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REVIEW PAPER

Immobilized Enzyme-based Novel Biosensing System for Recognition of Toxic Elements in the Aqueous Environment

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Abstract

Access to secure water sources has become one of the biggest challenges for human sustainability. Climate change and associated droughts make it difficult to guarantee the usual water source and move to groundwater use or to the re-use of treated wastewater remains unviable due the lack on the capacity of monitoring water quality. Moreover, reusing treated wastewater from repositories near anthropogenic sources represents a risk of high concentrations of emerging contaminants. The strategies involve a higher risk of encountering toxic elements with a heavy burden on human and environmental health. New accessible and reliable tools are required to detect any hazard from the waterbodies in real time to ensure safe management and also to decrease mismanagement or ilegal water discharges. One of the available options is to look into enzyme-based biosensors that can detect toxic elements in the water. The proposed biosensors require sensible elements to be accessible and durable for their proper function. The present revision shows in first place, the actual need of real time monitoring due the different sources and effects of emergent pollutants. Secondly, describes how enzymes can be immobilized for its application in biosensors and the rol enzymes play as bioreceptor element in biosensing. Thirdly, describes the transduction methods that can be observed, and finally the actual application of enzyme biosensors for the detection of different toxic elements. According to the presented literature enzyme-based biosensors have been successfully applied for the detection of a wide number of pollutants reaching detection limits comparable to traditional methods such as up to 0.018 nM of mercury. Furthermore, laccase seems to be the more applied enzyme in literature, but positive results are not limited to this enzyme and other candidates have been explored showing good detection rate.

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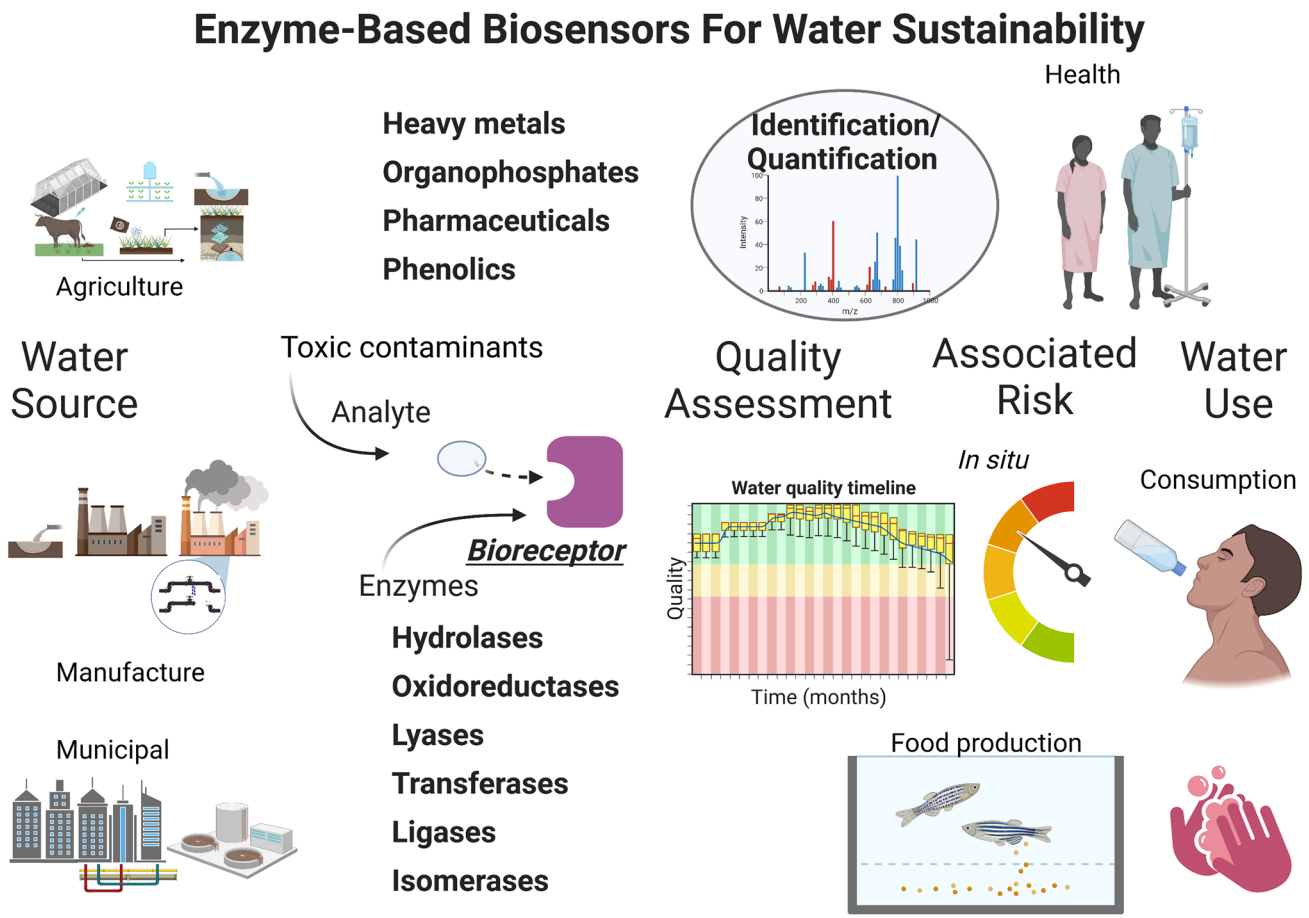
Graphical Abstract



Keywords Enzyme-based · Biosensor · Water contaminants · Toxic elements · Accessible biosensors

1 Introduction

Water access and security is a human right, and one of the most important goals for sustainable development. According to the United Nations one-third of the population still does not have access to clean water, so investing in the development and application of new technologies and infrastructure that ensure the protection of aquatic ecosystems is essential [1]. However, safely managed water sources can be contaminated due to many risk factors: chemical materials used in the water treatment system, pipeline corrosion, and leaching of elements from pipes of water distribution are some of the situations to allow the filtration of toxic compounds in water sources (Fig. 1) [2].

The uncontrolled population growth and anthropogenic activities, combined with accelerated industrialization [3], has caused the uncontrolled discharge into the environment of different toxic pollutants such as heavy metals and metals (mercury "Hg", lead "Pb", Cadmium "Cd", copper "Cu", chrome "Cr", nickel "Ni", selenium "Se", and arsenic "As" [2, 4], radioactive elements (radium "Ra" and uranium "U") [5], pesticides (organochlorine, organophosphate, carbamate, pyrethroid, neonicotinoid, phenylpyrazole, triazine, carboxamide, chlorinated hydrocarbon and chlorophenyl compounds [6], organic compounds (acrylamide and polyacrylamide [7], nitrite and nitrate [8], benzene [9], phenols (Polycyclic Aromatic Hydrocarbons "PAH´s" [10], bisphenol A [11], chlorophenol [12]), PFAS (polyfluoroalkyl and perfluoroalkyl substances) [13], among others, which characteristics of high stability, solubility, environmental persistence bioaccumulation potential, this characteristics, combined with the efficiency of conventional technologies for it removal

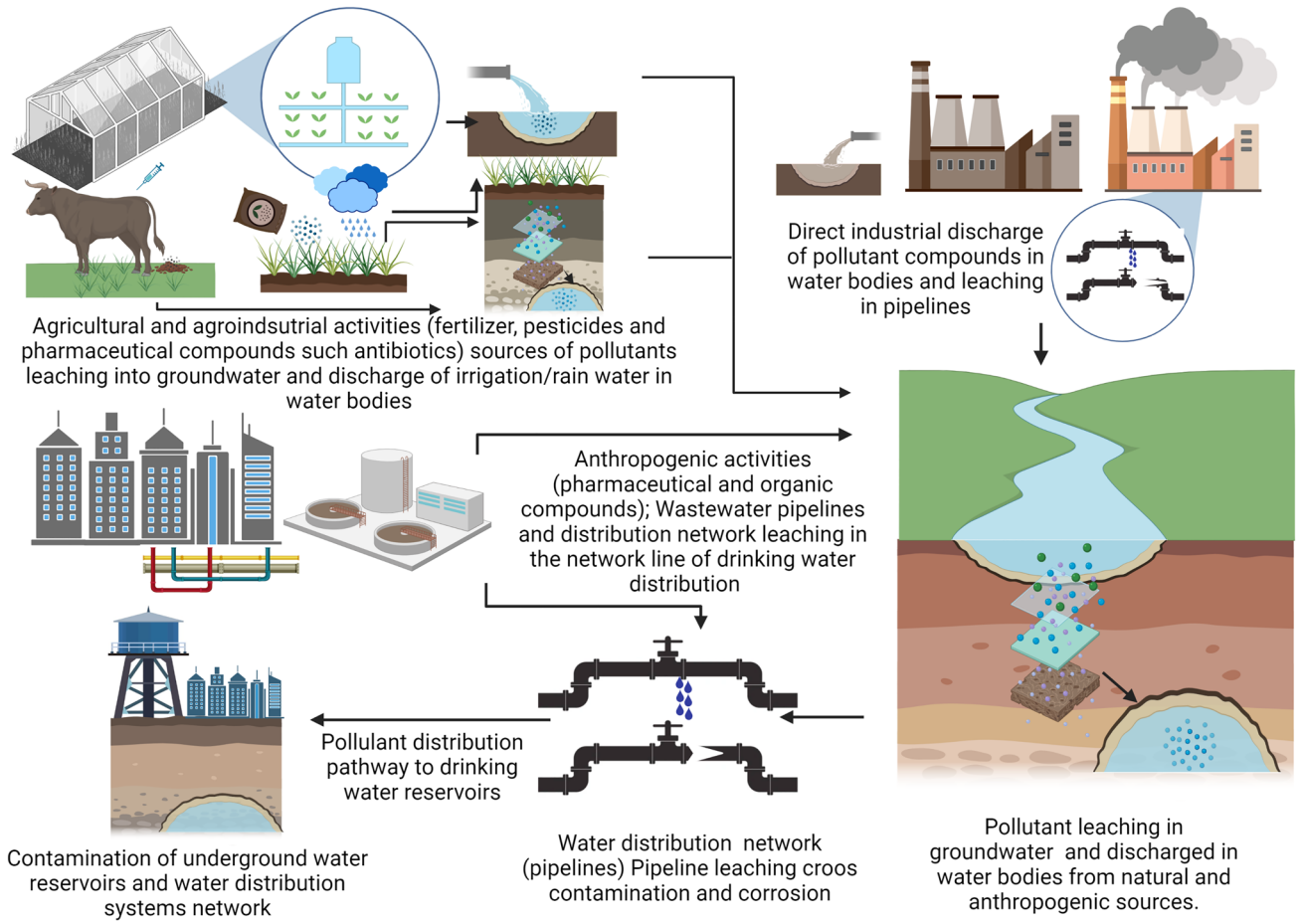


Fig. 1 Drinking water pollutants sources (anthropogenic and natural sources) and contamination routes at the water reservoirs

can cause several environmental hazards and human health risk (Table 1) [14–17].

Despite the environmental and health risk derivate from pollutants in water sources, the presence and diffusion not only of the mentioned pollutants but also its metabolites and transformation products in the environment are not tracked and understood. For example, it is known that there is no clear regulation, and the maximum concentration is not established, for PFAS in drinking water [13], o that, the development of methods and instruments that allows detection and quantification without requiring highly training personnel and high-cost equipment is extremely important [18, 19].

Conventional analytical techniques for heavy metals detection in water, such as the quantum dot method with fluorescence spectrometry [20], inductively coupled plasma-mass spectrometry (ICP-MS) [21], hydride generation atomic absorption spectroscopy (HGAAS) (Arsenic detection in drinking water) [22], graphite furnace AAS [23], X-ray fluorescence spectrometry and energy dispersive X-ray fluorescence [24], have been used for the detection of heavy metals, including arsenic, in drinking water samples and other complex matrices, ICP-MS method is the most common method used. However, despite these techniques being able to detect a low concentration of metals in water samples, low detectable concentration in heavy metals is in a range of 0.3 to 5.81 µg/L [25]. On the other hand, the conventional methods for the determination of organic compounds contamination in water are gas chromatography (GC), Mass chromatography (MC) [26], Gas chromatography with flame-ionization detection (GC-FID), and High-performance liquid chromatography (HPLC) [27]. However, despite the advantages of these techniques, the weakest points of their applications are: sophisticated instrumentation and specialized staff are required, also are expensive and high-demand time techniques, and the cost of analyses can be as high as $8–10 per sample [28].

Alternative techniques of hazardous pollutants monitoring have been evaluated to achieve more effective methods in the detection of pollutants (rapid, sensitive, accurate) also to be available for real-time surveillance and monitoring of the compounds at low operative cost, reducing risk to

Table 1 Effect of toxic pollutants on human health and symptoms during its exposure

Pollutant	Toxicology effects/symptoms	References
Heavy metals	Neurological effects: Disturbances of the nervous system, convulsions, pain, numbness, tremor in extremities, motor neuron diseases, dizziness and headaches, myasthenia, memory problems, insomnia, impaired cognitive development, neurological disorders, including Alzheimer's disease, learning and behavior problems Nephrological effects: Renal disorders, edema, foamed urine, nephrotic syndrome and hematuria Respiratory effects: Shortness of breath and chest tightness, lung fibrosis, pulmonary edema Gastrointestinal effects: Garlic taste in the mouth, pain in throat, chest, or abdomen, nausea, diarrhea and vomiting Reproductivity effects: reproductive diseases Dermatological effects: Erythematous skin rashes, dermatitis, hair loss, nail anomalies or loss and skin anomalies Cardiovascular: Cardiovascular disorders, heart failure and hypotension Oncological effects: lung cancer, nasal cancer and epigenetic effects	[112–119]
Pesticides	Neurological effect: Neurological affectations, neck flexions, weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, anxiety, confusion, drowsiness, emotional lability, seizures, hallucinations, headaches, insomnia, memory loss, neural disorders, driven suicides, anencephaly, behavior problems, autism spectrum disorder and psychosis Nephrological effects: Alterations in hepatic tissue, liver and renal injury Respiratory effects: Respiratory insufficiency, respiratory system malfunction Reproductivity effects: Infertility, pregnancy outcomes and sexual organ malformation Cardiovascular effects: Arrhythmias Oncological effects: Cancer development, lungs, prostate, breast, head, and neck cancer Endocrine effects: Endocrine disruption, hypothyroidism, hyperthyroidism, and hormone level alteration Immunological effects: Immunologic disruption	[120–129]
Organic compounds	Neurological effect: Neurodevelopmental delays Nephrological effects: Nonalcoholic fatty liver disease and chronic kidney diseases Gastrointestinal effects: Metabolic dysregulation Respiratory effects: Reproductivity effects: Cardiovascular effects: Oncological effects: Cancer development, breast, colorectal, esophageal, gastric and thyroid cancer Endocrine effects: Gland malfunction Hypothalamus, pituitary, gonadal malfunction Immunological effects: Allergic diseases, immune suppression and T cells downregulation	[130–133]
Phenolic and Poily-aromatic compounds	Endocrine effects: Gland malfunction Hypothalamus, pituitary, gonadal malfunction Immunological effects: Allergic diseases, immune suppression and T cells downregulation	[134]
Pharmaceutical compounds	Emergence of antibiotic resistance bacteria strains[a]	[135]

[a]No data related to human health risk in water sources has been found [135]

human health for chronic exposure [29]. In response to the above, biosensors arise as a low-cost, portable, and low-time response tool, a biosensor is a device characterized as an integrated system where, using a cell-free or a whole cell-based system, a bioassay is carried out and provides a detection signal for the presence of an analyte in a sample [30].

The biosensors employ a biological recognition element (bioreceptor), can be a whole cell-base system or cell part-based system, for the detection of toxic pollutants, these devices allow onside quantification and avoid the requirement of sophisticated equipment [31]. The development of a wide type of biosensors using different bioreceptors such as microbial fuel cells [18, 32–36], microorganisms (Whole cell-based) [37–40], antibodies [41–43], enzymes [44–50], among others has been reported in the literature. On the other hand, biosensors can be placed as a favorable alternative due to the variability of pollutants (Heavy metals, organic compounds, drugs, and microorganisms) that are capable of pollutant trace detection [29].

Bioreceptor selection is focused on obtaining the highest sensibility, selectivity, and simplicity. Biological sensing employing enzymes as biological recognition elements is one of the most popular biosensors used [51], development of biosensors appears as a promising alternative for water pollution and quality monitoring, to ensure environmental and health safety [29].

2 Enzymes Immobilization Applied as a Bioreceptor Element in Biosensing

Enzymes are biological macromolecules that play a role as biocatalysts in the progress of life, exhibiting catalytic activity, specificity, biodegradability, and selectivity in fundamental and sophisticated activities [52]. Biosensors are instruments that use biological substances such as enzymes, DNA, antibodies, cells or microorganisms as bioreceptors, which recognize and capture the contaminant or analyte with high sensitivity and selectivity and trigger a physicochemical reaction (generation of light or heat, change in pH, and mass change) that can be transformed by the transducer into a detectable signal form. The three-dimensional structure and the active center of the enzymes are responsible for the recognition and high specificity for the analyte, which allow the union between enzyme and analyte through hydrogen bonds, electrostatic forces, or other non-covalent interactions, to trigger a reaction through a catalytic effect, which converts the analyte into another product that can be quantified or measurable for analysis [53]. The use of enzymes as bioreceptors has the advantages of short response times, real-time continuous detection signals, a low detection limit, low application costs with high specificity, sensitivity, and reliability [54, 55].

Table 2 Advantages of different enzymes apply as bioreceptor of contaminants in water by enzyme-based biosensors

Enzyme	Compound	LOD (nM)	Stability	Advantages	References
Pesticides					
Choline oxidase	Dichlorvos	1.55	20 days at 4 °C	Low LOD, high selectivity and reproducibility	[136]
Phosphotriesterase	Praoxon	3	8 weeks at 4 °C	Low LOD, potential for implementation into high-volume manufacturing protocols	[137]
Organophosphorus hydrolase	Methyl parathion	5000	30 days at 4 °C	Great storage stability and reusability	[138]
Butyrylcholinesterase ALP tyrosinase	Paraoxon, 2,4-dichlorophenoxyacetic acid, and atrazine	2 50* NR atrazine	NR	Multianalyte detection, low LOD and low cost	[139]
Glutathione stransferase	Fenobucarb, temephos, and dimethoate	2.00* 4.00* 5.00*	NR	Capacity to detect carbamates and organothiophosphate pesticides	[140]
Heavy metals					
Glucose oxidase/horseradish peroxidase	Cr(VI), Cr (III)	0.20 10.00	30 days at 4 °C	Good selectivity, ability to detect both Cr(III) and Cr(VI)	[141]
Glucose oxidase	Hg^{2+} Cd^{2+} Pb^{2+} Cr^{6+}	2.30 1.75 2.70 2.44	20 days at 4 °C	Good selectivity and repeatability	[142]
Horseradish peroxidase	Pb^{2+} Ni^{2+} Cd^{2+}	8.00 3.00 1.00	2 weeks at 4 °C	Ability to detect Pb^{2+}, Ni^{2+}, and Cd^{2+} below WHO guideline values, good selectivity and reproducibility	[143]
Horseradish peroxidase	Cr^{6+}	20 M	2 weeks at 4 °C	Low LOD, short response time	[144]
Catalase	Hg^{2+}	0.018	NR	Low LOD, high selectivity	[145]
Emerging contaminants					
Tyrosinase enzyme	Bisphenol A	3.18	86.9% of sensing signal maintained after one month storage	Biocompatibility and environmental friendliness with	[146]
Xanthine oxidase	Bisphenol A	1.0	75% of sensing signal after 15 days	High sensitivity and low detection limit, with good selectivity and stability	[66]
Laccase and graphene oxide nano-sheets	Catechol	32	NR	Good stability and sensitivity	[147]

****LOD** concentration in ppb; *NR* conditions or data not reported

Enzyme-based biosensors can be classified into two categories based on the analyte monitoring mode, direct and indirect mode. The direct mode is defined by the detection of the analytes or the products originating from the biocatalytic action. This method is simple, continuously operable and portable, but the enzyme's high specificity limits the number of contaminants it can detect. The indirect method is based on the inhibition of enzyme activity by the analyte. It is a very functional strategy for the detection of pesticides and heavy metals, since the metal ions react with the thiol group of the sulfhydryl group of the enzymatic structure, creating changes in the structure of the enzyme and affecting the catalytic activity, generating continuous changes that can be read as a signal [53, 56].

The detection of various hazardous compounds in water based on enzyme activation or activity inhibition are usually applied in enzyme biosensors hydrolases (lipases, glycosidases, phosphatases, nucleosidases and peptidases), oxidases (laccases, GOx, monoamine oxidases), oxidoreductases (tyrosinase and nitrate reductase), peroxidases (e.g., horseradish peroxidase), and aminooxidases for the detection of several hazards based on either activation or activity [57]. Enzyme-based sensors are highly functional and highly sensitive to certain contaminants in water such as heavy metals and pesticides and some emerging contaminants such as BPA, Table 2.

Due to their high efficiency, enzymes have been widely employed in different industrial and medical applications, including the development of novel enzyme-based biosensors. They have exhibited many advantageous features such as cost-effectiveness, portability, and high specificity and sensitivity, among others. However, their full potential has been obstructed by some drawbacks including structural instability, high-cost manufacturing and storage, chemical sensitivity, and difficulties related to their recovery [58]. In this context, immobilization techniques are feasible solutions to avoid such limitations and achieve the successful application of natural enzymes. The immobilization of enzymes allows easy separation, effective recovery, high stability, and continuous and repetitive usage while maintaining enzyme activity [44]. The immobilization technique must be carefully selected since it plays a fundamental role in determining the catalytic activity and characteristics of specific reactions [59].

Immobilization methods are typically classified into two main groups: physical and chemical methods [60, 61]. The physical immobilization methods are simple and gentle procedures involving only physical interactions in which the enzymes and the supports are not modified. They are facile and fast methods that generally do not require the addition of any chemical reagent and that do not alter the activity and purity of the enzymes. However, the physical interactions are weak and can be easily dissociated under harsh environmental conditions, thus, affecting the reusability of the enzyme and increasing the possibility of enzyme leaching [61].

On the other hand, chemical immobilization methods involve chemical reactions to form stronger and more stable enzyme-support interactions [62]. Thus, chemical immobilization is preferable in applications that require high recovery and recyclability of enzymes. However, some of their drawbacks include complex and expensive procedures during immobilization. In addition, other variables must be considered such as functional groups, active sites, and pH ranges. Each immobilization method has its advantages and limitations, and hardly a single method can meet all the demands by itself. Therefore, the combination of different immobilization methods seems to be a good option to maximize the immobilization efficiency [61]. In addition to the immobilization efficiency, research has recently focused

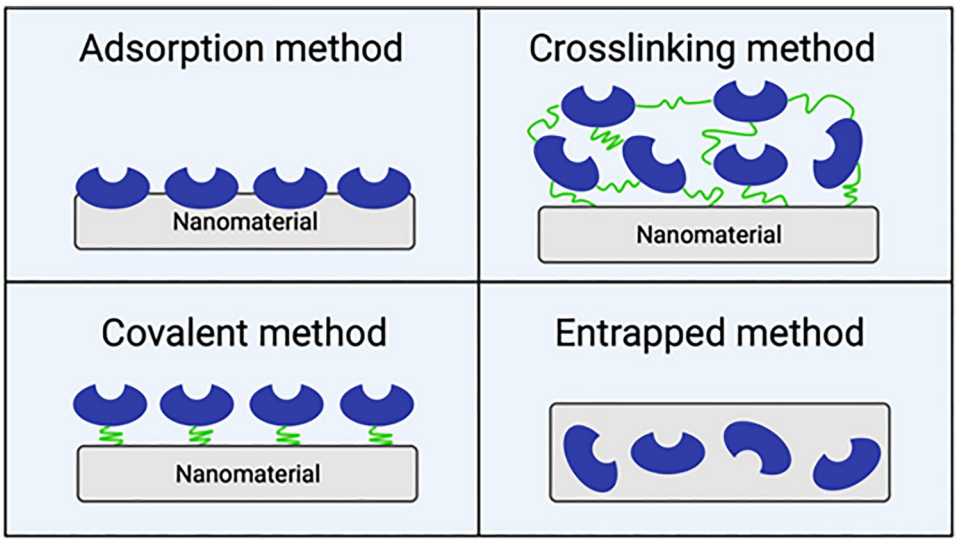


Fig. 2 Typical immobilization methods. Reprinted from Araújo et al. [17] with Permission from American Chemical Society

on reducing costs and complexity aimed to achieve feasible methods for large-scale production.

The most common immobilization methods are adsorption, crosslinking, covalent, and entrapped methods (Fig. 2). The adsorption immobilization method is the simplest physical methodology and consists of direct interaction between the enzyme and the support through adsorption forces (physical or charge adsorption); however, enzyme leaching might occur due to unstable interactions. [17, 61]. Adsorption immobilization methods have been successfully employed during the preparation of novel enzyme-based biosensors with environmental applications. For instance, Rafaqat et al. [63], prepared a biosensor for the rapid detection of chlorpyrifos and Reactive Red 195 (RR195) using fungal laccase and bacterial catalase. Enzymes were immobilized on carbon-felt electrodes by physical adsorption resulting in enhanced stability, and higher reusability while maintaining the catalytic activity. The biosensor exhibited good linear range, high stability, low limit of detection, acceptable reusability, and fast detection, thus, being a suitable biosensing tool for the monitoring of pesticides and dyes [63].

In contrast, covalent immobilization is achieved when a covalent conjugation is established between enzymes and the active group of the support. A more stable and stronger linkage is formed, but the enzyme activity can be affected due to possible modifications to the enzyme structure [64]. Different biosensors have been constructed by this methodology. As a representative example, Caetano et al. [65], constructed an electrochemical enzyme-based biosensor combined with a simple and low-cost microfluidic device for the sensitive detection of phenol in tap water. The electrodes were modified with nanocomposites formed by carbon nanotubes and gold nanoparticles, in which tyrosinase was covalently immobilized. The system showed a good performance in terms of linear range, response time, the limit of detection, operating stability, and sensitivity [65].

Similarly, cross-linking methods provide more stability and long-lasting immobilization by the employment of cross-linking agents connecting enzymes with the selected support. Thus, the constraint of conformational space associated with enzymes is dramatically reduced [17]. This immobilization method has been applied by different research groups during enzyme immobilization for sensing applications. For example, Messaoud et al. [66] constructed a simple biosensor capable of monitoring bisphenol A in water samples. Xanthine oxidase was immobilized onto the surface of a glassy carbon electrode by a cross-linking method using glutaraldehyde and bovine serum albumin. At optimal conditions, the biosensor showed a good performance in an ample linear range with a low detection limit of 1.0 nM; in addition, it exhibited good reproducibility, repeatability, stability, and excellent selectivity in interference studies [66]. Recently, other enzymes like laccases and dehalogenase have been immobilized by cross-linking methods to construct biosensors able to detect different pollutants in water samples [67, 68].

The entrapped immobilization method consists of the encapsulation of the free enzyme by the formation of the support material in the presence of the enzyme. This method possesses advantages like operational stability and negligible enzyme leaching and structure [69, 70]. The entrapped method has been used for the construction of enzyme-based biosensors with environmental applications. For instance, Chronopoulou et al. [69], prepared a biosensor using an engineered glutathione transferase which was entrapped in a sol–gel polymer for the determination of α-endosulfan. The system did not present an enzyme leaching effect and it showed excellent performance for the determination of pesticides in real water samples [69]. Other enzymatic biosensors have reported entrapped methods to immobilize different enzymes [70–72].

Recently, nanozymes have emerged as a suitable alternative to overcome the typical limitations of enzymes such as the costly manufacturing/storage and instability. Nanozymes are described as novel engineered nanomaterials able to act as artificial enzymes usually exhibiting enhanced catalytic performances [73, 74]. Nanozymes have a great potential for future catalytic applications—including, biosensing– since their manufacturing and purification can be achieved in a cost-efficiently manner. In addition, they are easy to modify and possess higher catalytic and structural stability in comparison to natural enzymes [73, 75]. In recent times, different studies have reported the development of a vast diversity of nanozymes and their employment in the detection of different compounds. For instance, Tran et al. developed DNA-copper nanoflowers by a simple method; the synthesized nanozyme exhibited laccase-mimicking capacity. Its catalytic activity was significantly higher than that one presented by the control materials. In addition, the nanozyme presented enhanced stability in terms of pH, ionic strength, incubation time, and temperature variations [76]. Similarly, a laccase mimicking activity was reported on Mn-Cu hybrid nanoflowers, which were applied for the construction of a biosensor able to detect phenolic compounds. The hybrid nanozyme presented excellent catalytic results in addition to advantages associated with higher stability at wider ranges of pH values, temperature, incubation time, and ionic strength. The based-paper microfluidic system fabricated using the synthesized nanozyme presented good results in terms of linear range values and limit of detection for phenolic compounds [77]. Likewise, Cu-tannic acid nanohybrids have exhibited pH-dependent laccase-like activity. The nanozyme presented optimal performance under physiological conditions; it showed resistivity to high temperatures and outstanding recyclability as well [78].

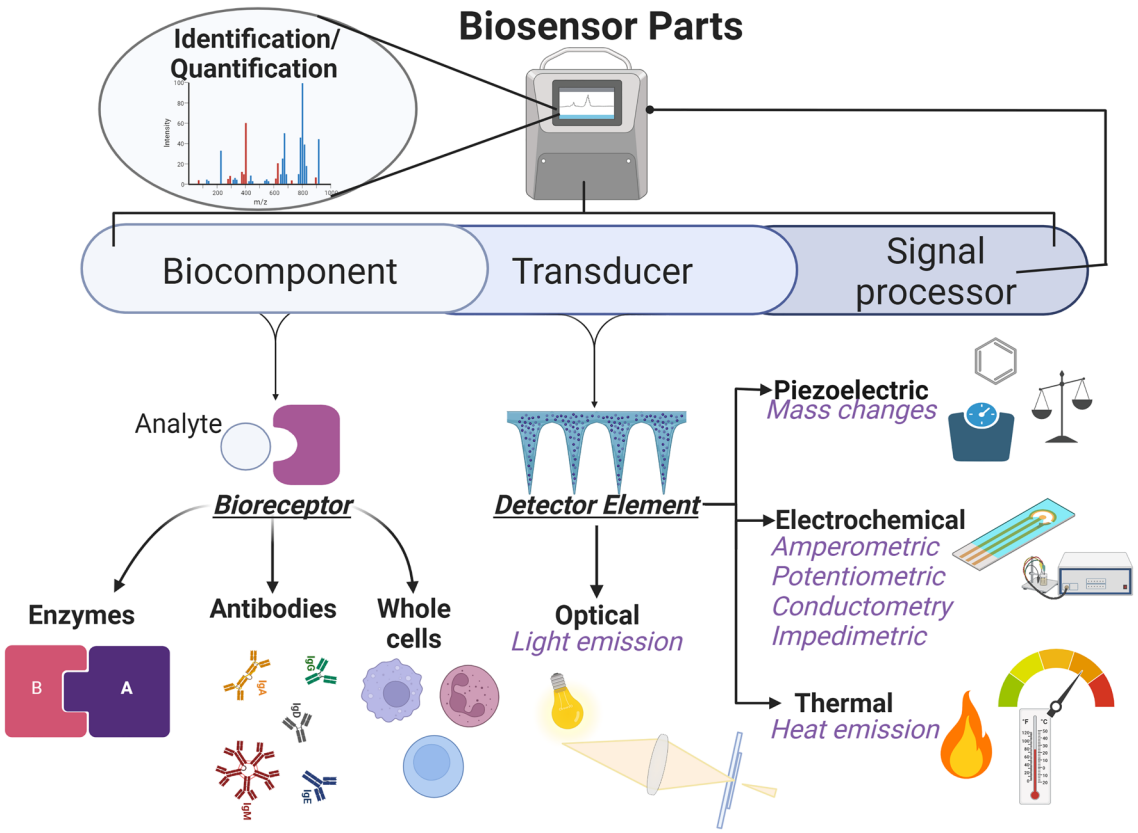


Fig. 3 Biosensor parts and their main components

3 Transduction Methods Used in Immobilized Enzyme Biosensors

Biosensors are composed of three main parts (i) a biocomponent, (ii) a transducer, and (iii) a signal processor (Fig. 3). The transducer, also known as the detector element, is the component in charge of translating the changes that occurred in the biocomponent/bioreceptor into a readable output that will be then translated into a friendly readable value for the signal processor [79]. The main transducers/detector elements employed in enzyme biosensors are piezoelectric, electrochemical, optical, and thermal/calorimetric.

Piezoelectric transducers use the voltage and sound vibration changes occurred during the interaction enzyme-analyte that generate mechanical stress on the surface of the bioreceptor due to piezoelectric effects and mass changes that occur during biological reactions and the formation of chemical bonds between enzyme bioreceptor and the analyte [31, 80].These types of transducers can utilize (i) quartz crystal balance: characterized by the availability to respond to both positive and negative charges, or (ii) surface acoustic device which responded to the changes of vibration frequency due to mass leads changes [81]. Analyte measurement by piezoelectric transducers is obtained by the Sauerbrey's equation (Eq. 1), employing the change in resonant frequency (ΔF), original oscillation frequency (*f*), mass changes (Δm), area of the coating (*A*), and a particular constant of the used crystal (*K*) [82].

$$\Delta F = \frac{K \cdot f^2 \cdot \Delta m}{A} \tag{1}$$

Electrochemical transducers convert biological enzymes reactions with the analyte occurring in the bioreceptor surface into a voltage or current changes enable the quantification of a pollutant [57, 83]. The electrochemical transducer can be classified into fourth main classes (i) Amperometric based on the movement of electrons by redox reactions in the bioreceptor, (ii) Potentiometric usually has an ion-selective electrode or field effect transistor that uses electronic potential changes caused by the reactions analyte-enzyme as a signal of analyte presence, (iii) Conductometric that use two electrodes that serve as reference and measurement element and the transducer detect the difference of conductivity between the electrodes, and (iv) Impedimetric, consider resistance and reactance as a factor for conductivity changes in the membrane or medium as a signal for the presence of the analyte [82]. Electrochemical transducer biosensors are

the most reported in the literature, due to different advantages such as high sensibility, easy scale-up, fast response times, low price, and small sample volume requirement, among others [57, 82].

Optical transducers perform analyte detection by exploiting the response of protons rather than electrons, to its exposure to radiations (UV, fluorescence or visible, near-infrared) that cause energy transfers from excited proton to an acceptor by dipole–dipole interactions (Kaur et al.). Optical transducers can be divided into two categories: label-free and label-based detection, which main difference is the direct detection of the analyte (label-free) or retention or the analyte for further transformation into an optical signal is then generated by different methods such as a colorimetric, fluorescent, or luminescent [84]. Label-free detection is one of the main advantages of these biosensor transducers due it can directly detect and quantify analytes with no requirement of sample preparation or label transformation of the analyte, which results in an inexpensive and easy-to-perform technique [85]. Despite optical signals having a high sensibility and specificity, selectivity, low noise and can be applied to chemical, organic, and biological compounds, the requirement of high-cost equipment for its application and high-cost limit the use of these transducers [82, 86]. Finally, the thermal/calorimetric transducers are used in the biosensing of analytes that produce exothermic or endothermic reactions during their contact and interaction with the bioreceptor [81].

4 Biosensing Technologies in Water Cell-Based Techniques

There has been an increasing water source contamination which calls for rapid detection of polluting molecules. Biosensing techniques effectively indicate water toxicity for animal and human health. During the past years, there has been proposed alternative for animal testing in ecotoxicology, such as in vitro cells models replacing acute lethality tests using fish, using fish cell line and mammalian cell line cultures when testing for water quality for fish acute toxicity detection [87, 88]. In recent years, biosensors incorporating detection systems cell-based and signal transducing elements offer advantages over other detection systems including rapid detection, portability, different sample applications, cost-effectiveness, real-time detection, and different field applications [88]. These techniques are based on the toxic manifestations of the biosensing cultured cells (detachment, changes in morphology, pigmentation, translocation, or cellular death) [89].

The basics of the different biosensing techniques using cell-based systems differ in the biosensing mechanism. These mechanisms include Electric cell-substrate impedance sensing (ECIS) where the culture medium is used as electrolyte with cells grown on an electrode surface cultured covered, where a non-invasive alternating current is applied to measure the cell electric impedance to indicate the cell status (showing the migration, morphology, interactions between cell to cell or cell to matrix, growth, death, among others) [90]. Other mechanisms to measure the changes in cell impedance after perturbation by chemicals, parametric changes such as pH or oxygen consumption, and resonance frequency through mass sensors. Among these cell-based methods, there are chromatophore-based techniques where the basis is the detection of the distribution of pigmentation changes in the chromatophores (pigmented cells found in fish, reptiles, and amphibians) these cells respond to biological pathogens and their toxins, as well as chemicals such as pesticides, polynuclear aromatic hydrocarbons (PAHs) and heavy metals [91]. These changes in the chromatophores include the translocation of the cellular pigments when the cell processes are disturbed, changes in the total area of color in the cells or the pigmented-covered area, changes in the light transmitted through the cell area or the light absorption, distribution of the chromatophores, etc.

Cell-based biosensing systems were already applied to monitoring heavy metal pollution in water sources including "Cu^{2+}" pollution (using microbial fuel based-biosensor "*Escherichia coli* Rosetta genetically modified strain") with a LoD of 28 µM [92], contamination with As^{3+} and Hg^{2+} could be detected with a LOD of 20 µM and 0.498 µM, respectively using an electrochemical cell-based biosensor [93]. Moreover, using an *E. coli*-arsR/zntA strain with an insertion in arsAp::egfp cell-based biosensor was used to determinate the presence of Pb^{2+} contamination with a LoD of 2.06 µM in water artificially contaminated samples [94], and for Cd^{2+} contamination in environmental water samples, using a TOP10/pPcad-ind biosensor (*E. coli* genetically modified strain tolerant to cadmium) with a LOD of 0.049 µM and 0.024 µM of $Cd^{2+}$of exposure in early exponential and lag phase respectively [95]. On the other hand, for pharmaceutical pollutants it was proposed a novel cell-based biosensor using the rat cardiomyoblast H9c2(2–1) cell line to determine the $LD_{50/96\ h}$ as a novel bioassay to determination of water contamination for a least 15 different pharmaceutical active principles and the determination the correlation of $LD_{50/96\ h}$ in H9c2(2–1) cell and contamination concentration, some of the results show the concentration of pharmaceutical compounds such as: Carbamazepine (27.00 mg/L), Sertraline hydrochloride (4.20 mg/L), 17α-Ethinylestradiol (6.70 mg/L), among others [96]. finally cell-based biosensors have been used in the identification of aromatic compounds BTEX (Benzene, toluene, ethylbenzene and Xylene), however this sensors are less sensitive than conventional methods (LOD of 50.00 mg/L of toluene contamination using a *E. coli* cell-based biosensor) [97],

meanwhile, the detection of pesticide compounds (Lindane and Paraoxon) using a cell-based biosensor in food matrix have been development using *Streptomyces* M7 and *E. coli* strains respectively achieving LOD of 120 µg/L of Lindane and 5 µM of Paraoxon respectively [98]. These results and indicators lead for a novel perspective of similar application in water samples, in fact, the application of enzyme based biosensors are more sensitive in the monitoring of pollutants monitoring.

Furthermore, many other biosensing mechanisms for real-time detection or specific detectable substances after chemical exposition include changes in fluorophores labeling targets [91], redox-mediated currents detection [99], and changes in bioluminescence [100], among others.

The selection of the biosensing technique is based on the chemical, toxic, pharmacological target compound to detect, the selection of the cell line [101] the time of detection, and/or the combination of the desired parameters. For this a combination of multiparametric biosensors has been rising in recent years, to determine biological and chemical threats in different water sources.

5 Toxic Elements in Aqueous Environments Monitored by Immobilized Enzyme-based Biosensors

Nowadays, many organic and inorganic chemicals pollute the environment causing damage to its quality, with aqueous sources being the most affected. Due to human and technological development, the regulated or unregulated effluence of inorganic elements like toxic heavy metals, organic elements such as organophosphorus compounds and pesticides, pharmaceutical and phenolic compounds, is a serious problem in human health [102]. As a consequence, there is a need for the detection of these contaminants in a reliable, efficient and low-cost way. Numerous immobilized enzyme-based biosensors have already been developed and applied for detection in the aqueous environment due to their ease of use, cost, greater sensitivity and precision, and portability making them also suitable for in situ analysis [103].

5.1 Heavy Metals

Inorganic contaminants, mostly heavy metals, are natural elements with a high atomic weight and a density of 4–7 g/cm^3, they are not biodegradable and tend to accumulate in living organisms. Lead, silver, iron, arsenic, nickel, chromium, cadmium, copper, zinc, and mercury are among the most frequently detected [104]. Heavy metals infiltrate the environment in various ways, such as mining, industrial waste, agriculture, dyes, and occupational exposure, among others. Therefore, timely detection of heavy metals in aqueous environments is of paramount importance. A variety of immobilized enzyme biosensors have been used for the detection of heavy metals based on the inhibition or activation of their enzymes [105]. Heavy metals have an affinity for certain enzymes. In some cases, heavy metals interact with thiol or methylthiol groups of enzymes and will cause a change in the structure and properties of the active center, decreasing the enzymatic activity. On the other hand, heavy metals are cofactors in metalloproteins and form an essential part of the structure–function for enzyme activation [103]. Heavy metals detection through either of the two pathways will produce a series of changes in the enzyme–substrate system that can be observed by optical means (color change and absorbance) or by different electrochemical methods (potentiometric, conductometric and amperometric [106]. In addition to the above, oxidoreductase is the group of enzymes most used for the detection of heavy metals.

5.2 Organophosphate

Organophosphorus compounds (OPs) are phosphate esters formed from a reaction between alcohols and phosphoric acid: O = P(OR)3 and have very low solubility in water [107]. OPs compounds are found both, in natural biomolecules and in pesticides, including insecticides and herbicides. With the intensive practices of agriculture worldwide, the continuous and excessive use of OPs has been increasing, regularly detecting residues in soil and aqueous environment [108, 109]. Chlorpyrifos, monocrotophos, quinalphos, malathion, parathion, diazinon, bisphenol A, glyphosate, dimethoate, ethion, dichlorvos, and fenthion are the leading agricultural OPs.

So far, the most efficient detection of OPs is enzyme-based biosensors due to their specificity and high sensitivity. Although there are reports of the use of various groups of enzymes for the detection of OPs such as Butyryl Cholinesterase, glucose oxidase, tyrosine, trypsin, urease, organophosphorus acid anhydrolase and hydrolase, the most popularly used are Acetylcholinesterase and Organophosphate Hydrolase (Table 3).

5.3 Pharmaceuticals Compounds

Pharmaceutical compounds (PhC) are a large and structurally diverse group of chemicals used in the treatment and prevention of various diseases in humans, animals, and plants. PhCs most consumed by humans include hormones, nonsteroidal antiinflammatory drugs, antiseptics, analgesics, antibiotics, cytostatics, antipsychotics, β-blockers, and antipyretics (1). The controlled environmental monitoring for

Table 3 Biosensors used for rapid water contaminants detection

Detecting toxic element	Enzyme	Biosensor/immobilization method	Method	LOD (μM)	Linear range /detection time	References
Hg^{2+}	Glucose oxidase	GCE/MWCNTs-RuO_2/GOx/Nafion® GCE/MWCNTs Direct adsorption of multi-wall carbon nanotubes	Amperometric biosensor with an electrochemical transducer	1.05	5–80 μM/10 s	[148]
Copper(II) sulfate	Luciferase and oxidoreductase	NAD(P)H:FMN-oxidoreductase + luciferase co-immobilized into starch gel	Luminescent biosensor with luminometer transducer	2.5×10^{6}*	NR/10 s	[149]
Cr^{6+}	Glucose oxidase	GOx-paper-SPCE Polymer entrapment: chitosan, sodium alginate and dextran	Chronoamperometry	5×10^{4}*	0.05–1 ppm/NR	[150]
Hg^{2+} Pb^{2+}	Glucose oxidase	GOD–Nb–SWNTs/Gr Cross-linked with glutaraldehyde	Amperometric biosensor with an electrochemical transducer	3 4	3–25 μM/ 50 s 4–35 μM/ 25 S	[151]
Pb Ni Cd Zn Co Al	Phosphatase alkaline	Cantilever nanobiosensor Covalent immobilization	Voltage signal	320* 870* 330* 480* 420* 390*	NR/ 30 min	[152]
Paraoxon	Phosphotriesterase	SPCE/rGO/YT-PTE covalent attachment	Conductivity and resistivity biosensor	0.11	$1–5\times10^{-6}$ mM/10 min	[152]
Chlorpyrifos	Acetylcholinesterase	NF/CS-AChE/Co-2Ni-B/GCE Chitosan entrapment	Amperometric biosensor with an electrochemical transducer	2.83×10^{-6}	0.003–300 nM/15 min	[153]
Dichlovos Fenthion	Acetylcholinesterase	AChE/CS/'AuNRs@ MS'@TiO2-CS/GC Chitosan entrapment onti TiO 2 gel	Bioelectro biosensor with differential pulse voltammetry (Amperometric biosensor)	5.3×10^{-3} 1.3×10^{-3}	0.018–13.6 μM/10 min	[154]
Paraoxon-ethyl	Acetylcholinesterase	AChE/AuPt-PDA Polydopamine- Capped gel	Amperometric biosensor with an electrochemical transducer	0.185*	0.5–1000 ng L^{-1}/15 min	[155]
Malathion Richlorfon	Acetylcholinesterase	poly(FBThF)/Ag-rGO-NH2/AChE/GCE Hydrophilic adhesion	Amperometric biosensor with an electrochemical transducer	32* 1*	0.099–9.9 μgL^{-1} 0.0206–2.06 μg L^{-1}/25 min	[156]
Pyrocatechol	Polyphenol oxidase	PPO-ODA/ITO Immobilization with Langmuir–Blodgett film technique (electrostatic interaction)	Amperometric biosensor with an electrochemical transducer	0.644	10–100 mM / NR	[157]
Epinephrine	Laccase	GCE/GQDs/Lac Physical adsorption	Amperometric biosensor with an electrochemical transducer	83×10^{-3}	$1–120\times10^{-6}$ M/10 s	[158]
Norepinephrine	Laccase and glucose dehydrogenase	PDA-laccase@Au-glucose dehydrogenase Covalent binding	Cyclic voltammetry with an electrochemical transducer	0.07×10^{-3}	0.0005–0.5 μM/60 min	[159]

Table 3 (continued)

Detecting toxic element	Enzyme	Biosensor/immobilization method	Method	LOD (μM)	Linear range /detection time	References
Epinephrine	Laccase	Laccase and nanostructured carbon black paste biosensor Incorporation onto nanostructured carbon black paste	Amperometric biosensor with an electrochemical transducer	1.84×10^{3}	4.98–285 μM/1–15 ms	[160]
Catechol	Laccase	Fe_3O_4@Au@ Lac Covalent binding	UV–Vis absorption Optical Biosensor	15	5.0–70.0 μM/ 40 min	[161]
Catechol ABTS	Laccase	ChLa/COOH–MWCNT/SPCE Electrostatic adsorption	Amperometric biosensor with an electrochemical transducer	N.D	0.0–0.102 μM 0.002–0.061/ 5 s	[162]
Phenolic azo dye (EBT)	Laccase	Biosensor immobilized laccase/ Co-crosslinking with BSA and glutaraldehyde/nylon Co-crosslinking with bovin serum albumin and glutaraldehyde	Amperometric biosensor with an electrochemical transducer	3×10^{6}*	8–25 mgL^{-1}/3 min	[163]
Catechol	Laccase	Lac/PArg/AuNPs/GCE Covalently bond	Cyclic voltammetry biosensor with an electrochemical transducer	18×10^{-3}	24.90–274.00 nM/NR	[164]
Catechol	Tyrosinase	GE/β-CD-AuNPs/ Tyr Hydrophobic interactions	Chronoamperometry biosensor with an electrochemical transducer	0.42	1.56–25 μM/15 min	[165]
Catechol Resorcinol	Horseradish peroxidase	Paper-based biosensor Chitosan entrapment with glutaraldehyde crosslinking	Colorimetric paper Optical Biosensor	0.45×10^{3} 0.09×10^{3}	0 to 5000 mg L^{-1}/NR	[166]
O_2^-	Superoxide dismutase	SOD@ATP/Tb-CPBA Encapsulation by a self-adaptive inclusion process	Luminescence spectrometer	0.025	0.1 to 300 μM/3 min	[167]
O_2^-	Superoxide dismutase	SOD/GNPs-CS-IL/GCE Electrochemical deposition	Cyclic voltammetry and chronoamperometry	1.7	5.6–2.7 × 103 nM < 5 s	[168]
S_2^-	Peroxidase	**CIP/chitosan/SPE** Covalently bond	Amperometric and cyclic voltammetry with an electrochemical transducer	0.3	1.09–16.3 μM 43 s	[169]
NO_2^-	Cytochrome C reductase	CcR-SAMGNP-PPy-SPCE Covalently coupled	Cyclic voltammetry with an electrochemical transducer	0.06	0.1–1600 μm NR	[170]
S_2^-	*Escherichia coli* BL21 (*E. coli* BL21) expressing sulfide:quinone oxidoreductase	*E. coli*/NPG/GCE Covalently bond	Cyclic voltammetry with an electrochemical transducer	2.55	50 μM to 5 mM NR	[171]

**LOD* limit of detection concentration on ng L^{-1}; *NR* not reported data

the detection of PhCs and their metabolites has become a huge concern, since the discharge in aqueous environments, such as municipal wastewater, often causes considerable amounts greater than ng L-1 causing damaging effects in the environment (1). The most widely used drugs to save lives are antibiotics produced by microorganisms or chemically synthesized, whose function is to inhibit the growth or death of pathogenic bacteria for the treatment of infections. Due to the above, the excessive use of antibiotics and their discharge in wastewater give rise to strains of bacteria resistant to these pharmaceutical compounds that cause concern and strict need in public health for their timely detection [110]. The enzymes commonly used for the detection and determination of PhCs are laccases, peroxidases, and tyrosinases.

5.4 Phenolic Compounds

The manufacturing industry of plastics, pharmaceuticals, detergents, disinfectants, and the producer of pesticides, is the main contaminant of phenolic compounds in wastewater. Some of the contaminants such as organophosphorus compounds, when degraded, form phenolic compounds. Phenolic compounds such as bisphenol A, chlorophenol 321, phenol, guaiacol and catechol, even in very low concentrations, can cause damage to living beings causing genotoxicity and mutagenicity, they can also repress photosynthesis and some reactions catalyzed by enzymes [111]. The main enzymes used for the detection of phenolic compounds in the environment are laccase, tyrosinase, peroxidases and xanthine oxidase.

6 Perspectives

Due to the complexity of the wastewater matrix, high sensitivity and specificity in detection methods are needed for cell-based and enzyme-based technologies that guarantee a wide spectrum of pollutant detection for on-site and real-time wastewater surveillance. In complement, from a toxicology perspective, the products of enzyme activity or leachate even from immobilized enzyme-based detection methods (such as hydrolases, oxidases, oxidoreductases, peroxidases, and amino oxidases) are imperative to evaluate metabolites produced. Moreover, test product's toxicity to ensure their safe application.

Further, it is important to consider the bioaccumulation of some pollutants, such as heavy metals (e.g. Hg, Pb, Cd, Cu, Cr, Ni, Se, and As), due to extended periods of exposure even at low concentrations of heavy metals. This toxic element's bioaccumulation can produce harmful effects on living beings. To conduct the development of novelty detection methods for pollutants of interest is necessary to keep in mind the adage "the dose makes the poison" aside from high sensitivity, specificity, portability, and low cost for an integral application.

In terms of portability and remote applications, cell-based and enzyme-based technologies still require equipment or minimal instrumentation to conduct sensing assays and quantification that require energy, thus, coupling to alternative power sources such as nanogenerators, and optical and thermal systems are needed, likewise integral control system for manage the systems.

Despite the novelty of emerging pollutants detection and quantification methods, it is needed better strategies such as a proper normative for water safeness and management that warrant early actions to prevent harmful environmental impact and human health impairment. Those normative should consider toxicity assessment aside from pollutants detection and quantification methods to provide proper information that allows diagnosing the anthropogenic activity based on their wastewater surveillance.

7 Conclusions

The presented cases in this review showcase the possibility to expand the application of enzyme-based biosensors to water quality monitoring. For instance, laccase has been reported the most in this type of application in this work's reviewed literature. Many other forms of this type of enzyme open the possibility to explore more applications as biosensors for other contaminants.

Laccases used as biosensors have proved to be versatile, they have been used for the detection of organic and inorganic toxic elements. Hence, the importance of designing durable and reliable biosensors requires huge efforts to provide a high-throughput mechanism which is often achieved with immobilized enzymes. During this revision, it is clear that immobilization methods and supports are widely variable but it has been proven that limits of detection have improved and preserved for the task. The research ahead points out improvement in sensitivity with the incorporation of microfluidics, or porous materials technologies.

Finally, the revision showcases the newly accessible technology to enable sustainable water quality monitoring for safe consumption. Advances in the catalysis for biosensors development can offer in situ monitoring for prompt response in contrast to traditional analysis.

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Declarations

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