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Cell-free arsenic biosensors with applied nanomaterials: critical analysis

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Abstract Arsenic is a ubiquitously found metalloid in our ecosystem because of natural and anthropogenic activities. People exposed to a higher level of arsenic become susceptible to several disorders, including cancer. According to current statistics, the population chronically exposed to arsenic has surpassed 200 million. Therefore, its detection in our environment is of great importance. There are many analytical techniques for the assessment of arsenic in different kinds of environmental samples. Among these techniques, the biosensor is considered a convenient platform and a widely applied analytical device for rapid qualitative and quantitative analysis in the field of environmental monitoring, food safety, and disease diagnosis. Today, there is a trend of including nanomaterials in sensors and biosensors because it empowers researchers to explore new arsenic detection methods and to enhance their analytical capabilities. In this review article, we summarized the latest developments in arsenic biosensors in particular with emphasis on the works based on cell-free approaches that are protein/enzyme-based, DNA-based, and aptamer-based utilizing various transduction platforms. In the meantime, we compared the capabilities that were related to these cell-free arsenic biosensors. This review article also highlights the development and application of novel nanomaterials for arsenic detection.

Keywords Arsenic detection · Cell-free biosensors · Protein-based · Nucleic acid-based · Aptamer-based · Nanomaterials

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Introduction

Arsenic (As) is a vastly toxic metalloid (semi-metal) that is deteriorating our environment (groundwater, soil, air) and health even in trace amounts (Hughes et al., 2011). It is present abundantly in nature, anthropogenic activities including the application of As-containing preservative on wooden electricity poles, fertilizers, pesticides, the release of untreated wastewater effluents, and oxidation of arsenopyrite and pyrite are also responsible for its wide occurrence in the ecosystem (Gumpu et al., 2015; Sarkar & Paul, 2016). The main problem in the treatment of As pollution is identifying the source of pollution as early as possible. Studies on As related to its effects on health and environment require the characterization of arsenic species having differing properties and toxicities. As toxicity varies highly due to its dependence on its chemical composition (inorganic or organic) and oxidation state (Ma et al., 2014). Although As exists in four pre-dominant oxidation states (−III, 0, +III, +V) in the environment, trivalent arsenite [As (III)] and

pentavalent arsenate [As (V)], in both oxidation states, As is highly toxic and common in groundwater.

Humans are exposed to As due to drinking groundwater from domestic wells, eating seafood, and eating crops that are grown in arsenic-contaminated soil (Sorg et al., 2014; Taylor et al., 2017). The facile uptake of As in the human body is responsible for the onset of several kinds of disorders such as cancer, neurological disorders, dermal diseases, cardiovascular and reproductive health problems, liver diseases, renal diseases, gastrointestinal disturbance, and fetal teratogenicity (Jomova et al., 2011). The maximum contamination level (MCL) in drinking water regulated by international organizations like the World Health Organization (WHO) and US Environmental Protection Agency (EPA) is 10 μg/L. Currently, in Asian countries that are As affected, the MCL of As in drinking water is 50 μg/L. Canada has reduced the MCL of As to 25 μg/L, and countries like USA and Australia have reduced the MCL to 5 and 7 μg/L (Ghosh et al., 2019). According to statistics, the number of persons chronically coming in contact with As (equals or more than the WHO threshold level) has surpassed 200 million. In more than 70 countries, including the USA, Australia, Canada, and India, some groundwater sources maybe containing As levels higher than the MCL. Most epidemiological data are from Argentina, Bangladesh, Northern Chile, and Taiwan, where As contamination is endemic (Minatel et al., 2018).

For quantitative analysis of As, analytical techniques developed in the last decades are electrothermal (or graphite furnace) atomic absorption spectrometry (Anawar, 2012), inductively coupled plasma-atomic/optical emission spectroscopy (Chen et al., 2009), inductively coupled plasma-mass spectroscopy (ICP-MS) (Entwisle & Hearn, 2006), gas chromatography-mass spectroscopy (Richter et al., 2012), anodic stripping voltammetry (Antonova & Zakharova, 2016), hydride generation-atomic fluorescence spectrometry (Sanchez-Rodas et al., 2010), hydride generation-atomic absorption spectrometry (HG-AAS) (dos Santos et al., 2017), and capillary electrophoresis (CE) coupled with ICP-MS (Liu et al., 2013). These methods have good sensitivity and selectivity, but still, required instrumentation may be expensive, and lengthy analysis times present restrictions for instant on-site identification of As. In comparison to these standard techniques, the biosensors designed for the detection of As are also highly selective and sensitive. Moreover, their results are approximately the same as the results that are obtained by these standard techniques such as ICP-MS.

The first biosensor was introduced by Clark and Lyons (1962) for measuring glucose. Since then, biosensing device has been implemented in the food industries for quality assurance and authenticity, in the assessment of environmental conditions, and medical fields (Vigneshvar et al., 2016; Mehrotra, 2016). The term biosensor represents an analytical device designed by a collaboration of biotechnology and microelectronics. Biosensors mainly include three main elements: a biorecognition unit, transducer, and an amplification unit as shown in Fig. 1 (Singh et al., 2008). Interaction of analytes with biorecognition unit occurs either by inhibition of some metabolic activity or by deforming the native structures of some crucial biomolecules such as DNA or Ag-Ab complex. The main result of these two strategies is either a decrease or an increase in the biochemical signal which is sensed with the help of a biorecognition unit and transformed into an intelligible signal by the transducer. Over the past decades, the number of literary reports on the construction of novel arsenic biosensors has increased exponentially. With the rapid progress in nanoscience, a growing number of researchers are showing interest in designing, synthesizing, and applying novel nanomaterials for experiencing extensive advancement in detection capability (Wu et al., 2019). The biosensor's performance (i.e., the limit of detection or linear range, etc.) is indirectly affected by the morphology or size of nanostructures, their method of preparation, and the principle of detection. Several novel nanomaterials are applied in recently developed arsenic biosensors. Although, few review articles are available based on the advancements in these nanomaterials for cell-free detection of As, outlining their operating principles and recent development (Mao et al., 2020; Kempahanumakkagari et al., 2017; Devi et al., 2019). This review article is structured in two segments elucidating cell-free biosensors and the modern nanomaterials for the identification and quantification of As. Lastly, this review article compares the overall performance of reported As biosensors to show the progress in the employment of nanomaterials.

Detection strategies of cell-free arsenic biosensors

Generally, the As biosensors are of two types, namely whole cell-based biosensors and cell free-based biosensors. In whole cell-based biosensor, the complete cell (e.g., bacteria) acts as a biorecognition unit. But

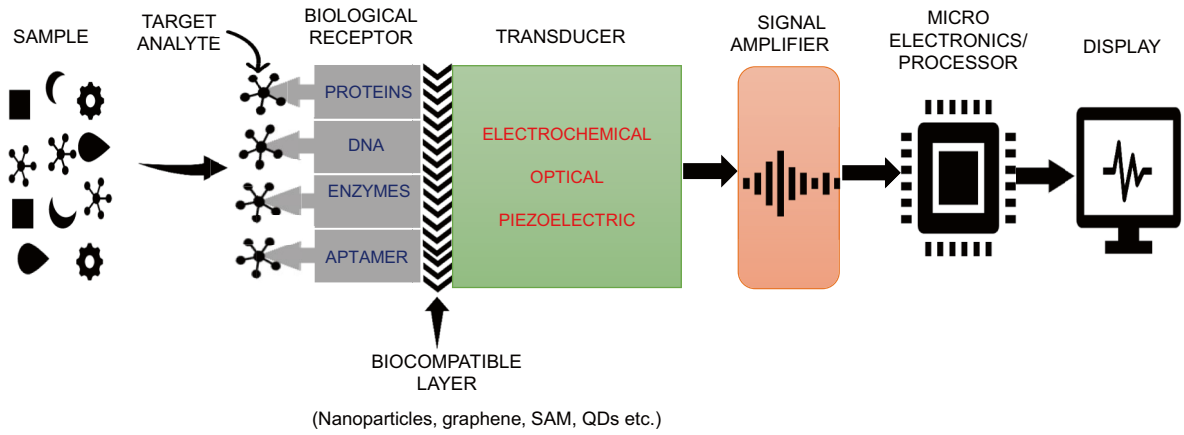

Fig. 1 Overview of biosensor concept

due to their drawbacks like non-reproducibility and practically non-feasibility, there is a requirement for some other alternative approaches, and cell free-based biosensors are emerging as new tools for the screening of hazardous environmental pollutants. The cell-free biosensors based have various advantages over cell-based biosensors. They are highly safe, highly tolerant, have quick response time, highly sensitive with low detection limit, highly stable by freeze-drying technology, and highly selective depending on type of bio-sensing elements. In cell free-based biosensors, proteins and DNA are preferred as a biorecognition element that could react with a target analyte and generate measurable signals through the transducer (Upadhyay et al., 2018; Chen & Rosen, 2014). Additionally, As (III) can also be detected using biomimetics like aptamer as a biocomponent (Kaur et al., 2015; Zhang et al., 2020a). This segment predominantly discusses the three different approaches based on biological components.

Protein/enzyme-based biosensors

Proteins such as metallothioneins (MTs), metalloproteins (cytochrome C), or enzymes are used as sensing components in arsenic biosensors because it is a well-known fact that metals like As [As (III)] can specifically bind with functional groups such as sulfhydryls or thiol groups present in them causing an alteration in their conformation or activity (Shen et al., 2013). The protein or enzyme-based approaches were adopted in the development of especially electrochemical (EC) As biosensors.

Metallothioneins (MTs) are ubiquitous proteins (found in animals, plants, eukaryotic, and prokaryotic microorganisms) with the capacity to bind heavy metal ions (mainly cadmium (Cd), zinc (Zn), or copper (Cu)) via metal thiolate clusters. The high content of cysteine (30%) and its occurrence in the polypeptide as Cys-Cys, Cys-X-Cys, and Cys-X–Y-Cys sequences (where X and Y are amino acids other than cysteine) are the reasons for the high-affinity towards metals in MTs. At low pH, MTs can form a coordination bond with As (III). Although, the reaction is slower compared with native metals (Zn or Cu) at neutral pH. The coordination bond present between Cd-MT and Zn-MT breaks below pH 3.5. As a result, metal-free apo-MT becomes available for the coordination with species of As. The detection technique based on MT does not require labeling. Also, it is possible to attain much higher sensitivity for lower concentrations of heavy metals as compared to cell-based devices with this technique. Recently, researchers for developing an inexpensive electrochemical biosensor based on metallothionein (MT) had shown great efforts for the detection of As and Hg (Irvine et al., 2017). Recombinant human MT 1a employed as a bioreceptor was physically adsorbed onto paper discs and deposited on SPCEs. This biosensor demonstrated the LOD of 13 µg/L for As (III) and 45 µg/L for Hg. The LOD was higher than the permissible limits for As (10 µg/L) recommended by the WHO. Anodic stripping voltammetry was the technique used

to detect the analytes. The unmodified disc exhibited As (III) peak at + 160 mV. But the sensitivity greatly enhanced with the MT-modified disc; the peak shifted to about − 60 mV. Hence, simply physically adsorbed protein onto the working electrode can enhance the signal without any expensive reagents and setups.

A simple biosensor was constructed by immobilizing Cytochrome C on a boron-doped diamond (BDD) electrode after the cleaning and activation with the help of nitric acid. This biosensor was applied to detect the trace level of As_2O_3 with the help of electrochemical impedance spectroscopy (EIS), square wave voltammetry (SWV), and cyclic voltammetry. The obtained detection limits were lower than the guidelines of WHO and EPA (Fuku et al., 2012).

Another biosensor was reported to estimate the quantity of arsenate by electrochemical method in drinking water. $_L$-cysteine (naturally occurring amino acid) was employed as a biorecognition component. Arsenate is reduced into arsenite by $_L$-cysteine, which itself oxidized into $_L$-cystine. This reaction resulted in electron transfer on the working electrode which produced a response that be measured amperometrically. Three types of sensing systems (S1, S2, S3) were applied. The S1 sensing system had a working electrode of carbon, S2 had glassy carbon, and S3 had platinum as a working electrode. All sensors can detect As below 10 µg/L with the LOD of 1.2–4.6 µg/L. The S3 shows the highest sensitivity. The developed biosensor is cheap, portable, and easy to handle by the layman (Sarkar et al., 2010).

In the case of enzymes, their catalytic centers play a crucial part in the catalysis of its substrate in redox reactions to generate an electron transport to the supporting electrode. Complexation can occur with ease between As ions and the functional groups of active centers that can cause rapid disruption in the catalytic center of an enzyme and induce weaker catalysis, which shows a decline in the obtained signal. Therefore, the changes in the response signal intensity can be used indirectly to determine inhibitor concentration (Amine et al., 2016). The basic working principle of a biosensor based on enzyme inhibition is depicted in Fig. 2. A similar approach was followed by Stotycheva et al. (1998) for the development of acetylcholinesterase (AchE)-based electrochemical biosensor to sensitively detect the As (III) and to differentiate As (III) and As (V) species. The working principle of this biosensor depends on the inactivation of enzyme acetylcholinesterase by the arsenate ions. The active center of acetylcholinesterase catalyzed the substrate acetylcholine iodide, resulting in the production of the electroactive compound thiocholine that provided the valid signal for the assessment of As (III). In the presence of As (III), thiocholine oxidation current decreased as a function of As (III) concentration. Another amperometric biosensor based on enzyme activity inhibition also due to As (III) was reported in the literature (Sanllorente-Méndez et al., 2010). Amperometric determination of arsenate ions was achieved by covalently immobilizing the AchE enzyme over the screen-printed electrode. This study encountered short storage stability (15 days) and non-specificity of the bioelectrodes at 4 °C. Last year, a new disposable amperometric biosensor for As (III) based on inhibition of AchE

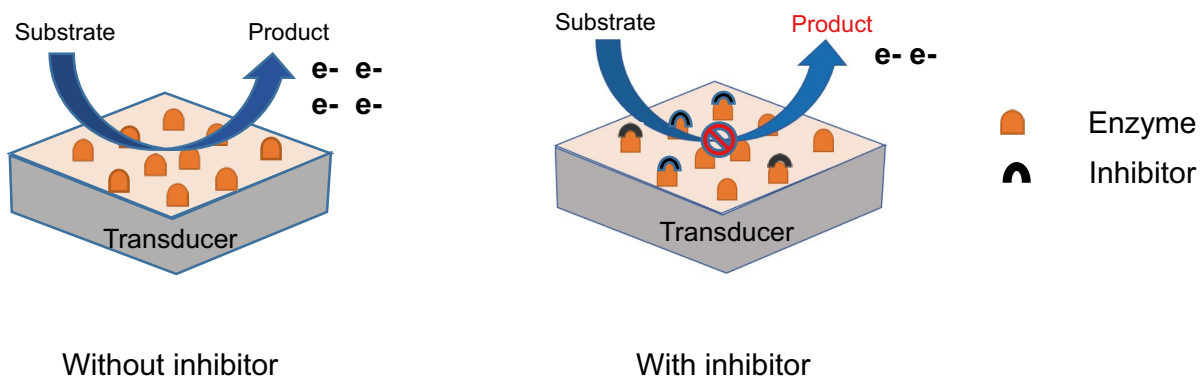

Fig. 2 Sensing mechanism of an enzyme-inhibition based biosensor

enzyme was developed that had shown a linear range of 0–1498 µg/L and LOD of 75–150 µg/L (Li et al., 2019). 4-Acetoxyphenol was used as a substrate that produces hydroquinone as a product after hydrolysis. They employed a carbon screen-printed electrode as a working electrode. The biosensor had shown stability for 150 days at room temperature.

Apart from this generally applied acetylcholinesterase, acid phosphatase (Sanllorente-Méndez et al., 2012), laccase (Wang et al., 2016), arsenite oxidase (Male et al., 2007; Hooda et al., 2021), and bi-enzyme system based on polyphenol oxidase-acid phosphatase (Cosnier et al., 2006) and acetylcholinesterase-acid phosphatase (del Torno-de Román et al., 2015) are employed in the development of As biosensors (Table 1). The average limit of detection (LOD) of these various arsenic biosensors using enzyme inhibition strategy is 1.0 µg/L to a few hundred ppb, and the lowest LOD can reach 0.015 µg/L.

However, most of these enzymes' inhibition-based As biosensors can only be applied a single time because As ions cause unrepairable damages in the enzymes. Apart from this, as discussed earlier, many other materials exert inhibitory effects on enzymes. Hence, biosensors based on enzyme inhibition typically exhibit very low specificity, limiting their succeeding applications in real environmental samples.

Nucleic acid-based biosensors

Due to the poor specificity of the enzyme inhibition-based biosensors, an improved approach for detection was required. In recent years, the application of nucleic acids as bioreceptor in biosensors for toxic compounds detection (particularly for metal ions) has enlarged considerably, as they have a higher affinity for nucleic acids (DNA/RNA) (Palchetti & Mascini, 2008). The association of nucleic acids with small molecules occurs mainly through three ways: noncovalent interactions with the nucleic sugar-phosphate structure having a negative charge, binding interactions with two grooves (major and minor) of dsDNA, and also by intercalation between the stacked base pairs. This association either results in positive or negative effects such as mutations or structural modifications. Heavy metal ions are present across the environment such as in water, food, soil, and plants. Hence, the study of the interaction between heavy metal ions and DNA is gaining considerable attention. Primarily, nucleic acid-based sensors provide signals after oxidative damage in DNA due to the presence of As. In the last decade, the first nucleic acid-based biosensor was constructed specifically to detect arsenic trioxide (Ozsoz et al., 2003). Arsenic trioxide intercalated into DNA and selectively interacted with guanine in DNA and has led to the oxidative damage in guanine and the formation of product 8-oxoguanine. This mutagenic product can be detected electrochemically. *Calf thymus* DNA (dsDNA and ssDNA) and 17-mer oligonucleotides were investigated as receptors with carbon electrodes as working electrodes and evaluated using differential pulse voltammetry (DPV) and potentiometric stripping. The detection limit was 1.0 mg/L. Another nucleic acid-based biosensor was designed by employing *Calf thymus* DNA attached on the surface of the screen-printed electrode (SPE) to detect the damaging effect of As compounds on DNA with the help of an electrochemical DNA marker $[Co(phen)_3]^{3+}$ and DNA oxidation catalyst $[Ru(bipy)_3]^{2+}$ (Labuda et al., 2005). The reported biosensor had shown an unsatisfactory limit of detection of 75,000 µg/L.

Several nucleic acid-based biosensors have been reported based on this similar strategy of oxidative damage in DNA. Nevertheless, biosensors based on these thick multilayers of biomolecules show limited sensitivity and not suitable for harsh experimental conditions.

A more advanced form of the nucleic acid-based biosensor was constructed for As (III) detection than the previous biosensors by Solanki et al. (2009). They utilized a self-assembled monolayer (SAM) because it forms a thin film and allows the rapid current flow. In their work, the double-stranded *calf thymus* deoxyribonucleic acid (dsCT-DNA) was immobilized onto a gold electrode. The surface plasmon resonance (SPR) technique had been employed for immobilizing bioreceptor (dsCT-DNA) and real-time detection of As (III). The LOD of a biosensor is as low as 0.01 µg/mL. But this biosensor also had limitations as it was difficult for field application and it had shown poor specificity for As (III).

The DNA is chemically more stable as compared to other biorecognition elements such as enzymes or proteins. However, biosensors based on DNA are often considered slow, and there is still a wide gap between the commercialization of DNA biosensors and DNA biosensors reported in the literature.

Table 1 Summary of various enzyme and protein-based arsenic biosensors

Analyte		Detection technique	Immobilization method	Substrate	Detection limit (µg/L)	Linear range (µg/L)	Sensitivity	Response time	Stability	Ref
As (III)	Acetylcholine esterase	Amperometric	Covalent linkage	Acetylthiocholine iodide	-	0.015 ± 75	-	-	-	Stotycheva et al. (1998)
As (III)	Acetylcholinesterase	Amperometric	Covalent linkage	Acetylthiocholine iodide	0.825	0.75–7.5	-	70 min	15 days	Sanllorente-Méndez et al. (2010)
As (III)	Acetylcholinesterase	Amperometric	Cross-linkage	4-Acetoxyphenol	75–150	0–1500	8.76 µA /mmol/L	-	150 days	Li et al. (2019)
As (V)	Acid phosphatase	Amperometric	Cross-linkage	Phenyl phosphate and 2-phospho-$_L$-ascorbic acid	8.25	-	-	70 min	-	Sanllorente-Méndez et al. (2012)
As (III) and As (V)	Laccase	Amperometric	Covalent linkage	2,2′-azino-bis (3- ethylbenzothiazoline-6-sulfonic acid)	974 As (III) and 9890 As (V)	-	0.91 ± 0.07 mV/mmol/L As (III) and 0.98 ± 0.02 mV/mM (As V)	-	.-	Wang et al. (2016)
As (III)	Arsenite oxidase	Amperometric	Electrodeposition	-	1		1.45 ± 0.06 nA/µg/L	10 s	.-	Male et al. (2007)
As (V)	Acid phosphatase-polyphenol oxidase	Amperometric	Entrapment	Catechol	0.15	5–592	-	-	-	Cosnier et al. (2006)
As (III) and As (V)	Acetylcholinesterase for As (III) and acid phosphatase for As(V)	Chronoamperometric	Cross-linking	Acetylthiocholine iodide and phenyl phosphate	2690 and 150	-	-	-	-	del Torno-de Román et al. (2015)
As (III)	Metallothionein	Anodic stripping voltammetry	Adsorption	-	13	-	-	-	-	Irvine et al. (2017)
As_2O_3	Cytochrome C	Cyclic voltammetry and square wave voltammetry	-	-	600 (CV) and 1650 (SWV)	0–0.3 (CV) and 0–750 (SWV)	2.1×10^{-8} A / µM (CV) and $1.9 \times 10.^{-8}$ A/µM (SWV)	-	-	Fuku et al. (2012)

Table 1 (continued)

Analyte		Detection technique	Immobilization method	Substrate	Detection limit (µg/L)	Linear range (µg/L)	Sensitivity	Response time	Stability	Ref
As(V)	L-Cysteine	Amperometric	Bulk in situ polymerization of acrylamide	-	1.7 for S1 4.6 for S2 1.2 for S3	-	-	-	-	Sarkar et al. (2010)

Aptamer-based biosensors

In recent years, a new class of biorecognition elements known as aptamers has been emerging. Aptamers are generally artificial and short stretches of ssRNA/DNA of approximately 15–100 nucleotides in length, and firstly they were reported by three individual groups (Ellington & Szostak, 1990; Tuerk & Gold, 1990; Robertson & Joyce, 1990). Aptamers exhibit several advantages over conventional bioreceptors like higher affinity, selectivity towards a wide variety of targets such as ions and complex molecules, lack of immunogenicity or toxicity, facile synthesis, and real-time monitoring. These features make aptamers a very promising bioreceptor in the field of biosensors. When a particular target analyte gets bound with its corresponding aptamer, then a signal is generated due to some structural modifications in aptamer. This signal will get transduced and converted into a comprehensible signal. Systematic evolution of ligands by exponential enrichment (SELEX) technology has been developed for the in vitro screening of aptamer having an excellent affinity towards a particular analyte. After this, the selected aptamers are ready to use as a biorecognition unit in an aptasensor for recognizing the target analyte. With the help of aptamers, numerous aptasensors with different signal transduction techniques such as EC, fluorometric, colorimetric, chemiluminometric, surface plasmon resonance (SPR), and resonance Rayleigh scattering (RRS) have been developed for As (Song et al., 2008). Ars-3 was the first DNA-based As specific aptamer reported by using SELEX (Kim et al., 2009). Several aptasensors based on colorimetric detection have been developed for the arsenic, using Ars-3 aptamer as a bioreceptor.

An aptasensor was developed by employing the hemin-peroxidase system for the colorimetric determination of As (III) (Wu et al., 2013). The working principle of this aptasensor was based on applying Ars-3 aptamer for inhibiting the catalysis of 3,5,3′5′-tetramethylbenzidine (TMB) by hemin, and this will result in the formation of cationic radical exhibiting blue color. The Ars-3 aptamer forms electrostatic interaction with hemin and reduces its catalytic activity. But in the presence of As (III), the aptamer Ars-3 forms a complex with As, which results in complete oxidation of substrate TMB by hemin and formation of diimine exhibiting yellow color. The LOD reported by this biosensor was

5.97 µg/L. In 2018, an As (III) biosensor was constructed, which has high sensitivity without any threat of indicator invalidation (Pan et al., 2018). This label-free fluorescence biosensor depends on an Exo III-assisted recycling amplification process. The triple helix molecular structure (THMS) generated by pre-hybridizing hair-pin shaped aptamer (flanked by two-arm segment) with signal transduction probe (STP) was applied as bioreceptor of As (III). ATMND/HP1 complex stays stable due to As (III) absence because THMS remains turned off, and STP was also bounded. So, Exo III was not able to digest it. Hence, it had exhibited low fluorescence. After the addition of As (III), ATMND/HP1 complex gets digested by Exo III, which results in the release of ATMND, STP, and secondary STP analog. This initially released STP and secondary STP analog begin a new cycle by recycling and hybridizing with another complex and producing a high amount of free ATMND with more fluorescence in the next round. This biosensor shows a LOD of 0.005 µg/L, much lower than reported by other methods such as electrochemistry and colorimetry. In the same year, an electrochemical As (III) aptasensor was produced, using a strategy based on EC signal amplification carried out by hybridization chain reaction and $RecJ_f$ exonuclease reaction (Gu et al., 2018). In this biosensor, immobilization of a DNA probe (CP) and another DNA probe (AptH0) containing As (III) specific aptamer sequence on the Au electrode results in the significant enhancement of charge transfer resistance (R_{ct}). If As (III) was present, it specifically interacted with As AptH0, and dsDNA duplex dissociated. And then, the released HCR product brings a significant reduction in R_{ct}, which further increased due to digestion catalyzed by $RecJ_f$ exonuclease. The biosensor exhibits a broad linear range from 0.1 to 200 µg/L and a LOD of 0.02 µg/L.

Another As (III) aptasensor based on the electrochemical method of detection was developed by Vega-Figueroa et al. (2018). They use electrochemical impedance spectroscopy (EIS) to study interfacial properties and performance of As (III) aptasensor. The gold electrode was modified with SAM of As specific aptamer (developed by Kim et al., 2009). Due to the binding of As, there was a change in conformation at the interfacial layer. This signal was recorded and linearly correlated with the As (III). However, this EC aptasensor had a higher LOD (60 µg/L) than optical aptasensors.

The aptamer-based biosensors have fewer limitations as they are more reliable than whole-cell and previously mentioned cell-free biosensors. In combination with microfluidics, aptamers are very helpful in developing miniaturized devices, e.g., lab on a chip.

Advanced nanomaterials in the fabrication of arsenic biosensors

Nanomaterials have provoked an intensive curiosity among researchers of the various disciplines of analytical chemistry because of their superior characteristics (e.g., large surface area, excellent conductivity, absorption or emission of light, tunable surface structures, high mechanical strength, and magnetism). The implementation of nanomaterials in the monitoring of environmental toxicants like heavy metals has grown rapidly over the last few years. A considerable amount of research literature is available on the application of nanomaterials in the development of biosensing devices for the analysis of As. In the development of EC biosensors, nanomaterials can be utilized as catalysts to increase the rate of reactions or as molecular wires for enhancing the transfer of electrons. In the optical sensing system, nanomaterials are applied mainly as optical probes for developing novel biosensors. In separation techniques such as chromatography, nanomaterials are often applied as stationary phases or adsorbents. Moreover, in solid-phase extraction (SPE), the application of magnetic nanomaterials can save time during the preparation of the sample, which is generally considered as a most exhausting step of environmental analysis (Kumar et al., 2017; Holzinger et al., 2014).

Herein, recently reported nanomaterials for As detection are briefly discussed (illustrated in Fig. 3). Most of the nanomaterials mentioned in this review article can also be employed in biosensors that are developed for the detection of other heavy metals ions. In biosensors, nanomaterials are also capable of providing binding sites for the immobilization of bioreceptors via covalent bonds. Generally, to attain lower LODs in arsenic biosensors, a nanomaterial with a higher surface area is applied so that it can provide more binding sites for immobilization of enzyme, DNA, or aptamer. Due to this, more response signals are generated as a result of an increased reaction between arsenic ion and enzymes, DNA, or aptamer.

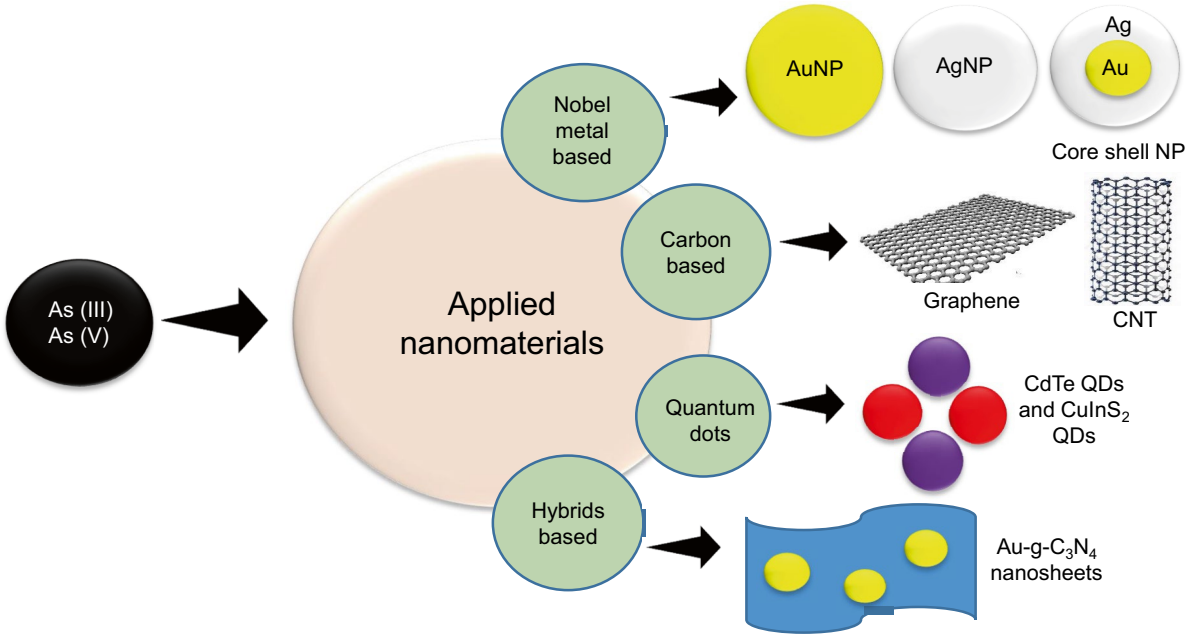

Fig. 3 Schematic illustration of applied nanomaterials in arsenic detection

Noble metal-based nanomaterials

Nanomaterials based on noble metals, such as gold (Au), silver (Ag), and platinum (Pt), are well known for their application in environmental analysis. Their interesting properties such as high catalytic activity and good electrical conductivity make them ideal for strengthening the response signals in biosensors for heavy metal ion detection. Although, noble metal-based nanomaterials have been well studied. Research in designing new morphologies of nanomaterials by controlling their nanostructures is gaining considerable attention for increasing their functional properties.

Gold nanoparticles (AuNPs) are most commonly utilized among other noble metal-based nanoparticles in the development of arsenic biosensors (Fig. 4). Colorimetric aptasensor was developed for the detection of As (III) based on an aggregation of AuNPs by cationic polymer (cetyltrimethylammonium bromide, CTAB) (Wu et al., 2012a). In their work, they synthesized AuNPs by the citrate reduction method. AuNPs of varying sizes were synthesized by combining different concentration ratios of trisodium citrate and $HAuCl_4$ in a controlled manner. The working principle depends on the aggregation of AuNPs, controlled by interactions among the Ars-3 aptamer, CTAB, and target [As(III)]. In the absence of As(III), the CTAB gets exhausted after interacting with the Ars-3 aptamer to form supramolecule. As a result, AuNPs do not aggregate. But in the presence of As(III), the Ars-3 is consumed in the development of an aptamer–As(III) complex. After this, subsequent addition of CTAB leads to aggregation of AuNPs, which results in notable variations in resonance scattering (RS) intensity and absorbance. This biosensor has shown high specificity among other metal ions and good recovery. The biosensor exhibited a linear range of 1–1500 µg/L for As (III) and LOD of 0.6 µg/L (by colorimetric method).

Resonance Rayleigh scattering (RRS) method-based aptasensor was reported for As(III) detection (Tang et al., 2014). They utilized aptamer modified with nanogold as a sensing probe. The nanogold was prepared by chemical reduction of $HAuCl_4$ with $NaBH_4$. During the absence of As(III), the nanogold particles interact with aptamer (ssDNA) and produce the Au–aptamer probe stable at high salt concentration. Contrarily, in the presence of As (III), Au–aptamer interacted with As(III) and resulted in the formation of As(III)–aptamer complex, and nanogold is released. Due to the high concentration of NaCl, these nanogold particles get aggregated into

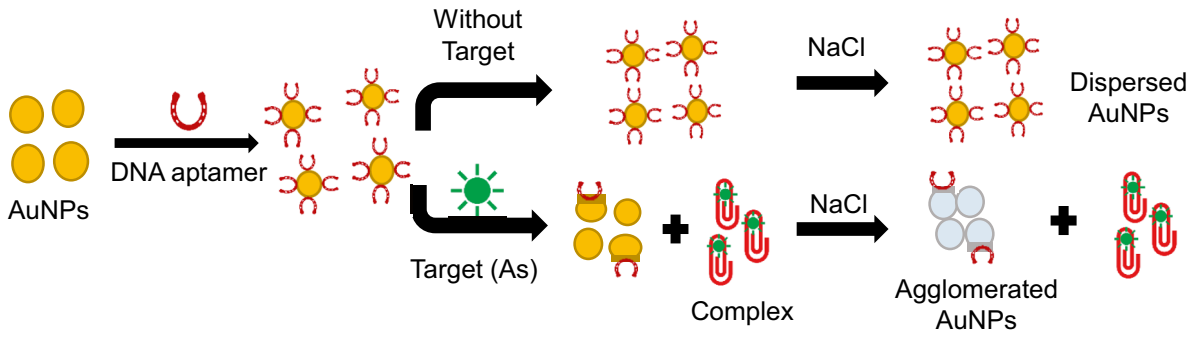

Fig. 4 Principle of gold nanoparticles-based aptasensor for arsenic

large aggregations, which results in enhancement of RRS intensity. This aptasensor based on the RRS technique was used, for detecting As (III) in water samples. This biosensor exhibited a linear range of 3.8–230.4 µg/L and LOD of 1.9 µg/L. Another colorimetric biosensor based on aptamer and AuNPs was developed for detecting As (III) in an aqueous solution (Zhan et al., 2014). In their study, As specific aptamer acts as a sensing probe and AuNPs as an indicator for colorimetric detection. This colorimetric assay has a concentration range of 1.26–200 µg/L and LOD of 1.26 µg/L. In the absence of As (III), the AuNPs displayed a solution of red color. The gold nanoparticles become aggregated in the presence of As (III), due to the formation of a complex between the aptamer and As (III), and thus produced a blue color solution. This colorimetric assay mainly depends on common reagents, and the presence of arsenic can be detected visually. Therefore, it holds great potential for monitoring arsenic in fields related to the environment and others.

Silver (Ag), another noble metal, is often incorporated in the construction of biosensing devices for detecting the levels of heavy metal ions. An As (III) aptasensor was developed by conjugating with AgNPs for colorimetric detection based on response surface methodology (Divsar et al., 2015). The AgNPs are prepared by chemical reduction of $AgNO_3$ with sodium borohydride ($NaBH_4$), and polyvinylpyrrolidone (PVP) was added to prevent their aggregation. The colorimetric detection was performed by recording UV–vis spectra with varying concentrations of As(III) ions, which interact with Apt–AgNPs to form a complex As(III)–Apt–AgNPs. This complex results in a decrease in the absorbance peak of AgNPs at 403 nm. The linear dynamic range of this colorimetric sensor was 50–700 µg/L, and a detection limit of 6 µg/L was obtained.

However, the application of Ag is less as compared to Au, due to its more reactive nature and weak stability than Au. To fix these defects, Ag is often utilized in combination with other metals to form various core–shell nanostructures. Core–shell nanoparticles exhibit higher electrocatalytic activity as compared to gold or silver nanoparticles alone. The first novel biosensing system was reported by employing Au@Ag core–shell nanoparticles for detection of As(III) based on aptamer and surface-enhanced Raman scattering (SERS) (Song et al., 2016). In their study, Au@Ag core–shell NPs were synthesized using seed growth technique. Firstly, AuNPs of 30 nm were prepared by reducing $HAuCl_4.3H_2O$ with trisodium citrate, and they are called seed particles. Afterward, $AgNO_3$ and trisodium citrate were added, and then this solution was boiled to prepare well-dispersed Au@Ag core–shell NPs, and then they were allowed to cool down at room temperature. 4-mercaptobenzoic acid (4-MBA) was employed as a SERS reporter molecule. Both 4-MBA and aptamer were absorbed on core–shell NPs. Upon addition of the As (III), the aptamer was displaced from Au@Ag, due to which the core–shell NPs get aggregated. As a result, the response of 4-MBA had increased. This biosensor shows an excellent linear range from 0.5 to 10 µg/L with a LOD of 0.1 µg/L, and the results also display that other ions are not interfering with As (III) detection.

Carbon-based nanomaterials

Carbon-based nanomaterials, such as carbon nanotubes (one dimensional), graphene (two-dimensional), have a wide range of applications in several biosensing fields due to their unique physical and chemical properties. In 1986, researchers successfully isolated the first carbon-based nanomaterial known as buckminsterfullerene (i.e., C_{60}) (Kroto et al., 1985). All carbon-based nanomaterials have similar elemental compositions (sp^2 bonded graphitic carbon). However, their various properties are mainly dependent on their nanostructures.

In the construction of arsenic biosensors, one of the earliest applied carbon-based nanomaterials were CNTs. Male et al. (2007) utilized multi-walled CNTs for developing As (III) biosensor based on the chronoamperometry (electrochemical) strategy. This biosensing scheme employed arsenite oxidase, which was deposited onto the active surface of a multiwalled carbon nanotube modified glassy carbon electrode (GCE), and it is specific for As(III) with a detection limit of 1.0 µg/L. This biosensor was applied for the estimation of As(III) in real water samples.

Wang et al. (2015) developed an electrochemical biosensor for label-free detection of As(III) by employing ssDNA functionalized SWCNTs. In their procedure, firstly, the complexes of ssDNA/SWCNTs were formed by allowing ssDNA to wrap SWCNTs via π-stacking. Upon addition of As(III), it was easily bound to G/T bases in ssDNA. Consequently, there was a decline in π–π interaction of ssDNA and SWCNTs, resulting in the dissociation of a certain amount of ssDNA from the complexes. These dissociated SWCNTs were selectively assembled on the Au electrode modified with SAM of 1-octadecanethiol. This assembly of SWCNTs restores efficient electron transfer between electroactive species and electrodes. The assembled SWCNTs could generate a considerably specific and sensitive strategy for signal transduction correlated to the As (III) concentration. Through this SWCNT-based biosensor, a LOD of 0.5 µg/L was achieved, and it represents a simple non-radioactive route for determination of As(III). Additionally, it provides a new method for the fabrication of biosensors with favorable electrochemical properties.

Graphene, another very popular and widely applied carbon-based nanomaterial, was invented by Geim. In 2014, he also won Noble Prize for it. Graphene has been utilized almost in every scientific field (Liu et al., 2015). Kumar et al. (2016) developed an electrochemical biosensor that is highly sensitive in the identification of arsenic. They employed ultra-thin nanosheets of graphene oxide (GO) and L-leucine as bioreceptor. The nanosheets of GO were synthesized by mixing graphite flakes and potassium permanganate in H_2SO_4/H_3PO_4 solution with constant stirring at 50 °C overnight. After this, the temperature of the mixture was brought down at room temperature and then filtered. This filtrate was centrifuged to obtain the pellet, and, then this pellet was further dried under vacuum. Finally, the fine powder of graphene oxide was obtained. The working electrode leucine/GO/Nafion/Au, together with Pt wire as a counter electrode and Ag/AgCl as a reference electrode, form the complete electrochemical biosensor. This fabricated biosensor exhibited a LOD of 500 µg/L. The improved sensing performance was enhanced due to the high surface-to-volume ratio and increased transfer of electrons between the electrode and L-leucine modified GO. It also demonstrated that there was no interference due to other common heavy metal ions that are present in water. As a result, it can efficiently apply in the routine examination of drinking water.

Although the carbon-based nanomaterials possess high electrical conductivity, which is beneficial regarding electron transfer, their weak catalytic activity remains a hurdle in further enhancement of detection performance of arsenic. Hence, to further increase the performance of carbon nanomaterials, these are often combined with other catalytic materials to build various composite nanomaterials.

Quantum dots

In the past decade, researchers are making great efforts in decreasing the dimensions of nanomaterials, i.e., from 3D to zero-dimensional, so that they can achieve novel properties for the enhancement of performance. Quantum dots (QD) are semiconductor crystals of the nano-meter scale and zero-dimension. Recently, QDs have attracted considerable attention owing to their unique electronic and optical properties including wide absorption band, high surface area, high photochemical stability, high molar

extinction coefficient, and excellent biocompatibility. They are considered a better alternative to traditional fluorophores in various fields, including environmental monitoring (Pu et al., 2018). The luminescent QDs were first utilized for constructing optical sensors (Frasco & Chaniotakis, 2009).

A highly sensitive and simple aptasensor was designed based on fluorimetric detection of As(III) based on cysteamine stabilized CdTe/ZnS QD aggregation (Ensafi et al., 2016). In this technique, an arsenic specific aptamer was utilized for aggregation of cationic cysteamine-stabilized CdTe/ZnS QDs. As a result, the fluorescence intensity was quenched. Cysteamine-stabilized CdTe QDs were prepared by sodium tellurite (as Te source) and a facile one-pot approach. The addition of As (III) leads to the formation of a complex between the aptamer and As(III), due to which the aggregation of QDs is prevented. Later, upon the de-aggregation of QDs, the fluorescence intensity of QDs was enhanced, depending upon the As(III) concentration. This fluorimetric biosensor demonstrated a very low LOD of 9.75×10^{-5} µg/L. The effect of interference due to other ions was also investigated, and obtained results confirmed the high specificity of this biosensor for As(III) detection. It was also successfully applied in several natural water samples.

A fluorescent nanosensor for As (III) detection was reported based on water-soluble green luminescent $_{L}$-cysteine capped CdTe QDs that were prepared using a microwave-assisted technique (Vaishnav et al., 2017). In brief, the NaHTe solution that was prepared from sodium borohydride and tellurium powder was injected into Cd^{2+} precursor solution (prepared from $_{L}$-cysteine and cadmium acetate). As a result, the color of the solution becomes yellow from colorless. The reaction mixture was irradiated with microwave radiation to produce green luminescent CdTe QDs. The QDs were precipitated and purified by adding an equal amount of acetone, followed by centrifugation. The $_{L}$-cysteine has a strong affinity towards As. Therefore, the addition of varying and increasing concentrations of As in purified $_{L}$-cysteine capped CdTe QDs results in a gradual decrease in their fluorescence intensity. The constructed label-free fluorescence nanosensor demonstrated a very good linear relationship with varying concentrations of As that ranges from 0.15 to 37.5 µg/L with a detection limit of 0.15 µg/L. QDs are very popular and one of the latest kinds of nanomaterials in the development of biosensor. As mentioned earlier, they have fascinating optical properties that will be beneficial for photoelectrochemical and electrochemiluminescence applications. However, the major obstacles in their further applications are the cost of synthesis, toxicity, aggregation of QDs, and loss of activity because of extremely smaller sizes.

Hybrid nanomaterials

As a valuable extension in nanotechnology, hybrid nanomaterials are becoming popular. The hybrid nanomaterials comprise either inorganic-inorganic, organic–inorganic, or organic-organic components. They have superior properties due to the combination of properties of both these components. Several hybrid nanomaterials are applied in electrochemiluminescence biosensors, as they possess both optical and electrochemical properties. However, As biosensors based on hybrid nanomaterials are relatively scarce. Some examples of As biosensors based on novel hybrid nanomaterials are discussed.

An ECL indicator-based assay for ultrasensitive As (III) detection was developed (Liang et al., 2018). Gold nanoparticles-graphitic carbon nitrite nanosheets (Au–g-C_3N_4 NSs) were used as luminophores or ECL indicators. Graphitic carbon nitrite is considered a highly stable allotrope of carbon nitride that has excellent chemical and thermal stability. The principle of this ratiometric biosensor depends on the combined quenching effect of As (III) and Ruthenium(II) tris-(bipyridine) [$Ru(bpy)_3^{2+}$] on ECL emission of Au–g-C_3N_4 NSs and simultaneous production of second ECL signal of $Ru(bpy)_3^{2+}$ with greater intensity. As a result of this dual quenching effect, the sensitivity and selectivity of the biosensor are greatly enhanced. The ultrathin nanosheets of g-C_3N_4 were prepared by the green liquid exfoliation route reported in the literature (Zhang et al., 2013). A novel nanosensor for As(V) was reported by using the "turn off–on" feature of ssDNA-$CuInS_2$ QDs@Fe_3O_4 NPs for the first time based on fluorescence detection (Liu et al., 2015). In their research, they prepared iron-oxide (Fe_2O_3) nanoparticles by co-precipitation method and ssDNA-$CuInS_2$ by hydrothermal method. As(V) exhibit strong adsorption onto Fe_2O_3 magnetic nanoparticles. In the absence of As(V), the ssDNA-$CuInS_2$ QDs@Fe_3O_4 NPs system had weak

fluorescence intensity. If As(V) was added, then the fluorescence was restored. This sensor indicates great potential in the monitoring of arsenate in the environment as it can be removed from the surrounding solution with the help of a magnet. Recently, Zhou and Tang (2018) designed a portable aptasensor for As(III) using GO gated MCM-41 type mesoporous silica nanocontainers (MSNs) with glucometer readout. The MSNs are synthesized by the co-condensation method reported in the literature (Zhang et al., 2017). In their research, the aptamer was first attached to MSN. After this, molecules of glucose (indicator) were gated into pores of MSN with the help of nanosheets of GO. When As(III) was added, it reacts with aptamer, and GO gets displaced from MSN due to which pores get exposed and molecules of glucose were discharged which can be evaluated with a portable glucometer. This method showed high selectivity among other ions.

Table 2 represents the summary of several other examples of advanced As biosensor based on nucleic acid and on various types of nanomaterials.

Evaluation of natural samples by As biosensors

For evaluating the stability and reliability of various cell-free As biosensors developed on different approaches, many reported biosensors were also tested for detecting of As in real samples. The following are the results of some recently reported cell-free arsenic biosensors that adopted natural water samples (from rivers and lakes) for evaluation.

Recently, a voltammetric biosensor for As (III) in water samples (tap water, river water, and lake water) was developed (Wen et al., 2017). The Au electrode was modified with an As specific binding ssDNA, capture probe DNA, and methylene blue (MB-indicator). On the addition of As (III), it displaces As-specific DNA that results in a decrease in the peak of methylene blue that was correlated to the concentration of As. The developed biosensor showed a LOD of 0.075 µg/L. The results had shown good accuracy as compared with ICP-MS. This strategy can also be used for other heavy metal ions.

A novel aptasensor based on simple and sensitive colorimetric detection of As(III) by employing CTAB and AuNPs was developed (Nguyen et al., 2018). This aptasensor exhibited a linear range from 1 to 100 µg/L and LOD of 16.9 µg/L for real samples. The working principle behind this aptasensor depends on the formation of a complex between aptamer and As ions, and then the addition of CTAB results in supramolecule formation. The AuNPs get aggregated due to the supramolecule, which results in a visual change.

An electrochemical biosensor was fabricated for the detection of As (III) by employing GO-assisted generation of Prussian blue NPs (Wen et al., 2018). Prussian blue NPs act as a redox signal probe. The developed biosensor was applied in real samples (tap water, river water, and lake water). The results obtained by this biosensor corresponded well with the results that were obtained via inductively coupled plasma mass spectrometry (ICP-MS).

Baghbaderani and NoorBakhsh (2019) reported a novel biosensor for As(III) based on colorimetric and impedimetric detection. They applied three approaches. Firstly, an electrochemical aptasensor that exhibited LOD of 0.058 µg/L, second electrochemical aptasensor with signal amplification that exhibits LOD of 0.0055 µg/L, and lastly an optical aptasensor with signal amplification that showed LOD of 0.45 µg/L electrochemical detection. The developed biosensor was tested for real samples (drinking water and industrial wastewater), and the results were compared with the HG-AAS. There is good agreement between these two techniques. Siddique et al. (2018) developed a smartphone-based optical aptasensor to detect As(III) in a spiked soil sample, demonstrating a LOD of 710 µg/L. This aptasensor is portable, reproducible, and reliable. The results are comparable with the standard ICP-MS technique. However, it is not applied in real samples yet.

Summary and challenges

The review abridged the research literature on recent progress in As biosensors based on cell-free approaches and the application of advanced nanomaterials in their construction. The detection principles behind different strategies, namely protein or enzyme inhibition-based, DNA-based, and aptamer-based, have been studied carefully to discuss their benefits and limitations. Diverse varieties of nanomaterials applied in As recognition have been elucidated with

Table 2 Various DNA, aptamer, and nanomaterials-based arsenic biosensors

Analyte	Biosensor description	Nanomaterials (NMs)	Preparation method of NMs	LOD (µg/L)	Linear range (µg/L)	Ref
Arsenite	Aptasensor based on SPR	Au-doped carbon dots	Hydrothermal reaction method	0.01	0.025–0.75	Zhang et al. (2020b)
	Liquid crystal-based aptasensor	Liquid crystals	_	3.75	_	Nguyen et al. (2020)
	DNA-based ECL biosensor	Polydopamine nanospheres	Oxidation and self- polymerization reaction	$1.2\times10.^{-3}$	$2\times10^{-3}\sim2\times10.^{3}$	Zhu et al. (2020)
	Aptasensor based on fluorescence detection	Zn_2GeO_4:Mn Nanorods	Chemical synthesis method	0.5	1–50	Chen et al. (2020)
	Aptasensor based on fluorescence detection	Magnetic beads	_	0.00015	0.00075–75	Zeng et al. (2019)
	Aptamer-based colorimetric biosensor	AuNPs	_	157.4	75–750	Matsunaga et al. (2019)
	Aptamer-based electrochemical biosensor	Carbon NPs and AuNPs	Thermal decomposition (CNPs) Electrochemical deposition method (AuNPs)	0.092	0.5–100	Mushiana et al. (2019)
	Aptamer-based QCM biosensor	AuNPs	Citrate reduction method	0.33	0.6–75	Yuan et al. (2019)
	Aptamer-based electrochemical biosensor	Ag–Au alloy NPs	Electrochemical deposition method	$3\times10.^{-6}$	0.01–10	Yadav et al. (2019)
	Aptasensor based on fluorescence detection	Silica NPs coated with streptavidin	_	0.034	0.150–37.46	Taghdisi et al. (2018)
	Aptasensor based on EIS detection	3D-rGO/AuNPs	Hummer's method for GO and AuNPs with chloroauric acid	$1.4\times10.^{-7}$	3.8×10^{-7}–$3.0\times10.^{-4}$	Ensafi et al. (2018)
	Aptasensor with glucometer readout	Graphene oxide (GO)-gated mesoporous silica nanocontainer (MSN)	Co-condensation method for MSN	0.0023	0.01–100	Zhou and Tang (2018)
	Aptamer-based fluorescence biosensor	MoS_2 nanosheets	Hydrothermal method	1.35	_	Ravikumar et al. (2018)
	DNA-based fluorescence biosensor	Quantum dots (QDs)	Hydrothermal method	0.2	1–150	Zhang et al. (2017)
	Aptamer-based fluorescence biosensor	Mesoporous silica NPs	Co-condensation method	0.9	4–60	Oroval et al. (2017)
	Aptamer-based FET type biosensor	Flower like MoS_2 nanospheres	Hydrothermal method	$7.5\times10.^{-5}$	$7.5\times10.^{-5}$–0.75	An and Jang (2017)

Table 2 (continued)

Analyte	Biosensor description	Nanomaterials (NMs)	Preparation method of NMs	LOD (µg/L)	Linear range (µg/L)	Ref
	Aptamer-based luminescent biosensor	G-quadruplex	_	0.57	3.75–22.5	Lin et al. (2017)
	Aptamer-based electrochemical biosensor	AuNPs	Citrate reduction method	0.011	0.015–7.5	Cui et al. (2016)
	Aptasensor based on SERS	Au@AgNPs	Chemical synthesis method	0.059	0.1–100	Yang et al. (2015)
	Aptamer-based SERS detection	AuNPs	Citrate reduction method	0.1	0.288–23.04	Ye at el. (2014)
	Aptasensor based on colorimetric detection	AuNPs	Microwave irradiation method	5.3	5–1500	Wu et al. (2012b)
	Aptasensor based on resonance Rayleigh scattering detection	Variety of NPs of different sizes	_	0.2	0.1–200	Wu et al. (2012c)
	DNA-SWCNTs hybrids-based electrochemical biosensor	SWCNTs	_	0.05	_	Liu and Wei (2008)
	DNA	MWCNTs	_	77,000	_	Ferancova et al. (2007)
Arsenate	FAM-labeled DNA	CeO_2 NPs and $CePO_4$ NPs	Chemical reaction method ($CePO_4$ NPs)	2.175	_	Lopez et al. (2017)
	ssDNA functionalized NPs-based fluorescent nanosensor	$CuInS_2$ QDs@ Fe_3O_4 NPs	Hydrothermal method	0.0098	0.015–15,000	Liu et al. (2015)
	DNA	Fe_3O_4 NPs	_	22.5	3.75–60	Liu and Liu (2014)

their method of preparation and morphology. By controlled synthesis of nanostructures, nanomaterials of consistent shape and size can be produced having improved properties with a positive effect on their performance. Additionally, some of these nanomaterials are highly sensitive as they have both electric and optical properties. These As biosensors based on cell-free approaches and advanced nanomaterials are not only highly selective and sensitive, but their results or detection limit is also corresponding with the results that are obtained by some currently widely utilized analytical techniques such as ICP-MS for As. These biosensors are rapid, inexpensive, and portable in nature. Also, these detection strategies can be applied for the detection of other heavy metal ions by utilization of different probes according to an analyte. With the help of microfluidics technology and miniaturization, a very small amount of sample is required for analysis. To achieve the on-site monitoring of the hazardous level of pollution caused by As in drinking water, the stability and reusability of these nanomaterials-based biosensors need furthermore study to allow long-term application. Despite this advanced progress that has already been made, there are some problems that need to be get solved in near about future mentioned as follows: The first problem is related to the target analyte; most of the As biosensors are based on the detection of inorganic As, and they demonstrated satisfactory result. But there are some other species of As that exist in organic form and are troublesome to detect. Therefore, effective protocols need to be developed for the conversion of

organic As in inorganic form or to directly detect the organic form of As. The second problem is related to the interference of other components in natural water samples. Ions or various organic component can easily cause harm to detection probes such as DNA; therefore, the developed biosensor should be stable and reliable for the complex sample solution. Lastly, further study is needed to produce the nanomaterial of controlled morphologies to increase the conductivity and interaction between these nanomaterials and the electrode. Also, the knowledge about the potential effects of nanomaterials on the human life is inadequate. Since, nanomaterials may not be detected after evacuation in the nature, they can lead to a variety of ecological problems if the remediation process is not secure. Therefore, further research is needed to systematically describe the functional relationships of nanomaterials in relation to their basic chemistry (e.g., toxicity and efficacy). In addition, a full risk assessment should be performed on nanomaterials that present a real risk of exposure during production or utilization. However, the green nanotechnology has been encouraged to make the existing nanomaterials more eco-friendly and to reduce the potential environmental and health risks from the manufacturing and application of nanomaterials.

Declarations

Conflict of interest The authors declare no competing interests. The authors alone are responsible for the content and writing of this article.

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