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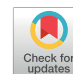
Review Article

Emerging biosensors in detection of natural products



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ABSTRACT

Natural products (NPs) are a valuable source in the food, pharmaceutical, agricultural, environmental, and many other industrial sectors. Their beneficial properties along with their potential toxicities make the detection, determination or quantification of NPs essential for their application. The advanced instrumental methods require time-consuming sample preparation and analysis. In contrast, biosensors allow rapid detection of NPs, especially in complex media, and are the preferred choice of detection when speed and high throughput are intended. Here, we review diverse biosensors reported for the detection of NPs. The emerging approaches for improving the efficiency of biosensors, such as microfluidics, nanotechnology, and magnetic beads, are also discussed. The simultaneous use of two detection techniques is suggested as a robust strategy for precise detection of a specific NP with structural complexity in complicated matrices. The parallel detection of a variety of NPs structures or biological activities in a mixture of extract in a single detection phase is among the anticipated future advancements in this field which can be achieved using multisystem biosensors applying multiple flow cells, sensing elements, and detection mechanisms on miniaturized folded chips.

1. Natural products

Natural products (NPs) originate from living organisms which include: (1) whole organisms (such as animals, plants, microorganisms), (2) parts of organisms, (3) extracts from organisms and (4) pure compounds from organisms [1]. In this context, the biosensing of the biomolecules produced by living organisms is considered. Approximately 25% of one million NPs obtained from plants and microbes are biologically active [2]. Although it has been hypothesized that all NPs essentially have some kind of receptor-binding activities (bioactivities), while finding these interacting receptors can be a challenging task [3].

Several technologies such as the targeted purification, molecular tracking, drug discovery, symbiotic investigations, biomechanics, proteomics, genomics, metabolomics, food science, computation, data mining, bioremediation and environment analysis benefit from monitoring the NPs [4]. Detecting the toxic NPs is also useful in the exploration of their ecological role and more importantly in assessing the potential effects of these toxins on human health [5].

Currently, NPs have multiple applications in human health, industry and environmental protection and they are anticipated to be involved in many more areas in the future. The large chemical structural diversity and consequently divergent biological activities of NPs has made them a prominent source for various pharmaceutical products, including antivirals [6], anti-Alzheimer compounds [7], immunosuppressives [8], antioxidants [9], antimicrobials [10], anti-inflammatory compounds [11], anti-adipogenic agents, digestive agents, and stimulants [12]. In the last decade, a decrease in NP discovery has caused a dramatic decline in discovery of new drugs [2].

1.1. Structural diversity of natural products

The chemical diversity and biochemical specificity of NPs render them leading candidates of drug discovery, in addition to their multiple uses in industrial applications. Due to this chemical diversity, NPs interact with a great number of targets and have a vast range of activities and stability patterns. Studies have shown that NPs possess more chiral centers and steric complexity. Moreover, heavy atom ration of aromatic NPs is less than their equivalents in synthetic or combinatorial libraries [13,14]. NP libraries also have a higher distribution of molecular properties including molecular mass, ring systems diversity, and octanol-water partition coefficient compared to the synthetic and combinatorial libraries [15].

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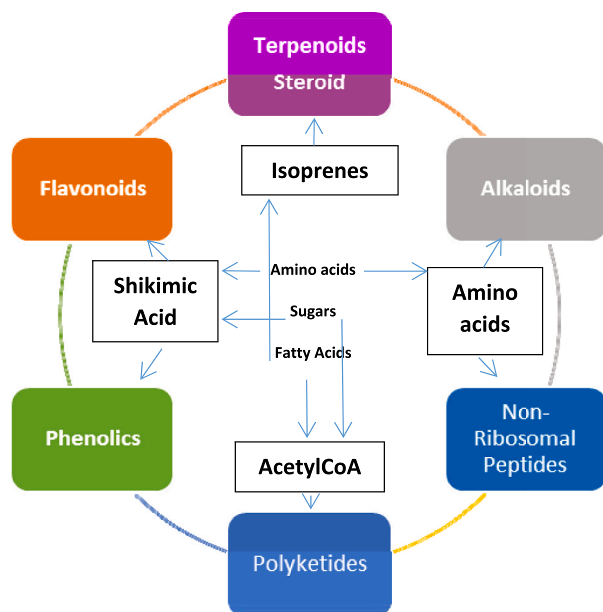

Fig. 1. The chemical structural origin and biosynthetic source of NPs from primary metabolism.

1.2. Source and biosynthesis of natural products

NPs have structural complexity with exclusive biosynthetic pathways which have been optimized during evolution to ameliorate the survival of produced organisms [16]. All NP structures are synthesized from the overflow of fundamental primary metabolites through multiple pathways as illustrated in Fig. 1. Bioactive NPs are produced by members of all three domains of life, for example by plants, vertebrates and invertebrates, fungi, and bacteria [17]. It has also been revealed that the mutualistic or symbiotic microorganisms are, in fact, responsible for producing the majority of NPs being isolated from animals and plants [18]. Hence, a considerable number of drugs/leads isolated from bioactive NPs indeed originate from microorganisms [19].

2. Current approaches in detection and quantification of natural products

The methods used in the detection or separation of NPs can be biological, chemical or physical. These physicochemical approaches are shown in Fig. 2. Despite the advantages of the analytical methods for the identification and screening of NPs, there are limitations in using these methods due to the complexity of NPs [20]. Thus, in addition to well established analytical methods for the detection of new NPs, group-specific or single structure-specific biosensors are needed to accelerate and simplify the detection. For instance, a group-specific biosensor is a biomimetic sensor for the detection of phenolic NPs that can also identify their antioxidant catechol equivalents with high sensitivity and specificity in a wide range of concentrations [21].

3. Biosensors design for detection of NPs

Biosensors are devices used for measuring the biochemical reactions through signals generated by the presence of a specific analyte. Three main parts constitute a typical biosensor: a sensing element called “bioreceptor” that is a biomolecule which recognizes the analyte (target molecule/NPs); a transducer converting the chemical/biological signals into a detectable signal; and a signal processor which measures the transducer signal [22,23].

In the last decade, extensive progress has been made for biosensor based monitoring of biological processes and diagnostics of the diseases using the detection or quantitative determination of biomolecules [24]. Biosensors have numerous proven applications in diagnostics [25], drug discovery [26], biomedicine [27], environmental monitoring [28], food safety and processing [29], and biosafety [30] by providing qualitative and quantitative information on these processes [31].

Biosensors have the advantage of being instant, specific, portable, sensitive, and disposable in contrast to the traditional analytical methods which are rather expensive, complicated, and time-consuming [32]. As a distinctive advantage, biosensors are often amenable to being miniaturized using microfluidics systems which lead to lower cost, portability, and rapid operation. Advances in hardware technology allow biosensors to be scaled down, making them portable, less toxic to the environment, and increase their penetration and sensitivity [33]. Moreover, most of the time, they show higher sensitivity and stability compared to conventional sensing methods [34]. Although biosensors have advantages over highly sensitive analytical techniques (Mass Spectrometry (MS), Liquid Chromatography (LC)-MS/MS, etc. (due to their rapid detection and quantification, they are rarely commercialized for industrial applications [35].

Accurate biosensor design requires fundamental knowledge on the chemical structure of the target NPs, the concentration levels of the analyte [36] and its interfering species, the type of matrix, and the type and volume of the sample [37]. The next step is selecting a biological process that mediates the detection of the target analyte [38]. Detecting a specific analyte in a complex sample is often the main objective in choosing the sensing element and selectivity can be considered as the most influencing parameter in the performance evaluation of a biosensor. Reproducibility, accuracy and precision of a biosensor significantly affect the reliability and robustness of the results [39]. Stability, or in other words, the degree of susceptibility to external perturbations such as temperature, affinity and degradation of sensing elements is the most critical feature in the sustainability of the results over long-term usage of a biosensor. Sensitivity or the Limit of Detection (LOD) and linearity are other important features that should be considered in designing biosensors [22].

4. Classification of biosensors

Biosensors can be classified according to two principal criteria: based on the type of their sensing element and based on the type of their transducer [40].

4.1. Classification of NPs biosensors based on sensing elements

A biosensor has at least one biological part as a sensing element. It can be an enzyme/protein [41], antibody [42], DNA/RNA [43], aptamers [44], or a whole cell [45] which are called enzyme sensors, immunosensors, DNA sensors, or aptasensors. Among different biosensors, enzyme-based biosensors have been most widely utilized as the detectors of NPs in pharmaceutical, biomedical, environmental and industrial analyses [32]. Sensing elements can also be categorized into three groups based on their mechanisms of interaction, which are biosystems, bioaffinity-biocomplexation, and biocatalytic categories (Fig. 3).

4.1.1. Biosystems (microorganisms)

Using whole cells as sensing elements has the benefits of lower cost and higher stability compared to molecule-based receptors; since the need for purification is eliminated, cells can be massively produced and required co-factors are already available inside the cells [46]. In these biosensors, changes in pH, cellular metabolism, and gene expression can be quantified by analyzing the response of transducers in the presence of target NPs [47]. Pfleger et al. introduced a microbial based sensor using *Escherichia coli* mevalonate auxotroph for high throughput screening and quantification of mevalonate in an extracellular environment [48]. Siedler et al. developed a fluorescent-based bacterial

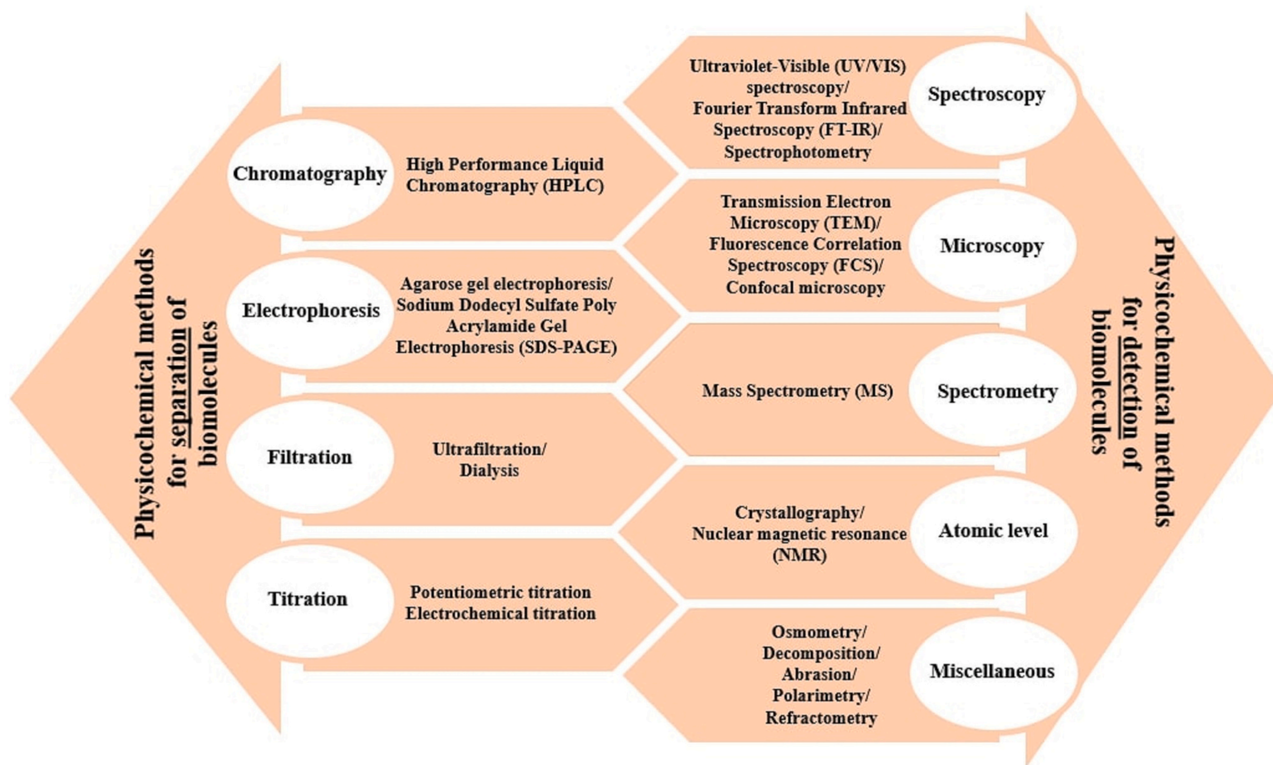

Fig. 2. Physicochemical methods of sensing the biomolecules adopted in biosensing of NPs.

sensor for the screening of extracellular p-coumaric acid. In their approach, *p*-coumaric acid producing cells were cultivated in microfluidic droplets and the sensing bacteria were injected into the droplet. After the induction, fluorescence signals of biosensor cells were sorted and analyzed [49]. Urban et al. proposed a *Bacillus subtilis* based sensor having a set of optimized promoters coupled with the firefly luciferase reporter gene for the detection of NPs interfering with the five major biosynthetic bacterial pathways including fatty acid synthesis, DNA/RNA synthesis, protein synthesis, cell wall, or diverse Mechanism of Actions (MOAs). They screened 14,000 NPs and demonstrated that the proposed *B. subtilis* reporter strains provide an effective way for universal high-throughput screening of bioactive compounds, hampering the five key biosynthetic pathways in bacteria [50]. Ding et al. proposed the fluorescence whole-cell biosensors of *Chromobacterium violaceum* CV026 and *Agrobacterium tumefaciens* A136 for the screening of NPs with Quorum Sensing Inhibitors (QSIs) activity. A database of Traditional Chinese Medicine (TCM) was screened using this biosensor to find QSIs with lower toxicity acting on *Pseudomonas fluorescens* as a food spoilage agent. The loss of blue color and purple pigment indicated that the test NPs can inhibit the production of long chain and short chain *N*-Acylhomoserine Lactones (AHLs), respectively [51].

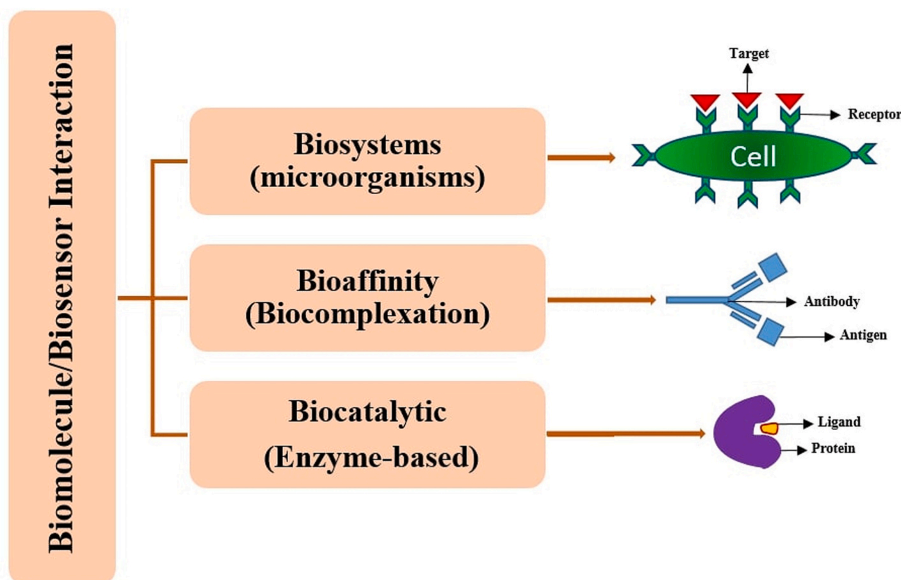

Fig. 3. Types of interactions between the biomolecule (NPs) and biosensor.

4.1.2. Bioaffinity (biocomplexation)

Bioaffinity-based biosensors are widely used in the separation and detection of biomolecules [52]. Bioaffinity biosensors use molecular components as the sensing elements such as antibodies, peptides, proteins, viruses, nucleic acids, aptamers and molecularly imprinted polymers to interact with corresponding NPs [53]. An affinity biosensor based on immobilized concanavalin A protein is used for the detection of glucose [54]. Masson et al. designed a Quartz Crystal Microbalance (QCM) bioaffinity sensor for detecting biotin. The sensor is based on a bioaffinity between avidin and desthiobiotin which is immobilized on a gold layer surface [55]. Mecklenburga et al. proposed a fluorescence-based biosensor for detecting NPs with an affinity for nucleic acids without the need for basic information about their structure. They used salmon sperm DNA as a sensing element and TP3 as a fluorescence molecule intercalating with DNA. When the sample solutions interact with DNA, the intensity of fluorescent signal reduces in proportion to the interacted NP. Their results showed that the polyphenolic constituents of tea extract strongly interact with DNA [56]. Rezler et al. proposed a Surface Plasmon Resonance (SPR)-based biosensor with biotin-labeled human telomeric oligonucleotide immobilized on a streptavidin-coated chip as a sensing element for the recognition of telomestatin. Detection of human telomeric G-quadruplex-binding ligands as stabilizers of the G-quadruplex structures aids in finding anticancer drugs. Telomestatin, an NP obtained from *Streptomyces anulatus* 3533-SV4, interacts effectively with G-quadruplex and inhibits telomerase activity [57]. Metabolite biosensors are sensors based on RNAs or genetically-encoded proteins that interact with metabolites and produce an actuator output. The output controls protein expression or function by modulating the rate of the transcription/translation, or post-translational parameters [58,59].

4.1.3. Biocatalytic (enzyme-based)

Enzyme-based biosensors are robust analytical tools in which enzymes are used as biological sensing elements. In some of these biosensors, the enzyme molecules can be immobilized on the transducer surface to enhance the reproducibility of the detection [32] (Fig. 4). Abdullah et al. represented an optical tyrosinase based biosensor for the quantitative determination of phenolic compounds. The enzyme is immobilized on a chitosan film, and the enzymatic oxidation of phenol produces *o*-quinone which further reacts with 3-methyl-benzothiazoline hydrazine as the reagent and the resulting complex produces a maroon color which can be detected by a spectrophotometer. This catalytic biosensor had LOD of 3.0, 1.0, 1.0, and 0.9 μM for *p*-cresol, *m*-cresol, phenol, and 4-chlorophenol, respectively. Also, the sensor retained its stability for about 2 months [60]. Andreescu and Sadic developed an amperometric tyrosinase based biosensor for detecting natural phytoestrogen polyphenols. This sensor can estimate the total phenolic content of natural phenolic estrogens such as genistein, resveratrol, and quercetin [61]. Kong et al. proposed an SPR-based biosensor consisting of a multi-enzyme nanoreactor with a hierarchical structure using α-Glucosidase (GAA) and Glucose Oxidase (GOx) for anti-diabetic drug screening of NPs. The generated glucose by GAA is oxidized by GOx and the byproduct of hydrogen peroxide changes the shape of silver nanoprism to nanodiscs which can be detected by SPR [62].

4.2. Classification of NPs biosensors based on transducers

Transducers are an integral part of biosensors, as they are responsible for creating a measurable signal by energy conversion. The intensity of the produced signals by transducers is usually commensurate to the numbers of the interactions developed between analytes and sensing elements [22]. Transducers are classified into five main groups based on the type of energies they produce upon receiving a signal from the sensing element, which consists of 1) electrochemical, such as amperometry, voltammetry, potentiometry, impedimetry, conductometry, and ion charge or field effective transistors; 2) optical, such as fluorescence, colorimetry, SPR, chemiluminescence, Raman scattering, optical fibers, Fourier-Transform Infrared Spectroscopy (FT-IR), and interferometry; 3) Mass change such as QCM, and 4) Miscellaneous that cannot be incorporated to any of the mentioned groups, such as calorimetric, magnetic, and combinatorial transducers [63–65]. The type of transducers for designing an NP biosensor can be selected from

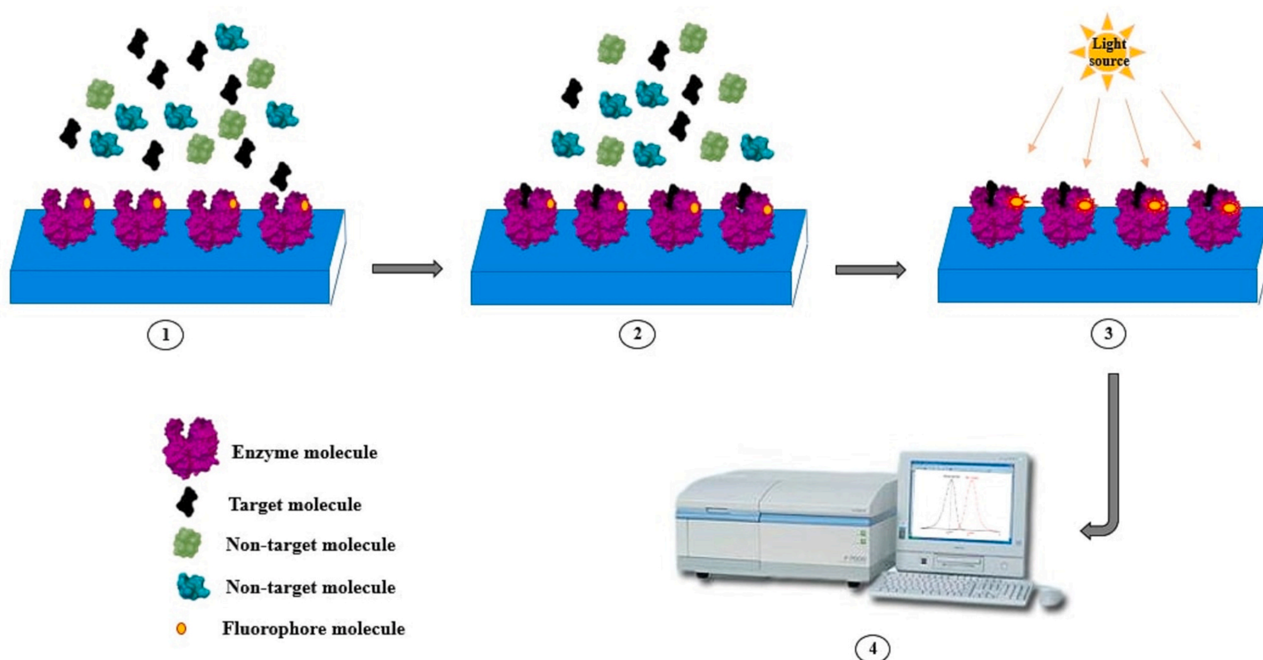

Fig. 4. Schematic representation of a luminescent enzyme based biosensor with an optical transducer. Enzymes as sensing elements are coupled with a fluorophore molecule and immobilized on a surface. 1) A solution of the NP is passed over the surface with immobilized enzymes. 2) Target molecules of NPs interact with the enzyme molecules. 3) After washing the unbounded molecules, an exciting wavelength is illuminated and the fluorophore molecules absorb the light and excite 4) Emitted photons are sensed by a luminometer/fluorimeter and further analyzed by analyzing software to validate the identity of target molecules.

the described classes in the following subsections.

4.2.1. Electrochemical transducers

Electrochemical transducers convert the biochemical signals resulting from analyte recognition to the electrical signals. This type of transducer shows excellent accuracy, repeatability, and resolution, but they can be easily influenced by temperature changes, resulting in a short shelf-life [66]. Electrochemical biosensors mainly utilize enzymes as the recognition part due to the specificity of enzymatic reactions [67]. One of the most commonly used biosensors employing the electrochemical transducer is glucometer. The interaction of glucose and oxygen molecules on the surface of an enzyme oxidizes hydrogen peroxide (H_2O_2) and produces electrons. The quantity of produced electrons is measured by the electrochemical transducer (electrode) that is transformed into a measurable signal to be further amplified and processed [68].

Another common type of electrochemical biosensor uses amperometric/voltammetric transducers in which the produced current by the potential difference between electrodes and the analyte contributes to a redox reaction [69,70]. Karyakin et al. developed an enzyme-based amperometric biosensor which transduces the oxidation of glutamate through Prussian Blue that selectively senses the reduction of the H_2O_2. The LOD of the sensor is estimated at 10^{-7} M [71]. Kochana et al. developed a voltammetric tyrosinase based biosensor for tyramine detection with a LOD of 1.5 μM for tyramine oxidation. Since tyramine concentration increases in proportion to the food spoilage, it is a suitable indicator of toxicity in the food industry [72]. Flampouri et al. proposed a cell-based voltammetric biosensor for cytotoxicity evaluation of NPs extracts. Renal cells were immobilized on a conductive polymer surface. To estimate the electrocatalytic activity in the interface of the renal cell/electrode, cyclic voltammetry was used. Carbon tetrachloride (CCl_4) was utilized as a nephrotoxicity agent and the plant extracts were assessed for their renoprotective effect. The proposed biosensor was able to consider the number of cells and their potential in monolayer formation as indicators of cell viability or cell toxicity [73]. Hsieh et al. proposed an amperometric Choline Oxidase (ChOx) sensor for the quantification of NPs with acetylcholinesterase (AChE) inhibitory activity. The natural chitinous membrane was covalently immobilized with an *Alcaligenes* sp. ChOx linked to a platinum electrode of the amperometric flow cell [74].

Other types of electrochemical biosensors use potentiometric transducers which sense the variations of hydrogen concentration resulting from biocatalytic or bioaffinity reactions [75]. Stepurska et al. developed an enzyme potentiometric biosensor based on field-effect transistors which are sensitive to H^+ ions to detect Aflatoxin B1 (AFB1) in food. Here, the inhibition of AChE activity on its corresponding substrate, acetylcholine chloride, was used as a sensing element to validate the presence of AFB1 in real samples [76].

Impedimetric transducers are another type of electrochemical sensor that measure the fluctuations in the charge conductance when the target molecule selectively binds on the surface of the sensor [77]. The impedimetric techniques have been used in monitoring the reactions catalyzed by enzymes or the biorecognition events of whole cells and microorganisms, antibodies, specific binding proteins, receptors, nucleic acids, lectins, etc. [78,79]. Porfireva et al. developed an impedimetric DNA sensor based on electropolymerization of proflavine layer for the detection of anthracyclines. Proflavine polymer is an electroconductive polymer. The recognition of the DNA deposition on proflavine polymers and intercalation of anthracyclines with the adsorbed DNA was recognized by measuring the redox change due to the electron exchange of the coated poly (proflavine) on the electrode [80].

4.2.2. Optical transducers

The optical transducers detect changes in the emitted wavelengths [81] and are classified into two groups: label-based (indirect) and label-free (direct). The label-based sensing implies that the target analyte is labeled with a reporter molecule and the detection process is performed using luminescent, fluorescent or colorimetric signals. In label-free type, the interaction of a sample with the transducer surface directly leads to a photonic signal [82,83]. Optical biosensors have high sensitivity and compatibility with remote monitoring but are vulnerable to external physical disturbances [84,85]. Kreiss et al. proposed a biosensor based on a whole-cell harboring bioluminescent reporter gene for the detection of NPs acting on the bacterial DNA supercoiling (antimicrobial activity). This sensor was able to identify the effect of inthomycin A on supercoiling of the bacterial genome in a raw extract [86].

Fluorescent-based biosensors utilize emission wavelength, emission intensity, fluorescence lifetime, or fluorescence anisotropy as analytical information. The signals may be derived from changes in pH, charge, polarity, or viscosity of fluorophores [87]. These biosensors use organic dyes, carbon quantum dots (QDs), and semiconductor QDs as fluorophores [88]. Castaño-Cerezo et al. proposed a fluorescence-based synthetic biosensor that could detect the production of benzoic acid in a genetically modified *Saccharomyces cerevisiae* both in *vitro* and *in vivo*. The sensor is composed of a pHBA (4-Hydroxybenzoic Acid)-binding domain of HbaR from *Rhodopseudomonas palustris*, the transactivation domain B112 and the LexA DNA binding domain at the C-terminus and N-terminus, respectively [89]. González-Andrade et al. developed a fluorescent-biosensor based on human fluorophore-labeled Calmodulin (CaM) for the detection of potential CaM inhibitors such as malbrancheamide and tajixanthone. They used hCaM M124C–mBBr, which is a human CaM with a cysteine unit at the position 124 labeled with fluorophore monobromobimane (mBBr) [90]. Hunt et al. proposed a fluorescent cell-based biosensor for evaluation of stimulation or inhibition of Quorum Sensing (QS). *Pseudomonas aeruginosa* PAO1-JP2, a mutant strain unable to produce AHLs, was used for this purpose. The bacteria contain plasmid pKR-C12 which harbors elastase gene *las*B (a virulence gene from *P. aeruginosa*) translationally fused to a green fluorescent protein gene (*gfp*). The Relative Fluorescent Units (RFU) were considered as QS Stimulatory values. The AHL biosensor strain *C. violaceum* CV026 was also used as a reporter organism for the identification of violacein synthesis which is a pigment regulated by QS [91].

Colorimetric transducers are another type of optical biosensors that act on the basis of changes in the wavelengths within the visible spectrum and have the advantages of rapidity and being observed with the naked eye [92]. Gold nanoparticles and silver nanoparticles are commonly used in colorimetric assays due to the straightforward distinction of their color transformation [93]. Rebets et al. designed and developed a luminescent whole-cell (*Streptomyces albus*) biosensor for detection and measurement of pamamycins, the macrodiolide antibiotics. The biosensor used TetR transcriptional repressor in recognizing and optimizing the antibiotic producers [94]. Zhu et al. developed a dual colorimetric biosensor for simultaneous quantification of ochratoxin A (OTA) and AFB1 using aptamers as sensing elements. The sensor showed 0-5-80 ng ml^{-1} and 5–250 ng ml^{-1} LOD for OTA and AFB1, respectively. The color change was analyzed for OTA under alkaline conditions and for AFB1 under acidic conditions, which generate different colors without interfering with each other [95].

SPR is an optical mechanism used by some transducers based on photonic excitation without any need for the labeling process. Interaction of the target molecule with the biosensor immobilized on an SPR transducer induces a shift in the refraction index [96]. SPR based detection can qualitatively and quantitatively measure the biomolecular interactions with high sensitivity, compatibility with a wide range of target molecules, and real-time monitoring [97]. Peng et al. used a series of SPR- High Performance Liquid Chromatography (HPLC)-MS/MS for the detection of Human Serum Albumin (HAS) binders in natural extracts. The SPR-based part of the sensor used a bicell-photodetector. Using this system, they identified 22 HAS binders in extracts of *Eucommia ulmoides* bark [98]. Saleh et al. also proposed an SPR based biosensor for detection of Madindoline A. The Recombinant Fc-HA and

Table 1
Biosensors developed for the detection of Natural Products (NPs).

Detected Natural Product	Bioreceptor	Type of Signal Transduction	Obtained Information and Application	Year	Ref
NPs with an affinity for nucleic acids	DNA helix	Fluorescence	Detection of anti-mutagenic compounds	1997	[56]
Glutamate	Glutamate oxidase	Amperometry	Monitoring the glutamate in food industry	2000	[71]
Phytoestrogen polyphenols	Tyrosinase	Amperometry	Detection of phenolic Endocrine-Disrupting Chemicals (EDCs) related to reproductive tract disorders	2004	[61]
Telomestatin	Biotin-labeled human telomeric oligonucleotide	Surface Plasmon Resonance (SPR)	Detection of human telomeric G-quadruplex-binding ligands which stabilize the G-quadruplex structures for anti-cancer drug discovery	2005	[57]
Madindoline A	Human glycoprotein 130 conjugated to the Fc fragment of the immunoglobulin (gp130-Fc-HA)	SPR	Analysis of gp130 interacting NPs in inhibition of IL-6 and IL-11 in related diseases	2005	[99]
Phenolic compounds	Tyrosinase	Colorimetry	Quantification of 4-chlorophenol, phenol, *m*-cresol and *p*-cresol	2006	[60]
NPs with Acetylcholinesterase (AChE) inhibitory activity	Choline Oxidase (ChOx) enzyme	Amperometry	Quantification of cholinesterase inhibitory activities in NPs	2007	[74]
Macrolides	A recombinant bacterial strain	Luminescence	Finding new producers of known macrolides or producers of new macrolide core structures	2007	[114]
Antibiotics	Whole-cell *Bacillus subtilis* reporter strains	Luminescence	Detecting the Mechanism of Action (MOA) of mechanistically underexplored antibiotics	2007	[50]
Malbrancheamide and tajixanthone	Human fluorophore-labeled Calmodulin (CaM)	Fluorescence	Identification of potential CaM inhibitors	2009	[90]
ent-kaurene diterpenoids	HeLa–C3	Fluorescence Resonance Energy Transfer (FRET)	Detection of apoptosis inducers aimed at finding anticancer agents	2010	[115]
NPs with cytotoxic activities	Panc-1 cell	Photonic Crystal (PC)	Cytotoxicity detection on pancreatic cancer cells	2010	[104]
Citropin, maculatin, caerin	Lipid	SPR	Evaluation of potential antibiotics	2010	[100]
Inthomycins and related NPs	*Escherichia coli* with bioluminescent reporter gene	Bioluminescence	Bioactivity of NPs against bacterial DNA supercoiling (antimicrobial activity)	2010	[86]
(+)-2-(1-Hydroxyl-4-Oxocyclohexyl) Ethyl Caffeate (HOEC)	5-Lipoxygenase (5-LOX)	Surface Acoustic Wave (SAW)	Finding anti-inflammatory NPs	2012	[111]
N-Acylhomoserine Lactones (AHL)	pKR-C12 plasmid containing *Pseudomonas aeruginosa*	Fluorescence	Examining the mechanisms that regulate microbial colonization through Quorum Sensing (QS) regulatory system	2012	[91]
Human Albumin Serum (HAS) binders	Bicell photodetecteor	SPR	Identifying HAS binders in natural extracts	2013	[98]
Niacin	Human carcinoma cell lines	Resonant Waveguide Grating (RWG)	Finding anti-hyperlipidemic agents	2014	[102]
NPs with anti-hemoglobinase activity	Hemoglobin (Hb)	Quartz Crystal Microbalance (QCM)	An efficient screening method for inhibitors of enzyme bovine Cathepsin D (CatD)	2015	[110]
NPs with effect on insulin secretion	β cells	Fluorescence	Discovery of insulin secretion suppressors and potentiators	2016	[116]
Tyramine	Tyrosinase	Voltammetry	Application in detection of tyramine in food and food quality control	2016	[72]
NPs with cytotoxicity or cytoprotection effects	Renal cell	Voltammetry	Preliminary crude drug screening and *in vitro* cytotoxicity studies	2017	[73]
Hazardous NPs (scopolamine, hyoscyamine, chelerythrine and sanguinarine)	Muscarinic acetylcholine M2 receptor	RWG	Discovery, monitoring and control of hazardous NPs	2017	[117]
Protease-Activated Receptor 1 (PAR-1) antagonists from NPs	Human epidermoid carcinoma A431 cell line	RWG	Screening bioactive compounds targeting PAR-1 and G Protein-Coupled Receptors (GPCRs)	2017	[103]
NPs with α-Glucosidase (GAA) inhibitory activity	GAA and Glucose Oxidase (GOx)	SPR	Detection of GAA inhibitors (anti-diabetic activity) in extracts of NPs	2017	[62]
p-coumaric acid	Bacterial cell	Fluorescence	Screening of extracellular production of p-coumaric acid in yeasts	2017	[49]
NPs as QS inhibitors in *Pseudomonas fluorescens*	Whole-cells of *Chromobacterium violaceum* and *Agrobacterium tumefaciens*	Fluorescence	Search for Quorum Sensing Inhibitors (QSIs) to control the microbial deterioration of food	2018	[51]
Macrodiolide antibiotics of pamamycin	Whole-cell of *Streptomyces albus*	Luminescence	Detection and quantification of pamamycin antibiotics	2018	[94]
Alkaloid NP pharmacophores (tryptamines, aporphines and protoberberines)	Cyclic Adenosine Monophosphate (cAMP)	Luminescence	Pharmacological profiling for candidates with anti-schistosomalactivity	2018	[118]
Benzoic acid derivatives	Multi-peptide	Fluorescence	Detection of benzoic acid derivatives in a genetically modified yeast strain of *Saccharomyces cerevisiae*	2019	[89]
Volatile Organic Compounds (VOCs)	Odorant Binding Proteins (OBPs)	SPR	Olfactory detection of VOCs in solutions	2019	[101]
Phenolic compounds	Tyrosinase	Voltammetry	Detection of phenolic compounds in aqua solutions	2019	[119]
Aflatoxin B1 (AFB1)	Anti-AFB1 antibodies	SPR	Detection of small molecules of mycotoxins	2020	[120]
Phenolic compounds	Laccase	Amperometry	Recognition and control of hazardous phenolic compounds in environmental pollution	2020	[121]
OTA and AFB1	Ochratoxin A (OTA) and AFB1 aptamers	Colorimetry	Simultaneous detection of OTA and AFB1	2020	[95]

gp130-Fc-HA proteins were covalently linked to two distinct flow cells on a dextran polymer. After injection of different concentrations of Madindoline A into the flow cell containing gp130-Fc-HA and the reference flow cell containing Fc-HA, bound Madindoline A induced a steady-state equilibrium response of Resonance Units (RUeq) which was calculated by subtracting from the reference sensorgrams [99]. Chia et al. proposed a lipid based SPR biosensor for evaluation of potential antibiotics such as Citropin, Caerin, and Maculatin. The antimicrobial peptides were serially diluted in Phosphate Buffered Saline (PBS) and passed over the flow cells containing phospholipids. The bounded peptides to phospholipids at equilibrium were measured [100]. Hurot et al. developed a SPR based olfactory biosensor that uses immobilized Odorant Binding Proteins (OBPs) as sensing elements to examine the presence of Volatile Organic Compounds (VOCs) in solutions [101].

There are several other types of optical biosensors used in the detection of NPs. Zhang et al. proposed a cell based Resonant Waveguide Grating (RWG) to identify niacin in fractions of TCM plants. The affinity of niacin for its agonist, hydroxyl carboxylic acid receptor, changes the RWG and the Dynamic Mass Redistribution (DMR) profile was studied [102]. Tang et al. proposed a cell-based RWG biosensor for screening of the Protease-Activated Receptor 1 (PAR-1) antagonists among NPs. The cellular DMR was measured by RWG as an indication of cellular response to stimulation of PAR1 by NPs [103]. George et al. used an adenocarcinoma cell line (Panc-1) Photonic Crystal (PC) for the detection of NPs with cytotoxicity effect on pancreatic cancer cells. The sensor measured the local changes of the Peak Wavelength Value (PWV) of the reflected light caused by binding the cell occurrences on top of the sensor surface [104].

Chemiluminescence, a process similar to bioluminescence is induced by chemical reactions without external illumination [105,106]. Meyer et al. established a chemiluminescence protein-based biosensor for the detection of tetracyclines in food and environmental samples. They used a competitive assay of the sensing element using immobilized DNA oligonucleotide containing *tetO* operator sequence, and repressor protein TetR with biotin tag. In presence of tetracyclines, released TetR from its operator sequence is sensed by the illumination of the HRP-conjugated streptavidin catalysis linked to TetR [107].

4.2.3. Mass transducers

Piezoelectric, QCM, Bulk Wave (BW), magnetoelastic, and acoustic wave transducers are based on mass change detection. Mass-sensitive biosensors are label-free sensors in which fluctuations in mass are induced by the biological recognition processes [108,109]. Cornelio et al. described a biosensor for real-time investigation of Hemoglobin (Hb) degradation as a screening method for NPs with inhibitory activities by covalent immobilization of Hb on a quartz crystal surface. Common Hb hydrolysis assays use spectrophotometric approaches that are not real-time monitoring and are influenced by interferences. Hb hydrolysis by the enzyme activity causes a mass change, which is evaluated by monitoring the turnover number (kcat) of bovine Cathepsin D (CatD) after inhibition by NPs. Change in the frequency of the quartz crystal can be detected as an indicator of Hb cleavage by CatD activity [110]. Li et al. proposed a 5-Lipoxygenase (5-LOX), Surface Acoustic Wave (SAW) based biosensor for detection of inflammatory NPs such as (+)-2-(1-Hydroxyl-4-Oxocyclohexyl) Ethyl Caffeate (HOEC) which was detected in an indigenous plant that had been traditionally used for the treatment of inflammation. Targeting the 5-LOX as a vital enzyme in arachidonic acid cascade by HOEC was validated by this biosensor-based affinity detection. In this sensor, mass loading changes due to biomolecular interaction processes result in phase changes of the SAW on the surface of the sensor chip [111].

Calorimetric or thermal transducers are another type of mass transducers that measure the enthalpy fluctuations and have substantial potential in bioanalytical assays. Two types of this approach include adiabatic calorimetry (without any heat exchange between the NPs and the external environment) and heat conduction calorimetry (which measures the heat transferred from the NPs to the environment) [112]. Gaddes et al. designed a calorimetric enzyme biosensor coupled with a thermometer, Quartz Crystal Resonator (QCR), for detection of urea based on the reaction heat transfer. They used immobilized layers of urease on glass beads integrated with a flow reaction tube. The produced heat during the enzymatic catalysis of urea was measured as an indicator of urea content [113].

The instances of employing biosensors in detection of NPs are provided in Table 1. As can be inferred, the use of biosensors for NP detection or screening of their biological activities mostly dates back to recent decades. Most of the cases used optical transducers in designing biosensors.

5. Emerging biosensor-based detection methods of natural products

5.1. Cell-free biosensors versus cell-based biosensors

Whole cell-based biosensors are utilized for monitoring different NPs such as antibiotics, toxins, pesticides, herbicides, etc. The application of cell-based biosensors provides some advantages over the commonly used biosensors using purified biomolecules. There is no need for purification and isolation of biocomponents in designing cellular and tissue biosensors. Furthermore, cells tolerate a broad range of physicochemical stress, namely temperature and pH levels compared to the purified biocomponents. The biocomponents have higher activities; but, cell-based biosensors have a longer lifetime than the molecular based biosensors. Indeed, the presence of the cell membrane protects the contents against denaturation and provides a longer lifetime for a whole-cell compared to the free molecules. Nevertheless, due to the requirement of diffusing the substrate, the process would be longer in these biosensors [122]. Moreover, there are some challenges in cell storage, regeneration, heterogeneity in the cell population, and cost of instrumentation for their larger scale production. Kalwat et al. developed a fluorescent β cell-based biosensor for screening of marine NP fractions to find potential inhibitors and activators of glucose-stimulated insulin secretion pathway. They expressed the insulin-luciferase reporter in β cells and treated the cells with NPs. Using this system, they could examine the effects of compounds on glucose secretion caused by changes in gene expression or post-translational modifications [116]. Korpela et al. proposed a novel type of cell-based sensor using genetically engineered *E. coli* to detect tetracycline antibiotics. This strain carries an operon of luciferase under the control of the tetracycline-responsive promoter *tetA* and the *tetR* repressor which emits blue light in the presence of tetracyclines [123]. Möhrle et al. proposed a luminescent whole-cell based biosensor for identification of macrolide groups with any possible biological activity. The macrolide biosensor consists of *E. coli* strain SM101 containing the mphR promoter and MphR repressor binding site next to the lux reporter genes which is coupled by an operon controlling the regulatory resistance of erythromycin. Macrolides presence leads to releasing the repressor protein and expression of the lux operon genes results in a luminescence signal [114]. Han et al. proposed a FRET whole-cell based biosensor using HeLa–C3 cells for detection of *ent*-kaurene diterpenoids which induce apoptosis. They combined a biosensor with High-Speed Counter-Current Chromatography (HSCCC) approach for identifying a potent apoptotic component from Chinese herbal extracts [115]. The parasitic blood fluke, *Schistosoma mansoni*, produces serotonin (5-HT) which targets the cyclic Adenosine Monophosphate (cAMP) to regulate the parasite movement. Marchant et al. proposed a co-expressed Sm.5HTRL receptor in mammalian cells beside a luminescent cAMP-biosensor for finding the anti-schistosomal drug candidates such as aporphines, protoberberines, and tryptamines which was previously shown to regulate Sm.5HTRL [118].

The developments in cell-free synthesis technologies have led to

using these systems such as aptamers, transcription factors, toehold switches, and aminoacyl tRNA synthetases, etc., as the recognition elements. The nature of *in vitro* cell-free biosensors leads to higher flexibility and operational facility of these sensors in contrast to the microbial cell-based sensors with higher LOD for the target analytes [124]. Another advantage of cell-free biosensors in comparison to the cell-based biosensors is their higher sensitivity and specificity, and less false negatives than the cell-based systems when ligands reach a toxic level for cells [125,126]. Song et al. used a muscarinic acetylcholine M2 receptor based RWG for optical biosensing of the hazardous NPs (scopolamine, hyoscyamine, chelerythrine, and sanguinarine). In the BTPP method (Biosensor-based Two-phase Pharmacological Profiling) a RWG biosensor is used in the determination of intracellular changes which are induced by the protein relocalization following the stimulation of receptors by the toxicants. The detection principle in this sensor is to convert DMR, caused by the intracellular protein delocalization, into a measurable optical signal [117].

5.2. Nanotechnology based biosensors

Using nanomaterials in biosensor design is a direct approach for intensification of signals, due to their exceptional conductivity, biocompatibility, and the great loading of signal molecules which amplifies the signal [127,128]. As a result, nanomaterials can increase the sensitivity and decrease the LOD substantially, which leads to an enhanced performance of the biosensors. Nanomaterials can be used in specific immobilization of the sensing elements. The covalent binding of biomolecules to nanomaterials has the advantages of stability, reproducibility of surface functionalization, and lowering the unspecific physisorption [129]. Nanomaterials have also been implemented as the biorecognition element in SPR-based biosensors to amplify the signal change [130]. Various types of nanomaterials such as metal nanoparticles, carbon nanomaterials, nanowires, and semiconductors can be used as electrochemical signal amplifiers [70].

Wee et al. developed a voltammetric tyrosinase based biosensor for the exploration of phenolic compounds in aqueous environments. They applied Carbon Nanotubes (CNTs) to make a solution of Enzyme Adsorption, Participation and Crosslinking (EAPC) by crosslinking with tyrosinase molecules. Using these nanostructures, the sensitivity of the sensor was improved, as the LOD for phenol and catechol reached 35 and 14 nM, respectively [119]. Bhardwaj et al. developed a SPR-based biosensor using antibodies to detect AFB1. The surface immobilization of anti-AFB1 antibodies by coating with AuNPs amplified the signal and reduced the LOD to 0.003 nM [120]. Othman and Wollenberger achieved an amperometric biosensor using immobilized laccase as the sensing element in the detection of phenolic NPs. They used a layer of carboxyl CNTs on Screen-Printed Carbon Electrodes (SPCEs) as the immobilization surface of laccase. The coating upgraded the amperometric response to the highest level and the CNTs allowed the fast detection of phenolics on the electrodes [121].

5.3. Magnetic beads application in biosensors

Magnetic beads are used in biosensors to concentrate the analyte with a spatially distributed gradient using an external magnetic field. Magnetic beads loaded with specific targets can be moved within the sensor to a desirable point [131]. Using conjugates of magnetic nanoparticles can enhance the mass alterations and decrease the nonspecific binding on the near-surface of the sampled region, which in turn enhances the sensitivity of the detection [130]. Xin et al. developed a mast cell-based nanosensor for identification of Botulinum Neurotoxin Type B (BoNT/B). They used immobilized nano-magnetic beads coated with anti-BoNT/B polyclonal antibody for concentrated absorption of targets in sample solutions. The sensor detects 100 pM BoNT/B in less than an hour [132]. Lin et al. developed a field-effect enzyme biosensor for quantification of urea, glucose, hydrogen ions, and specific proteins in solutions. Calcium alginate microcubes were used for enzyme immobilization in a magnetic powder. The magnetic beads acted as enzyme carriers by fixing the enzymes on the surface of the sensor using an external magnetic field. In such a system, the measured target directly interacts with the surface of the sensor, making the quantitative measurement of the target concentration feasible [133].

5.4. Microfluidics in biosensors

Advantages of microfluidic devices include providing rapid operation, need for a small volume of samples and reagents, higher sensitivity, lower power demands, and less waste production [134,135]. Furthermore, biosensing analysis in microfluidic scales increases the throughput, controllability and reliability of assays, and reduces the cross-contaminations. Microfluidics confine the preprocessed cells or biomolecules in a defined region, and as a result, allows sensing from a smaller sample size [136]. Olcer et al. developed a biosensor in integrated microfluidic systems consisting of channels with 10 μL capacity for detecting Deoxynivalenol mycotoxin in wheat grain using its antibody as the sensing element. The LOD of this electrochemical immunoassay biosensor was 6.25 ng/ml [137]. Labroo and Cui designed an enzyme-graphene based biosensor on a microfluidic paper for multiplex detection of different metabolites, simultaneously. In this sensor, every metabolite is recognized by a signal produced by the activity of an oxidase enzyme on the testing metabolite. The sensor recognized glucose, xanthine, lactate, and cholesterol in less than 2 min by LOD of 0.3 μM for all of the analytes [138]. Fournel et al. used a SAW-based biosensor for real-time monitoring of phycotoxin of Okadaic Acid (OA). Integrating a microfluidic device in this sensor, increased the flow rate and mass convection on the bio-functional surface which improved the quality of response trend and diminished the required detection concentration of OA [139].

6. Conclusion

NPs are chemical compounds produced by living organisms with progressing applications especially in the food and pharmaceutical industries. Both bioactive and toxic NPs need to be detected and measured for multiple purposes. Furthermore, monitoring NPs concentration or finding their biological activities demands more sophisticated tools or devices. Biosensors as analytical tools can be a new screening approach for improving the speed and LOD of NPs. Biosensors can directly determine the concentration of a NP, indirectly monitor their interaction with biological species or find their intrinsic function in a biological process. Thus, biosensors can detect specific NP structures among a mixture of compounds with similar mutagenic and/or toxic characteristics or conversely, a biological interaction regardless of the chemical structure of the NPs. However, the performance of a biosensor is related to the materials used in its process design, and selecting the appropriate detection methods. Despite all the developments in biosensors, analyzing the NPs in complicated matrices still has deficiencies in most cases. Improving these parameters can further optimize the design process of emerging biosensors in the upcoming years as a new field of interdisciplinary research. Incorporation of the technologies such as microfluidics, nanomaterials, and magnetic beads in designing a biosensor are among the developing approaches to improve the specificity and precision of the detecting system leading to faster, cheaper, and more accurate detection of NPs.

Using multisystem biosensors to detect almost all of the NPs present in a biological extract will be the next step in the area of NPs detection. Biosensors with the ability to be applied in all the environmental and physiological conditions with the minimum possible LOD will be developed in the future and they are certain to provide much applicability in NPs determinations, considerably.

CRediT authorship contribution statement

Firoozeh Piroozmand: Investigation, Writing - original draft. **Fatemeh Mohammadipanah:** Conceptualization, Investigation, Writing - review & editing. **Farnoush Faridbod:** Writing - review & editing.

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