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Review Article

Interventions in Biosensor Surfaces for Arsenic Detection

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Abstract

Arsenic is a naturally occurring element in earth crust which is known to be heavy metals that is a very harmful environmental pollutant that has a strong link towards human health. Arsenic may cause gene mutation, alterations, cognitive disorders and malignancy in a person, even causing infertility when it gets consumed either unknowingly when it comes to pollution debris or deliberately in case of homicidal. Arsenic is one of those heavy metal which can be able to cross blood brain barrier and directly affects the central nervous system and also infants in case of pregnant lady therefore, its detection at nano level becomes so important. A vast range of biosensors for qualitative and quantitative classification and recognition of arsenic have been developed over the last few decades. Biosensors are analytical instruments with great specificity, accessibility, relatively low consumption and convenience of being used that can be used to monitor an aspect of diverse analytes qualitatively and quantitatively. Because of its widespread presence in nature and substantial toxicity to living organisms, arsenic must be evaluated often in groundwater, sediment, agricultural and dietary samples.

The purpose of this review is to highlight some recent advances in biosensor development by focusing on recombinant entire cells or specific arsenic-binding nucleotide sequences and peptide. Surface plasmon resonance recombinant technology, reusable enzymatic strips for on-the-spot detection have also been proposed as future technologies.

Keywords: Arsenic Toxicity; Biosensors; Surface Plasmon Resonance Sensor; Whole Cell-Based Sensors

Introduction

Arsenic (As) falls into the metalloid family of elements. A metalloid is a chemical compound that has both metal and non-metal properties. Arsenic seems to be the 53rd most abundant component, accounting for around 1.5 ppm of the Earth's core [1]. They are known to be a monoisotopic element as it has only one stable isotope i.e., (75As). Depending on their oxidative state such as As0, As+5, As+3 and As-3 its chemical activity is complicated and frequency in the environment [2]. Arsenic species may be found in a variety of settings and can originate from both natural and man-made sources. Arsenic species could be found in a variety of settings and can arise from both naturally and man-made sources [3]. Natural sources of arsenic include rocks containing arsenic compounds, volcanic eruptions and numerous biological activities. Anthropogenic sources include mining and several forms of businesses (pesticides, wood preservatives and pigments). When arsenic compounds enter groundwater, distinguishing between anthropogenic and natural arsenic species can be challenging [4]. Arsenic species can be found in water in solution or precipitated form, depending on the oxidation-reduction conditions and microbiological environment and they can also adsorb or desorb from preexisting precipitates. There are both inorganic and organic forms of arsenic that are soluble in water. Inorganic pecies (iAs) contain both arsenite and arsenate, whereas monomethylarsonic acid and dimethylarsinic acid a pentavalent methylated inorganic arsenic (iAs) species which can reduce to for trivalent arsenic species [5]. Those molecules which carry 'carbon' atom as its major calls as an organic species (oAs). The chemical equilibrium constants for every molecule or ionic form of arsenic in water can be used to identify the present species.

Inorganic arsenic is the most abundant kind of arsenic in water when it comes to identifying and assessing its presence. When As^{3+} is present, two important considerations must be made. Even at low concentrations, As3+ is more toxic than As^{5+}. Aside from its extreme toxicity, As3+ is quickly oxidized [6]. Traditional reference arsenic levels in the atmosphere do not reach 3 mg/m^3; in soil, 100 mg/kg; and in freshwater, 10 µg/L according to WHO [7]. Arsenic testing is not generally included in water quality analyses. Arsenic compounds have no color or odor. Therefore, due to all its properties is widely regarded as a poison (Fig. 1) [8].

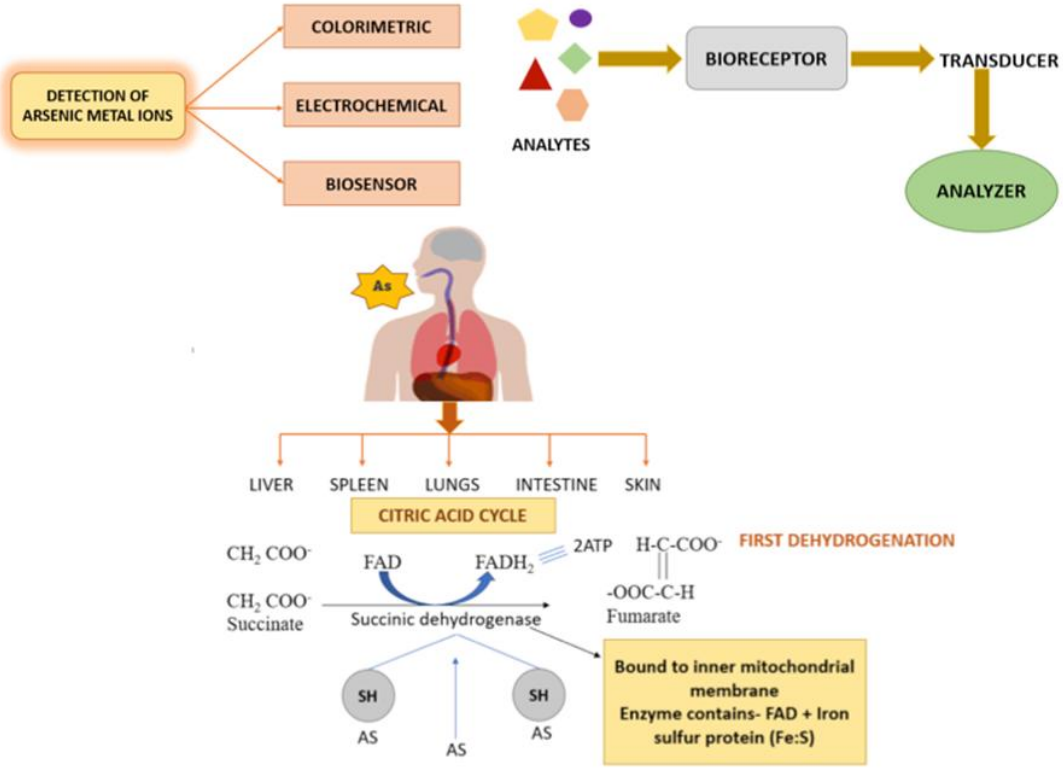

Figure 1: Graphical abstract.

Because arsenic is a natural component of the environment, we know that most individuals are exposed to it on a regular basis. The majority of people are exposed to arsenic through their diet and drinking water and their exposures are quite low. However, arsenic levels in drinking water are naturally high in other regions of the world, including India, Bangladesh, China, the United States and others, resulting in dangerous manifestations in these populations [9].

In the environment, particularly in groundwater, arsenic is a widely dispersed and extremely hazardous heavy metal. Given that groundwater is one of the most significant and reliable sources of drinking water, arsenic would enter the human body system through the food chain. Therefore, a quick, easy and affordable arsenic assessment is turning into a top priority for environmental monitoring and analytical science research. However, the majority of conventional procedures for making determinations, such ICP-MS, AAS and AFS, typically need not only expensive instruments but also take a long time and require operators who have undergone formal training. Aptamer sensors have been described as a new analytical platform for the detection of arsenic in the last ten years as an alternative technique. In this paper we outlined traditional as well as the most recent advancements in arsenic biosensors, placing a focus on works based on methods that are protein/enzyme-based, DNA-based and aptamer-based and utilizing diverse transduction platforms. Arsenic sources, chemistry, toxicity, sign and symptoms on human are also discussed here.

Arsenic Chemistry

As a metalloid, it is present in the four oxidation states such as 0, 5, 3 and 3 (As0, As+5, As+3 and As-3). There are two types of arsenic: "organic" and "inorganic." Arsanilic acid, methylarsonic acid, dimethylarsinic acid and arsenobetaine are examples of organic molecules that have carbon atoms attached to them, whereas arsenic trioxide and arsenic pentaoxide, which do not

contain carbon but merely act as molecules of arsenic, are examples of inorganic molecules. Out of all types, inorganic forms-such as As3+, which makes up 70-80 percent of all arsenic are the most toxic. As5+ is more stable, less mobile and ten times less dangerous than As3+ in oxygenated environments. Arsenite and Arsenate or H_3AsO^3, H_2AsO^3, $HAsO_3^2$, AsO_3^3, H_3AsO^4, H_2AsO^4, $HAsO_4^2$ and AsO_4^3, respectively, are the two categories of arsenic depending on pH. Arsenic often appears in aqueous media as AsO_4^{3-}, H_2AsO^{4-} and mostly as H_3AsO^4 (aq.), AsO_4^{2-} or H_2AsO^{3-}. While arsenic pentoxide has an oxidation state of 5+ and can be soluble at 20°C, arsenic trioxide has an oxidation state of 3+ and is soluble in dilute acids and alkalis but is basically insoluble in organic matter or solvents. Water solubility for arsenic trioxide occurs at 25°C.

Arsenic Poisoning

Intake or inhalation are the two usual routes of arsenic absorption[10]. Trivalent arsenic oxide can be absorbed in the skin somewhat, as it is lipid soluble rather than penta-valent. When the touch is ingested, the reaction is dominated by symptoms of acute GI (Gastro-Intestinal) discomfort [11]. If the route of initial contact is inhalation, respiratory discomfort is a significant driver of early symptoms [12]. But when Arsenic is ingested, a wide range of possible symptoms representing the variety of potential organ injuries can be caused by the vascular circulation. Arsenic is swallowed, inhaled or absorbed by the human body [13]. The gastrointestinal tract consumes half of ingested trivalent arsenic. It is distributed in many organs such as the lungs, liver, kidneys and skin. Inflammations can be seen on epidermal layer of skin while on nails a significant rain-drop pigmentation also known as 'Aldrich-mees lines' are observed on those individuals who are under log time exposures [14]. When it gets ingested through lungs and GI-tract, 95-99% of the arsenic is discovered in erythrocytes and attached to globulin of haemoglobin, which is subsequently transferred to various parts of the body, Urine excretes approximately 70% of arsenic whereas after 2-4 weeks of distribution via blood their molecules can be found in keratin rich tissues such as 'Hair', 'Nail' etc. Arsenic is present in many water sources across the world, causing health problems or illnesses like cancer as shown in graphical abstract showing arsenic toxicity when absorbed in body. Infertility has been characterized as a major health concern and a rising medical problem worldwide because it disproves the notion that living and the condition of the surrounding environment may have a considerable influence on reproductive potential both in human and animal populations [15]. Arsenic can impact the female reproductive system by reducing ovarian steroidogenesis, prolonging diestrus, degenerating ovarian follicles and lowering plasma levels of estradiol and progesterone [16]. Based on WHO data, more than 10% of women are at risk of infertility due to heavy metal exposure, such as arsenic, which is a prominent environmental pollutant that can cause reproductive problems [17,18]. Arsenic exposure has a direct effect on the male reproductive system because it affects certain reproductive organs and the neuroendocrine system, as well as disrupting sertoli cells during fetal development. Sertoli cells proliferate during the prepubertal, fetal and neonatal periods, which are particularly vulnerable to the effects of arsenic. Interrupting spermatogenesis at the cell differentiation stage can lower overall sperm count and damage sperm DNA [19].

Sign and Symptoms

There are four classical stages which show arsenic poisoning symptoms in those who have had long time exposure:

1. Stage- Nutritional + Gastro-intestinal disturbance
- Weakness
- Loss of appetite
- Nausea
- Intermittent attack of vomiting and diarrhoea

2. Stage- Catarrhal changes
- Symptoms such as cold, rhinorrhoea, conjunctivitis

3. Stage- Skin rashes
- Pigmentation on hair, skin and nails such as: "Rain drop type" on skin while similar to "Addison's disease pigments" and "Aldrich-mees" lines on nails
- Hyperkeratosis in palms and soles
- Fall out of Hair and nails.

4. Stage- Nervous disturbance
- Tingling and Numbness on hand, feet

- Renal and Hepatic damage
- Bone marrow suppression with anaemia

Fatal Period

- Narcotic form Large doses take 2-3 hrs
- Gastro-intestinal form takes 12-48 hrs
- Survived person takes 7-10 days

2. Recent Detection Techniques

Arsenic in the environment whether it is in water or in soil it is important to know about its presence and features it is imparting over there. So, in the forward section the existence of arsenic in various matter has been mentioned. Traditional techniques are present for quantifying the metal ions such as Atomic absorption spectroscopy, Inductively coupled plasma-mass spectroscopy, HPLC, graphite muffle furnace atomic absorption spectroscopy etc. [20-22]. There is no doubt that these techniques are using from many years and been justifying the results but with pros there are some cons as well such as they require highly equipped laboratories, trained professionals, chemical consumptions etc., therefore in recent times many researchers are exploring different techniques in field of nanotechnology through which a better on the spot method can be developed. In search of this there are three major fields that were evolved which are as-colorimetric, electrochemical and biosensors. In colorimetric techniques researchers developed suitable nanocomposites which selectively aggregated with arsenic ions and resultant into color shift [23,24]. Sericin capped gold nanoparticles (SS-AuNPs) are recently used for the detection of this metal ion whose limit was upto 2.94 ppb [25]. Whereas in electrochemical techniques nanoparticles were utilized as suitable coating on electrodes to determine Arsenic in a simple, sensitive, selective and efficient manner [26]. Noble-metal nanoparticle-free coatings are possible. Electrodes built with the features of being portable, affordable, efficient and especially practical are in high demand as the field of electrochemical determination. The overall goal of a manufactured sensor is to be used in field measurements as a cost-effective commercial instrument, which is considered as extremely promising for regular arsenic assessment [27]. The commercialization of electrochemical sensors will facilitate the development of chemically modified electrodes in future research. Electrochemical techniques can be integrated with nanomaterials and flow-injection systems to develop electrochemical sensors that can detect Arsenic in real time and react quickly [28]. By delivering a high specificity, this combination made it easier to design and manufacture integrated sensing device [29]. The use of nanoscale compounds in the manufacturing of these sensors improved their sensibility, reactivity and repeatability. A sensing system at ppb level was created, which is an important feature for arsenic tracking devices for drinking water. As a result, electrochemical systems including nanomaterials and nanotechnologies have a lot of potential for developing efficient sensing surface [30]. Reusable catalytic electrodes, particularly useful in detecting arsenic in the field quickly and cheaply [31]. Furthermore, because of the synergistic noticed when multiple nanoparticles are mixed, the development of adequately interconnected sensing devices may lead to development of continuous or implanted arsenic sensors helpful for both environmental investigations and other domains such as clinical examination. Moreover, in recent times there some study which are focused on removal of arsenic from water by electrocoagulation technique [32]. However, researcher also prepared a Micro Flower nanosheet (MF-δ-Bi_2O^3) where arsenic adsorption was analysed which later contributed towards the removal technique [33]. In the field of toxicology, these techniques can be integrated into existing procedures to eliminate the employment of various heavy instruments such as atomic absorption spectroscopy, inductively coupled plasma-mass spectroscopy etc, because during experimental work, various chemicals are employed to identify the presence of arsenic, as stated previously. In a time when technology has advanced to the point where on-the-spot detection and lab-on-a-chip are in high demand, similar techniques may be beneficial in this sector as well [34]. Lab on chip technology will lead us towards green and less chemicals fiasco more accuracy in detection of heavy metals. In this approach various researchers worked on developing biosensors to detect arsenic ions at nano level.

Here, in this review article we are talking about a sensor based on bio-recognition site i.e., a biosensor [35]. It is a synergistic analytical gadget that combines biotechnology with microelectronics. The three fundamental components of biosensors are a biocomponent (enzyme, whole cell, antibody, DNA, etc.), a transducer (electrochemical, optic or thermo) and an amplifying unit [36]. It is possible that biosensors for any molecule significant to toxic compounds, people's health or environmental conservation will be developed. Analytes disrupt biorecognition by inhibiting enzymatic activities (growth or enzyme activity) or altering the native structure of key macromolecules (DNA and Antigen/Antibody complexities). Both methodologies strive for a decreased or augmented biochemical signal, which the biorecognition component recognises and the transducer converts to an

understandable signal. Here biosensing approaches categorized according to the biological component used in the construction of arsenic biosensors. Novel arsenic biosensors have been created as a result of advances in material science and a better knowledge of diverse arsenic-binding processes. There are different types of methods available as shown in Fig. 1 which widespread to detect the presence of arsenic at lower level since they are highly specific and sensitive towards the metal ion have been discussed here (Fig. 2).

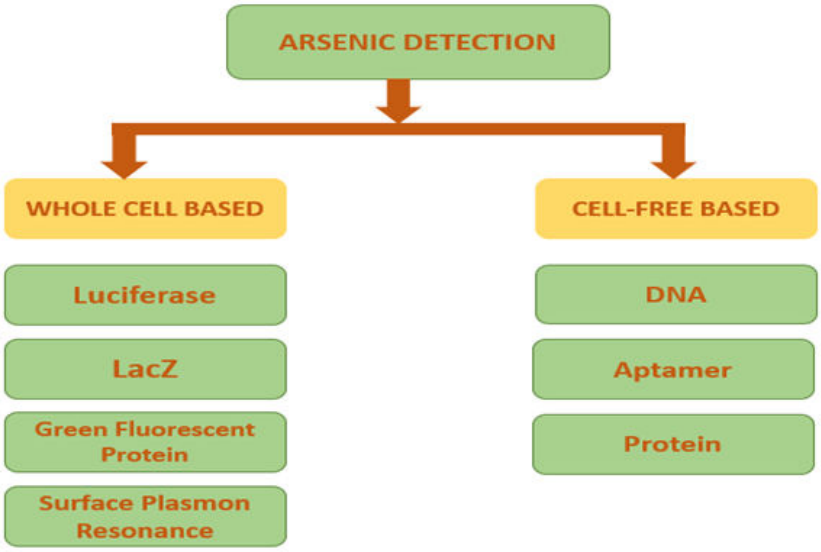

Figure 2: Shows different types of biosensor's present for the detection of arsenic ions.

Whole Cell Based Biosensor

A whole cell-based sensor is an analytical device with a full cell as the biological component. It does have a high-selectivity physical transducer that generates a measurable signal in response to analyte concentration. Whole cell biosensors provide a high level of specificity and are very affordable. They provide a number of benefits, including ease of use, portability and the ability to provide constant real-time readings. Synthetic biology is a concept that allows for the altering of a cell's gene makeup. Combining a signal-generating reporter gene with a contaminant-sensing mechanism that reacts to chemical or physical changes in response to exposure to a specific analyte might accomplish this. Fig. 3 depicts a complete cell biosensor.

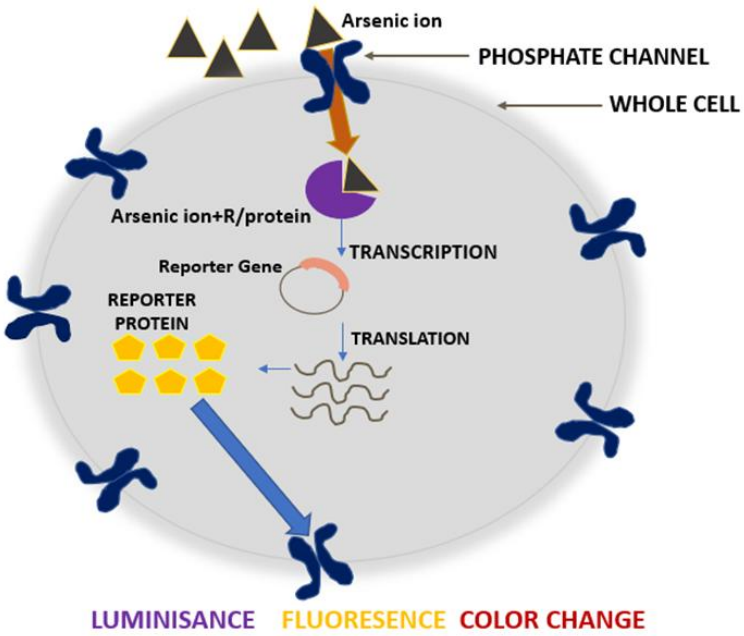

Figure 3: Diagrammatic representation of the function of a biosensor in a whole cell.

When the biosensor being subjected to a specific analyte, the cell's detecting component activates the reporter gene via a metabolic mechanism [37]. Then the reporter gene then generates a measured response that shows the analyte's qualitative or quantitative value. Arsenic whole cell biosensors, for example, utilize the As responsive promoter [38].

The reporter gene then generates a measured response that determines whether the analyte is qualitative or quantitative. The r-genes which can be induce into a plasmid or a selective chromosomes. The expression of the As operon, which can be located on a bacterial plasmid or chromosome, causes bacterial resistance to arsenic. As a result, the methodology depends on bacterial arsenic resistance mechanisms or metabolic activities for identification. *E. coli* plasmid R773's demonstration of arsenic resistance mechanisms includes As operon expression by Kaur and Rosen 1992. The five-gene As operon, known as arsRDABC, was isolated from *E. coli* plasmid R773. Regulation-related proteins are encoded by the arsR and arsD genes. ArsA and ArsB are two genes that code for parts of an ATP-driven As3+ pump, with ArsA serving as the catalytic subunit and ArsB as the trans-membrane component. Partial tolerance to As3+ is provided by arsAB gene deficiency. As5+ resistance is brought on by the arsC protein, which causes As3+ to be extruded by the transport system [39]. ArsR controls the smallest amount of protein expression, whereas arsD controls the highest degree of protein expression. The As repressor binds to the Arsenic operon's either operator or promotor site in the absence of As5+ and prevents further expression [40]. The arsR repressor binds to As5+ in the presence of it, causing a conformational shift that isolates the arsR protein from the operator [41]. Intrinsic bacteria carrying the As operon do not provide a significant analytical signal during response, making them unattractive for biosensor development. The arsR gene and its responsive promotor are typically coupled to a marker gene that can readily assess protein, such as luc or galactosidase, in whole cell biosensors for arsenic As5+ whole cell biosensors can be classified as luc, galacto or GFP based on signal transduction methods [42]. Recently *E.coli* DH5α was developed with positive amplified feedback whose detection limit was found to be 1μM. When measured using half-saturation Arsenic concentration, the sensitivity of the WBC (Whole Cell Biosensor) with positive feedback is about a tenth of magnitude higher than that without positive feedback. Fast reaction is crucial for in-situ activities and the WCB was able to provide identifiable signals in less time due to the output signal's amplification. Additionally, when compared to other metal ions, the WCB with the positive feedback amplifier shown extraordinarily high specificity for As3+ [43].

Luciferase Based Detection Protocols

A luc-based gene product is a kind of oxidation based enzyme that produces luminescence within. The gene is a good substrate for developing a recombinant strains and using them to make highly sensitive and simple signals that can be detected simply because of its bioluminescence activity. Corbisier, et al., 1993 described lucAB gene constructions and regulation in fusion with the As-resistance operon. The structure includes Vibrio harveyi luc-encoding lux gene, ampicillin and chloramphenicol selective markers and gram (+ve) and (-ve) bacteria replicating sources. In addition, two transcriptional gene fusions, arsB-lucAB and Cd-A-lucAB (both derived from *S. aureus* pI258), were created in that construct and tested for transcriptional activity in *E. coli* and *S. aureus* [4]. Using the firefly luc-gene, Tauriainen, et al., published a luminous r-strain of bacteria for As detection. MC1061 (pTOO31), AW3110 (pTOO31). are two novel As sensor strains developed by the researchers. Plasmid pTOO31 was created by combining the arsR gene and ars promoter from plasmid R773 with the luc-gene. The strains were utilized to determine As5+ and Hg^{2+} and the results were found to be comparable to standard As^{3+} or Hg^{2+} solutions.

By synthesizing a regulator-reporter gene combination and coupling it to a shuttle plasmid capable of reproducing in both gram (-ve) and (+ve) bacteria, the same group created viral sensors for detecting the presence of particular metals or metalloids. The promoter was in charge of luc expression as a reporter gene. The created sensors provide a reliable indication of the presence of the metal sensitive gene and provide results in as little as 30 mins, with optimal induced durations ranging from 60 to 240 mins. They also confirmed that an As-contaminated sample could be tested with a freeze-dried luminous bacteria strain. Their lab has also developed and tested bioreporters such as luc-gene expression in the monitoring of the arsenic operon of the S. aureus plasmid P1258 inside a shuttle vector plasmid pT0021 in three separate host strains, including S. aureus RN 4220, B. subtitles BR151 and *E. coli* MC1061. Trang, et al., presented a significant environmental assessment of a microbial reporter-based test to measure levels of As in freshwater resources. A bio-luminescence-producing As-inducible bacterium based on *E.coli* served as the reporter organism. At and above 7 mg/L As concentrations in groundwater, bioreceptor cell sensitivity was shown to be good. Between 10 and 100 μg/L, the bio-luminescence signal increased in a directly proportionate manner (Trang et.al., 2005). The bio-luminescent bacteria E.coli DH5 (pJAMA-arsR) harbouring the lucAB gene from Vibrio harveyi was demonstrated to interfere with the formation of bioluminescence by the lucAB gene from Vibrio harveyi. By adding EDTA, the metal inhibition

was abolished and As was partitioned from other channels, yielding a correct measurement for As in ordinary water.

When the arsABC DNA component was separated from the concept that enabled arsenate to accumulate in the cell, the recognition limit was reduced by a factor. To simplify luminous signals in an exposure time, the lucCDABE gene was installed on the chip of a bacterial biosensor [44].

β-Galactosidase Based Detection Protocols

LacZ 2-galactosidase has also been utilized in arsenic identification since it provides accurate and quantitative results. For sol-gel-based signal transduction, the electrochemical polarisation of 4-aminophenol generated from 4-amino may be used. colorimetric response on phenyl 2-D-galactopyranoside on Xgalacto, either enzymatically or via an enzyme-catalysed reaction. This method was discovered to be quicker than Luciferase-based methods.

In 1997, the first arsR-2-galactosidase fusion strain using the plasmid R773 regulatory region and *E. coli* as a vector was reported. Scott, et al., created a genetically engineered bacterial strain containing the reporter gene 2-galactosidase on a plasmid controlled by the As operon promoter. In the absence of antimonite or arsenite, the plasmid also encodes an arsR protein, which inhibits 2-galactosidase production. The sample activity of the arsR protein is hindered in the presence of analytes (Sb^{3+} or As^{3+}), resulting in 2-galactosidase expression. The enzyme's activity was measured electrochemically using the substrate p-aminophenyl 2-D-galacto pyranoside. This galactosidase-based bacterial sensing system exhibits a high selectivity for arsenite and antimonite, while being insensitive to As^{5+} and PO_4^{3-}, SO_4^{2-}, NO^{3-} and CO_2^{3-}.

Another article claims that spore-forming microorganisms like B. subtilis and B. megaterium were used to produce luminous sensing devices for two model analytes: As & Zn. These recognising cells were turned into spores, which could subsequently be germinated to become living, metabolically active cells. After 6 and 8 months of storage at ambient temperature, these spore-based sensing devices maintained their analytical performance. On-site sensing with whole-cell biosensors enables for recognition in both mild and hostile environments. According to Daunert, et al., 2007, another bacterial bio reporter was created from spore forming B. subtilis and contains the 2-galactosidase gene, which is regulated by the arsR regulatory protein [45]. Aleksic, et al., developed a whole-cell biosensor that uses a pH shift as an output to detect arsenic in drinking water [46]. The design was made using the *E. coli* As detoxification system's As5+ responsive promoter. Urease raises the pH when As5+ is absent from the analytical system, whereas 2-galactosidase decreases the pH when As5+ is present. The pH-reducing 2-galactosidase system successfully responded to As5+ concentrations as low as 5 ppb, with a WHO advised value of 10 ppb. The arsR and arsD genes are repressors that govern the synthesis of lac repressor and 2-galactosidase. Urease production might be hampered by their suppressive function, which raises pH even when arsenic isn't present. The arsR-2 galactosidase gene construct in E. coli DH5 (strain 2245) is extremely selective for arsenic detection, with a detection limit of 0.02 μg/L, however it takes 22 hrs to incubate, making it a time-consuming method.

GFP-Based Detection Protocols

Green Fluorescent Protein-based biosensors were created because they can detect molecules without a substrate, which makes sensing less expensive than 2-galactosidase and luciferase-based techniques. They also make continuous end-point measurements possible. Roberto, et al., developed a biosensor for detecting arsenic in the environment by mixing transcriptionally bioactive components with GFP from marine jellyfish [47]. They reported a less costly As detecting biosensor or As3+ and As5+ sub-microgram estimation. The quantity of analyte may be determined by measuring the emission of green fluorescence caused by the synthesis of green fluorescent protein. The sensitivity of the green fluorescent protein system is lower than that of the 2-galactosidase system. The method employs green fluorescent proteins, which allow for real-time monitoring of substrates and cell death.

The GFP reporter gene is unaffected by the microbe used to produce the biosensor, as well as the microbial cells' internal reducing agents. GFP is rapidly being employed in biosensors due to its simplicity of detection and decreased metabolic cost to the host cell. The GFP's stability and spectrum characteristics can be altered by its three-dimensional physiologically active structural configurations. As a result, the chances of obtaining long-lasting GFP gene mutants have improved, making it easier to improve/modulate fluorescence intensity.

Stocker, et al., constructed a GFP bioreporter for arsenic detection by integrating the arsR gene, some few fragments of arsD and the GPF of Aequorea victoriasourceisto on an *E. coli* plasmid with a promoter, p1RC1140 has been developed. The generated GFP biosensor showed a constant fluorescence signal after a 12-hour induction time and had a recognition limit of 1 mg/L. The GFP-based biosensor, even with recombinant strains, has limitations due to environmental inputs via Stocker et.al., 2003. They designed a method for detecting color changes in which the sensor cells were glued to the paper strip, dried and then submerged in an aqueous solution for 30 minutes. Additional GFP-based biosensors for detection and monitoring of As5+, As3+ and Sb3+ in water have been developed and published.

In one GFP based sensors, the arsenic promoter as well as its gene of staphylococcus aureus control, synthesis of green fluorescent protein (plasmid l258). Truffer, et al., developed a biosensor that causes *E. coli* cells to manufacture green fluorescent protein genes [48]. A microfluidic chip made of polydimethylsiloxane holds $C_24H_38O_{19}$-enveloped bacteria in device. This device is able for measuring as well as storing outcomes simultaneously. At 80 minutes, this device reacted towards 10 mg/L and at 120 mins, it reacted to 50 mg/L.

SPR-Based Detection Protocols

SPR based sensors basically measures the changes occurs in mass concentration at a planar interface between the two substrates (mixture of analyte & bio-recognizing substrate which is placed on the sensor area) when polarised light is focused towards the sensor surface, the dielectric transmittance possesses an opposite signs. So when polarised light collides with a surface, an electric field is created. As demonstrated in Fig. 4, linear polarised light with an electric field vector either parallel or perpendicular to the incoming light axis can generate SPR.

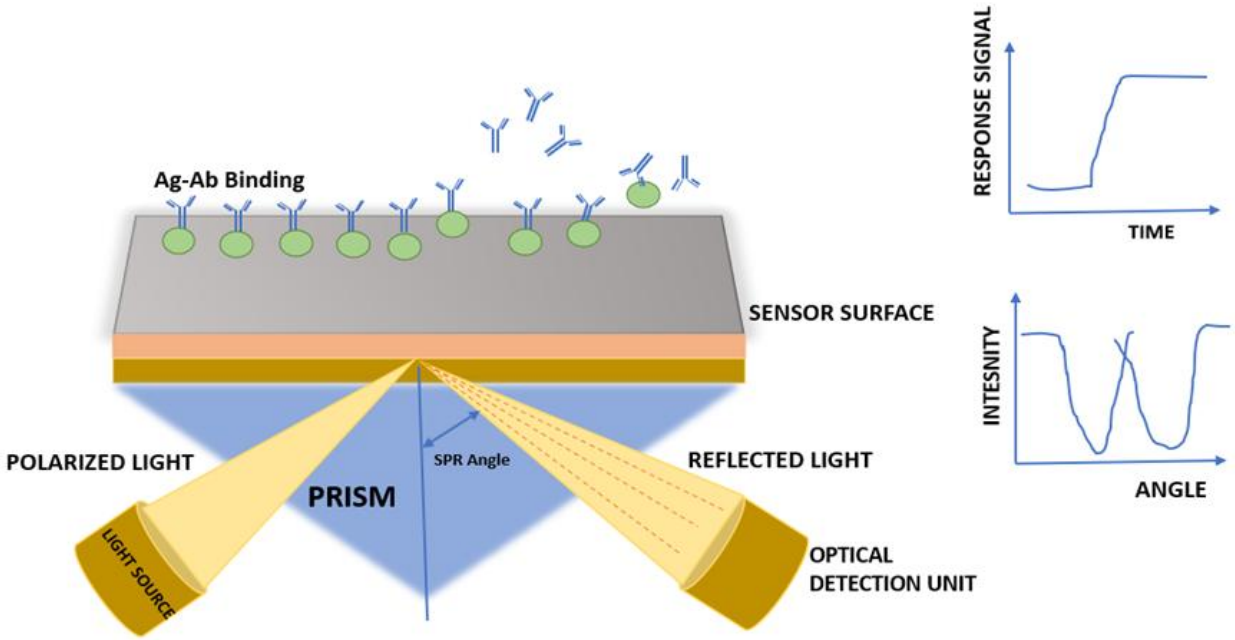

Figure 4: Shows a working mechanism of SPR based Biosensor.

SPR is a common method for examining biological processes including biomolecule binding and medication development. In 2006, organic R-SH were used as sensor probes and an extremely sensitive surface plasmon resonance-based sensor with a detection limit of 0.010 mg L-1 arsenic in a water sample was built [49]. Another SPR-based biosensor for the detection of arsenic used a self-assembled monolayers formed of 2-mercaptoethanol, which was subsequently placed on a gold substrate. 1-ethyl-3-[3-(dimethyl amino)propyl]carbodiimide and $C_4H_5NO_3$ were used to immobilize the D-SS calf thymus DNA on the 2-mercaptoethanol/Gold-electrode, with a detection limit of $0.01x10^{-6}$ mg/L [50]. Recently, new breakthroughs in SPR based sensors have been realized owing to the utilization of an optical multilayer structure as a sensor that supports long-range surface plasmons.

3. Cell-Free Based Biosensors

DNA-Based detection protocols

Because whole-cell biosensors are non-reproducible and essentially impossible to make, further biorecognition components are required. For this objective, DNA offered the necessary platform. Electrostatic interface with the negatively charged PO_4^{3-}, bonding connection with the minor and major grooves of the DNA and intercalation between the stacked base pairs of native DNA are the three forms of interactions. DNA-based biosensors can be used to identify between strains due to their intrinsic physicochemical stability. These sensors are powered by the polymerization of a particular DNA sequence on the transducer's surface [51].

DNA-based biosensors also employ SPR and piezoelectric detection techniques. They measure oxidative reaction occurs within the arsenic ions. A sequence DNA as (5'- TAATATCGGTTGCGGAGGTG-3') was utilized to trace the *E. coli* named as (O157:H7 EDL933). Mussels have the potential to alter function in response to changes in the environment, as well as respond to and collect water toxins that are hazardous to sea food consumers. Mussels, on the other hand, are rapidly being utilized in pollution monitoring, despite the fact that their genomic activity are mostly unknown.

Calf thymus DNA was studied because it contains a 17-k polynucleotide that can be used as a bio-component for arsenic(III)oxide studied[52]. A carbon paste electrode was used to investigate the arsenic-DNA interaction via DPV technique. The detection limit was set at 1 mg L-1. Ferancová, et al., in 2007 developed a comparable biosensor with 1,10-phenanthroline as a marker to detect the intact DNA concentration after exposure to As3+ & Sn2+ by immobilising DNA with CNTs film on the SPCE. DNA-based biosensors for sensing arsenic ion have advanced further due to the layering of DNA on channelized SWCNTs-hybrids [53]. Magnetic nanoparticles covered with DNA probe may detect bacterial RNA by determining the oxidation state of guanine monomer. Voltammetry was employed with PGE in this method mentioned [54]. Random sequence libraries have enabled the development of nucleic acid-based sensor manufacture. Any type of analyte may now be identified and bound by nucleic acids. A DNA-based biosensor with fluid handling and real-time PCR technique has been in used to detect salmonella enteric. The interaction of small strands of nucleotide is detected by a biosensor with a microarray chip. This method may also be used for a variety of other purposes, such as disease detection and genome screening. The development of a genetically encoded biosensor in vitro with an Arsenical resistance operon Repressor (ArsR) and a GFP reporter gene. The effects of cell extracts, temperature, pH, incubation and equilibrium time were examined and it was determined that equilibration of reaction mixtures for 30 min at 37ºC prior to arsenic treatment is essential for *in-vitro* arsenic detection [55].

Aptamer-Based Detection Protocols

Aptamers are a relatively new sort of biorecognition technology. Aptamers are SS-RNA or DNA polynucleotides that have been preorganized in vitro for specific binding to a variety of target analytes [56]. Their self-organized induced identification behaviour has been used in a variety of sensing modalities and they have the benefits of selectivity, real-time monitoring and on- site monitoring, all of which make biosensors commercially viable [57]. In ionic affinity for As3+ species, these features separate the aptamer from DNA [58]. The fundamental bioassay technique for identifying As3+ is based on the aptamer as (Ars-3) affinity for arsenic and various cationic polymers or surfactants, causing gold nanoparticles to assemble. Changes in particle properties affect the absorption or frequency dispersal test of AuNPs. A water-soluble cationic polymer, $(C_8H_{16}NC_l)n$ poly-DADMAC , was used to form cluster with AuNPs and hybridise the Ars-3 aptamer by an electrostatic interactions in a preliminary investigation [59]. The addition of As3+ caused the creation of an aptamer-As3+ complex, allowing $(C_8H_{16}NC_l)n$ to aggregation with AuNPs resulting into a color shift from wine red to blue. In the absence of As3+, $(C_8H_{16}NC_l)n$ hybridises to Ars-3, rendering it inaccessible to aggregation with gold nanoparticles, resulting in the red wine coloration. A cationic surfactant which is CTAB was used in the similar method to improve sensitivity and it resultant into a considerable improvement with 40 mg L-1 limit of detection by naked eye, 0.66 mg L-1 for colorimetric while 0.77 mg L-1 for resonance scattering test.

Protein Based Detection Protocols

In addition, DNA, aptamers as well as proteins have been used for arsenic ion detection. According to the Hard and Soft Acid Bases (HSAB) principle, it states that arsenic ions have affinity towards binding with sulphur molecule present in protein structures, therefore these are utilising to detect arsenic ions [60,61]. Apart from that, in the presence of arsenic, the sulphur in cysteine is vulnerable to oxidation and could be used for determining. The processes through which arsenic interacts with proteins are thought to be. The bioassay principle employed acetylcholinesterase catalysing the oxidation of acetylcholine iodide

to produce the redox active product thiocholine, which supplied the signal for As3+ measurement. Thiocholine oxidation current reduced in the presence of As3+ to values proportional to As3+ concentration. In addition, a technique for separating As3+and As5+ in water samples as devised.

A fascinating work was published by Parker, et.al., in 2015 in which a fluorescent analysis of As3+ was performed by using napthyl-labeled C10C16N3O6S- peptide. Because As3+ is neutral and possesses a R-SH group affinity, cys-preorganized peptides for quenching-florescence based determination of As3+ were developed and synthesised. To reduce the impact of positively charged ions, amino acids with positively charged side chain at neutral pH were inserted to the peptide sequences. Arsenic binds to proteins and either inhibits or promotes their function. Most protein dependent biosensors, on the other hand, function on the concept of enzyme inhibition. The idea behind a protein-based arsenic sensor is to investigate arsenic's inhibitory influence on protein function. Immobilized urease, a biological ingredient, is utilised in the creation of an arsenic specific biosensor on a sol-gel basis. According to Ilangovan, et al., in 2006, this sensing gadget is an excellent technique for identifying the presence of heavy metals in water samples [62]. Biosensors are a type of sensor that blends microelectronics and biology, making them useful for detecting contaminants in the environment. To make sensitive and functioning biosensors, new enzymes or enzyme substrates might be used. Assimilated biosensors are in great demand in order to attain practical applications. More research is needed to increase the biocomponent's stability, as well as to incorporate a multispectral system for simultaneous analysis and the use of nanomaterials to minimize detection time and promote activity. Various studies have been reported in the last few years which showed good specificity towards arsenic ion detection based on fabricated surface responses as discussed in Table 1,2.

Several arsenic biosensors have been invented as of this time, some of them are based on whole-cell biosensors and others on cell-free (protein, DNA)-based biosensors. Some are trustworthy reporters of the presence of arsenic in environmental samples including soil and groundwater. Biosensors have the potential to be quick, sensitive and dependable solutions to the issue of measuring arsenic in the groundwater in rural regions given their benefits, including time and cost effectiveness, small size, durability and ease of use. Currently, only a small number of biosensors are used for environmental applications; the majority are only lab curios. The detection thresholds, reaction times and specificity must all be optimized. Engineered biology might be used to advance biosensor technology. For instance, the addition of signalling systems from other species may increase the range of situations in which reporter assays are applicable for in-situ environmental monitoring. The development of biosensors for the concurrent monitoring of several environmental factors is one of the next problems. Bacterial signal-responsive regulatory units have been employed as a platform to design and construct whole-cell bacterial biosensors for reporting toxicity. With the increased development in synthetic biology and understanding of arsenic-binding mechanisms, novel biosensors have been developed for arsenic determination. However, little research has been conducted to address the largely unresolved concern of the “shelf-life” of the biosensor. It is essential that the cells have sufficient energy for sensing function within the formulated product. A weaker response will be obtained from cells with a compromised energy status. It is important for environmental biosensors to enable long storage at room temperature. Failure to maintain the survival and activity of biosensors will hamper their implementation. To meet these demands various conservation techniques have been reported, including freeze drying, vacuum drying, continuous cultivation and immobilization in biocompatible polymers of organic or inorganic origin.

Electrode	Method	Linear Range (ppb)	Detection Limit (ppb)	References
SBP-DNA	DPV	0.1-200	0.075	[63]
GT_{21}ss-DNA/PB@GO	DPV	0.2-500	0.058	[64]
GH-APTES-Fe_3O_4NP	SWV	13.3-65.8/117-241	1.6	[65]
SAMs	ASV	Feb-40	0.5	[66]
AuNP-rLA-Lcyst	SWV-ASV	Mar-25	3	[67]
MTs	ASV	5-1000	13	[68]
AgNPs/Ct	DPASV	10-100	1.2	[69]
Chitosan- $Fe(OH)_3$	ASV	2-100	0.072	[70]
E. coli	CV	0.94-3.75/3.75-30	0.8	[71]
Whole cell	CV	100	-	[72]
E. coli	CV	-	1.5	[73]

Ars 3	DPV	0.015-7.49	0.011	[74]
C-AuNPs	SWV	0.5-100	0.092	[75]
Ars3/AuNPs-GO-MB	DPV	0.4-10,000	0.2	[76]

Table 1: Biosensor based electrode for detecting arsenic ions.

Sample	Preparation	Method	Limit of Detection
Blood	Dry ash	HGAAS	0.5 µg/L
Hair/Blood	Wet ash	HGAAS	0.1 µg/L
Serum	Irradiation, with nitric acid	NAA	0.088 ng/L
Urine	Irradiation epithermally	NAA	40-100 ng/g
Urine	Drying sample, irradiation with X-ray	XRF	0.2 µg/L
Hair	Wet ashing	HGAAS	0.06 µg/g
Soft Viscera	Digestion with nitric acid/sulphuric acid	GFAAS	0.2 ppm
Nails	Wet ashing	HGAAS	1.5 µg/g
Urine	Digestion with nitric acid	Colorimetric photometry	0.5 µg/ sample
Urine	Pre-treatment with L-cysteine	HGAAS	0.1 µg/L
Blood/Viscera	Acidification with HCL	GLC/ECD	0.1 mg/mL

Table 2: Traditional analytical techniques for determining arsenic ion from different biological samples [77].

Conclusion

This review paper discussed arsenic occurrence, toxicity as well as its recent biosensor techniques through which it can be traceable at very low level. Arsenic is a naturally occurring element that people come into contact with on a daily basis through food, drink, soil and air. Though it is still being studied whether low-level environmental emissions have an influence on human health, people have long been aware of the dangers of arsenic. Due to these facts arsenic detection becomes important. In terms of detection various techniques have been reported yet based on nanotechnology claiming to be selective, sensitive as well as rapid out of which we discussed here about biosensors technique. Herein, the key finding of this review was to discuss the methodology, design and mechanism of developed sensors for arsenic metal ions. Various promising arsenic detection results have been obtained via whole cell based sensors, which includes DNA based ligands, enzyme based, green fluorescent protein-dependent biosensors, as well as certain aptamers which have been manufactured especially for arsenic ions with the goal of assessing arsenic in a cheap, precise, discriminating and efficient method. Biosensors are a type of sensor that blends microelectronics and biology, making them useful for detecting contaminants in the environment. To make sensitive and functioning biosensors, new enzymes or enzyme substrates might be used. Assimilated biosensors are in great demand in order to attain practical applications. Further research in this field is needed to increase the biocomponent's stability, pH sensitive well as to incorporate a multispectral system for simultaneous analysis and the use of nanomaterials to minimize detection time and promote activity.

Conflict of Interests

The authors declare no conflict of interest in this publication.

Ethical Approval

This review article does not contain any studies with human participants or animals performed by any of the authors.

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