbiological cultures | [68] | 0.5 to 30 µM | 145 ng mL$^{-1}$ (0.5 µM) | N/A |
| Human serum | [69] | 0.001 to 50 ng mL$^{-1}$ | 0.0003 ng mL$^{-1}$ | 10 days |
| Human serum | [58] | 0.125 to 2.0 fg mL$^{-1}$ | 0.0014 fg mL$^{-1}$ | 3 weeks |
| Human serum | [70] | 20 pg mL$^{-1}$ to 2 µg mL$^{-1}$ (112 fM–11 µM) | 16 pg mL$^{-1}$ (90 fM) | 2 weeks |
| Human serum | [71] | 10 fM to 10 nM | 0.8 fM | 10 consecutive cycles (in same day) |
| Human serum | [72] | 1 nM–200 nM for both PDGF-BB and thrombin | 1.0 nM for PDGF-BB and 1.5 nM for thrombin | N/A |
| Human serum | [73] | 1−60 nM | 521 pM | N/A |
| Human serum | [59] | 1.0 pM to 100 pM | 0.70 pM | 21 days |
| Human serum | [74] | 1.2 × 10$^{1}$ to 1.2 × 10$^{8}$ CFU mL$^{-1}$ | 1 CFU mL$^{-1}$ | N/A |
| Human serum | [75] | 1.0 × 10$^{-13}$ M to 1.0×10$^{-8}$ M | 2.5 × 10$^{-14}$M | 2 weeks |
| Vaginal fluids | [60] | 1 to 25 nM | 0.2 nM | N/A |

*Concentration units in this table vary depending on the target analyte. CFU mL$^{-1}$ is used for microbial counts; pg mL$^{-1}$ and ng mL$^{-1}$ are used for protein or biomarker mass concentrations; nM and µM indicate molar concentrations. All values are reported as per the original studies.

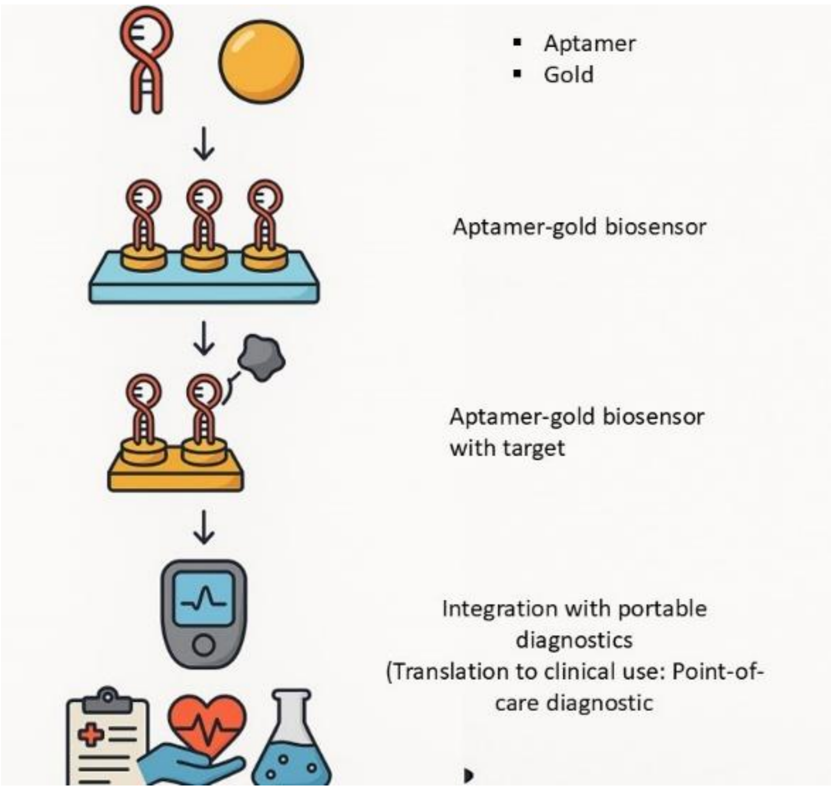


**Figure 2.** The illustration depicts the sequential process: conjugation of aptamers with gold nanoparticles, target recognition, signal generation, and final integration into portable point-of-care diagnostic devices

Gold nanoparticles exhibit unique optical properties that vary with their size, shape, and aggregation state due to their localized surface plasmon resonance (LSPR). In colloidal suspension, both dispersed and aggregated gold nanoparticles display strong extinction coefficients, enabling sensitive colorimetric detection visible to the naked eye. Typically, well-dispersed gold nanoparticles appear red in solution, whereas aggregation induces a shift in LSPR, leading to a distinct colour change from red to blue. The gold nanoparticles can amplify colorimetric signals, making them visible to the naked eyes, which is advantageous in point-of-care settings where rapid and accessible results are critical. Generally, in this colorimetric aptasensor, the unfolded aptamer adsorbs onto unmodified gold nanoparticles, stabilizing them and preventing salt-induced aggregation. Upon binding to its target, the aptamer undergoes a conformational change and detaches from the GNP surface, leading to GNP aggregation in the presence of salt. Only targets that induce a conformational change in the aptamer can be effectively detected using this strategy.

In medical diagnostics, aptamer-gold nanoparticles conjugates have been successfully used for detecting biomarkers associated with various diseases including cancer [49], cardiovascular diseases [61,69], kidney diseases [56] and infectious diseases [57,58,65]. For example, aptamer-gold nanoparticles conjugate-based biosensors are being developed to detect cancer biomarkers in blood or serum, allowing early diagnosis and real-time monitoring of disease progression. Similarly, aptamer-gold nanoparticles conjugate-based biosensors are being deployed for detecting viral [57] and bacterial pathogens, which is valuable in managing infectious diseases in both clinical and low-resource settings.

Aptamer-gold nanoparticles conjugate-based biosensors for environmental monitoring, offer sensitive detection of pollutants such as heavy metals [81], pesticides [82] and environmental pathogens [18], which are critical for accessing water and soil quality. The unique properties of aptamer and gold nanoparticles, allow the rapid, on-site detection of harmful substances, providing a valuable tool for environmental surveillance. This enables real-time, in field analysis, helping regulatory agencies and environmental organization to detect contamination events and monitoring ecosystem health.

In food safety, aptamer-gold nanoparticles conjugate-based biosensors have been applied for detecting contaminants such as toxins [19,48], allergens [55], and pathogenic microorganism [54,67,74]. Foodborne illnesses post significant public health risks and rapid, reliable testing methods are essential for ensuring food safety throughput the supply chain. Aptamer-gold nanoparticles conjugate-based biosensors are particularly suited for this purpose due to their high sensitivity and ability to deliver fast results, often without the need for complex equipment. By enabling real-time testing, these biosensors can help prevent outbreaks and improve food quality control processes, to protect consumers and supporting regulatory compliance.

Integrating aptamer–gold nanoparticle conjugate-based biosensors into real-world applications remains challenging due to issues related to stability, selectivity, reproducibility, and scalability. These limitations primarily arise from the intrinsic properties of both aptamers and gold nanoparticles. Aptamers, as single-stranded nucleic acids, are highly sensitive to environmental conditions such as temperature, pH, and ionic strength, making them prone to degradation under harsh conditions or during long-term storage. At the same time, gold nanoparticles are susceptible to aggregation, which can alter their optical and electronic properties, thereby compromising the stability and reliability of the sensor signal. To overcome these limitations, chemical modifications are often introduced to improve the stability of the aptamer–gold nanoparticles conjugates; however, such modifications may inadvertently affect the aptamer's binding affinity or specificity.

Moreover, while aptamers are designed to recognize specific targets with high selectivity, structurally similar molecules present in complex matrices such as blood or environmental samples can lead to cross-reactivity. This is further complicated by the presence of interfering substances that may disrupt aptamer–target interactions, potentially resulting in false-positive signals. Together, these factors underscore the importance of carefully optimizing aptamer–gold nanoparticles biosensors for robust performance in practical applications.

## Research gaps and future perspectives for improvement

### Comparative analysis of gold nanoparticle-based biosensors with traditional analytical techniques

A comparison between conventional analytical methods and aptamer-gold nanoparticle conjugate-based biosensors highlights several crucial areas that need to be developed to fully realize the potential of AuNP biosensors. These new biosensors still need to overcome some obstacles to compete with more well-established techniques like polymerase chain reaction (PCR), high-performance liquid chromatography (HPLC), and enzyme-linked immunosorbent assays

(ELISA). The standard was set by traditional methods, which are renowned for their great sensitivity and low detection limits. While PCR is superior at amplifying and identifying minuscule amounts of DNA, ELISA can detect analytes at concentrations of zeptomolar ($10^{-21}$) moles/assay [83]. Although biosensors based on aptamer-gold nanoparticle conjugates exhibit remarkable sensitivity, Léguillier and co-workers stated that consistent performance in intricate biological matrices still need further development [84]. The extensive validation and well-established protocols of classical techniques are among their main advantages. But these approaches frequently need drawn-out, multi-step processes, which adds to the turnaround times. As opposed to this, AuNP biosensors offer quick detection, normally in a matter of minutes, making them perfect for point-of-care diagnostics.

Research continues to focus on integrating these biosensors into automated ELISA-style high-throughput platforms that can manage various analytes and enormous sample volumes. Additionally, aptamer-modified AuNP biosensors may be more affordable and user-friendly, which qualifies them for environments with limited resources [85]. Conventional methods such as mass spectrometry and HPLC are costly and require specific training. AuNP biosensor development and improvement, however, can involve a significant investment of resources. To cut costs, research should concentrate on test designs. that are simpler and more scalable for production processes. Reagent stability is still another important consideration. Conventional methods frequently need very strict storage conditions, which might be constrictive. According to Díaz-García and co-workers, AuNP biosensors may provide more stability and less reliance on cold-chain logistics [86]. To validate their robustness, however, in-depth research on the biosensors' long-term stability under varied environmental circumstances is required.

Lastly, incorporating conventional methods into automated systems reduces human error and allows for high-throughput analysis. One of the biggest challenges still facing us is creating automated platforms that can integrate aptamer-modified AuNP biosensors seamlessly. The development of suitable systems and interfaces should be the top priority for research to improve the usability and practicality of these biosensors in field and clinical settings. In a nutshell aptamer-gold nanoparticle conjugates-based biosensors have several benefits over conventional analytical methods; yet there are still several unanswered questions. Important aspects include raising throughput, decreasing expenses, assuring environmental stability, enhancing sensitivity and specificity, improving reproducibility, creating automated integration techniques, and lowering prices. It will be possible for this potential biosensing technology to be widely adopted and applied with the help of targeted studies in these areas.

**Limitations and challenges associated with biosensors**

Although aptamer-gold nanoparticle conjugates-based biosensors have considerable potential for the sensitive and targeted detection of biomolecules, a number of important obstacles prevent their widespread use. The stability of AuNPs and aptamers is one of the main issues. Since aptamers are based on nucleic acids, they can be broken down by enzymes in biological samples, but AuNPs can oxidize or aggregate with time, losing their optical and electrical characteristics. To increase their stability and extend their useful life, techniques including surface passivation and chemical changes are being investigated.

The particularity of these biosensors is another important concern. Aptamers can nonetheless show cross-reactivity even when they have a high intrinsic specificity for their targets. This is particularly true in complex biological matrices like serum or urine, where other proteins may obstruct binding interactions. For increased specificity and fewer false-positive results, blocking agents, competitive assays, and improved aptamer selection procedures could be used. Another major challenge is ensuring repeatability of biosensors across multiple batches. Inconsistencies in sensor performance can impact sensitivity and reliability due to variations in aptamer synthesis techniques and AuNP production methodologies. Achieving consistent results and facilitating the comparability of data from many experiments requires standardizing synthesis techniques and putting strict quality control measures in place.

Furthermore, it is still a difficult challenge to include aptamer-gold nanoparticle conjugates into biosensors to produce useful devices appropriate for point-of-care diagnostics. The stability of the aptamer-gold nanoparticles conjugate is one of the challenges that need to be overcome. The environmental factors such as pH, ionic strength and temperature may weaken and disrupt the binding of gold nanoparticles-aptamer. Functionalizing gold nanoparticles with aptamers require a good surface chemistry to ensure that the aptamers are correctly oriented and accessible to the specified target. Overcrowding on the gold nanoparticles surfaces or incorrect aptamer orientation can reduce the binding efficiency.

Another main challenge is aggregation of gold nanoparticles. Gold nanoparticles tend to aggregate especially in the presence of salts or other ions in the sample. The aggregation of gold nanoparticles can change their size and reduce the surface area for the immobilization of aptamer. This situation can affect the detection signal and compromise sensor accuracy. Assuring device portability, durability, and usability, which are all crucial for use in clinical settings, presents challenges. Although there have been encouraging developments in portable detection systems that make use of these biosensors, practical deployment of these systems will depend on resolving challenges with sensor reliability and sophisticated data interpretation. Significant obstacles also stand in the way of commercialization and regulatory approval. Biosensors need to go through a rigorous validation process to meet regulatory standards for clinical usage. This process takes a significant amount of time and money. Cost-effectiveness and production scalability are also essential factors for their successful commercialization.

In summary, although aptamer-gold nanoparticle conjugates-based biosensors present remarkable potential for sensitive and specific biomolecule detection, their widespread use in biomedical research and diagnostics will depend on their ability to overcome obstacles pertaining to stability, specificity, reproducibility, device integration, and regulatory approval. To fully realize the potential of these biosensors to advance personalized medicine and enhance patient care, more research and innovations addressing these problems are required.

**Conclusion**

The review underscores the auspicious possibilities of aptamer-gold nanoparticle conjugates in biosensing, particularly with point-of-care diagnostics. Both optical and electrochemical biosensors have shown improved sensitivity and specificity by utilizing the special qualities of AuNPs. While electrochemical biosensors, which translate biological recognition events into electrical signals, offer simplicity and low cost appropriate for point-of-care applications, optical biosensors, which use mechanisms like absorbance and fluorescence, offer high sensitivity for detecting low-abundance targets. Aptamers and AuNPs work together to substantially enhance signal output, making it possible to detect extremely low analyte concentrations, which is a critical step in the early diagnosis of disease.

Notwithstanding these developments, issues with repeatability, stability, and specificity still need to be resolved if these biosensors are to reach their full potential. Enhancing these elements and creating standardized procedures for real-world application must be the main goals of further research. Aptamer-modified AuNP biosensors have enormous potential for developing extremely powerful diagnostic instruments that have a big potential to improve health around the world. Future attempts to get beyond present obstacles and accomplish wider applications in medical diagnostics will be guided by ongoing development and improvement.

**Declaration of competing interest**

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

**Credit authorship contribution statement**

Nur Syamimi Mohamad: Investigation, Conceptualization, Data curation, Formal analysis, & Writing-Original Draft. Eda Yuhana Ariffin: Supervision, Visualization, Validation, Writing-Original Draft, Review & Editing. Lee Yook Heng: Supervision, Writing-review & Editing.

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