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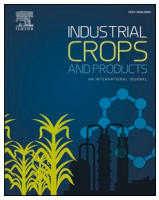

Nano-immunosensors for the rapid and sensitive detection of foodborne toxins; Recent advances

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Abbreviations: Ab, Antibody; Abs, Antibodies; AFP, A-fetoprotein; AFs, Aflatoxins; AG, Antigen; AgNPs, Silver nanoparticles; Anti-MC-LR, Microcystin-LR Ab; AuNPs, Gold nanoparticles; AZT, Azaspiracid toxins; Br-Py, Pyridinium bromide; BSA, Bovine serum albumin; BT, Botulinum toxin; BTX, Brevetoxins; C-AuNPs, AuNPs capped with cysteamine; CB, Carbon black; CdSe-ZnS, Cadmium selenide-zinc sulfide; CE, Capillary electrophoresis; CNTs, Carbon nanotubes; CT, Cholera toxin; CTnT, Cardiac Troponin T; CTX, Ciguatoxins; CQDs, Carbon quantum dots; CVD, Chemical vapor deposition; 3D, Three-dimensional; DA, Domoic acid; DAb, Diabodies, domain specific Abs; DDR, Dynamic detection range; DON, Deoxynivalenol; DsDNA, Double stranded DNA; E, Estrone; ECL, Electrochemiluminescence; EDC, N-3-dimethylaminnopropyl-N-ethyl-carbodiimide hydrochloride; EI, Electrochemical IS; ELISA, Enzyme-linked immunosorbent assay; E. NIS, Electrochemical NIS; Fab, AG-binding fragment; FAO, Food and Agricultural Organization; FB1, FUM B1; FBPs, Fluorescent probe particles; FDMA, Ferrocenedimethylamine; FET, Field-effect transistors; FTs, Foodborne toxins; FUMs, Fumonisins; Fv, Fragment variable; GC, Gas chromatography; GCE, Glassy carbon electrode; GCE-pNap-AuNPs, Glassy carbon electrode GCE modified with AuNPs electro-synthesized on a 1 naphthylamine polymer pNap film; G-C3N4, Graphitic carbon nitride; G-C3N4-PdNPs, Palladium-doped graphitic carbon nitride nano-sheets; GNP, Gold nanospheres; GNST, Gold nanostars; H, Heavy chains; HACCP, Hazard analysis and critical control points; HPLC, High-pressure liquid chromatography; HRP, Horseradish peroxidase; Ig, Immunoglobulin; IS, Immunosensor; ITO, Indium tin oxide; KLH, Keyhole limpet hemocyanin; L, Light chains; LDR, Linear detection range; LOD, Limit of detection; MAbE, Anti-E monoclonal Ab; MAbs, Monoclonal antibodies; MNPs, Magnetic nanoparticles; MS, Mass spectrometry; MTs, Marine toxins; Mw, Molecular weight; MWCNTs, Multi-walled CNTs; NHS, N-hydroxysuccinimide; NISs, Nano-immunosensors; $NMoS_2$NPs, Molybdenum disulfide nanoparticles; NMR, Nuclear magnetic resonance; NMs, Nanomaterials; NPs;OA, Nanoparticles;Okadaic acid; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; OTA, Ochratoxin A; PAH, Polycyclic aromatic hydrocarbons; PEI, Polyethyleneimine; PIT, Photochemical immobilization technique; PLTX, Palytoxin; PPIA, Protein phosphatase inhibition assay; QCM, quartz crystal microbalance; RAbs, Recombinant antibodies; RAbs, Recombinant Abs; ScFvs, Single-chain variable fragments; SEB, *Staphylococcal enterotoxin B*; SERS, Surface-enhanced Raman scattering; SPR, Surface Plasmon resonance; SsDNA, Single stranded DNA; ST, Shiga-like toxin; STX, Saxitoxin; TLC, Thin layer chromatography; TTX, Tetrodotoxin; UPLC, Ultra-performance liquid chromatography; UV, Ultraviolet; VOCs, Volatile organic compounds; ZEA, Zearalenone.

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ABSTRACT

Foodborne toxins pose significant risks to public health, necessitating rapid and accurate detection methods to ensure food safety. Traditional detection methods, such as chromatography and mass spectrometry, are often time-consuming, expensive, and require extensive sample preparation. Nano-immunosensors (NISs), which are biosensors that incorporate nanoscale materials (e.g., nanoparticles) to detect specific analytes (e.g., bacterial pathogens such as *Salmonella* and *Escherichia coli*, mycotoxins like aflatoxins and ochratoxin A, marine toxins such as ciguatoxins and saxitoxins, and chemical contaminants including pesticides and heavy metals), offer a promising alternative, leveraging the unique properties of nanomaterials to achieve high sensitivity and specificity in detecting a wide range of toxins. These sensors enable real-time monitoring with minimal sample preparation, making them highly suitable for complex food matrices. Additionally, NISs can be integrated into portable devices, facilitating on-site testing and immediate decision-making, which is critical in food safety management. Their ability to detect multiple toxins simultaneously further enhances their utility in diverse food safety applications. This review explores the development of NISs, focusing on their applications in detecting bacterial, fungal, and marine toxins, as well as chemical contaminants. Key advantages, such as rapid detection, cost-effectiveness, and enhanced sensitivity compared to conventional methods, are highlighted. The potential for future advancements in NIS technology to further improve food safety and public health outcomes is also discussed, emphasizing their role in meeting the increasing demand for safer food products.

1. Introduction

Food safety has generally been a global issue, and it is the most urgent concern of governments and citizens all over the world because it is tightly associated with the health and safety of consumers. Governments in various countries have enacted legislation to control and detect foodborne pathogens to ensure food safety over the decades. This mainly refers to contaminated food raw materials or final products with harmful bacteria, fungi, viruses, and parasites (Inbaraj and Chen, 2016; Neethirajan et al., 2018). Annually, world statistics show that around 48 million people are affected by food poisoning, leading to about 120,000 hospitalizations (Das et al., 2017). Four classifications of main foodborne toxins (FTs) are known as bacterial, fungal, marine toxins and chemical toxicants which can spread foodborne illnesses from farm to consumer. Consuming these harmful substances can result in a spectrum of toxicological impacts on the human body, from immediate to long-term effects, potentially culminating in the consumer's fatality; therefore, the accurate and fast detection of FTs is a crucial factor to warrant the food safety (Malhotra et al., 2014).

The conventional methods to assess the presence of FTs are mostly time-consuming with a high-cost (Zhang et al., (2021). However, FTs are typically analyzed *via* various techniques including fluorescence techniques, ultraviolet (UV) absorption, thin layer chromatography (TLC), high-pressure liquid chromatography (HPLC), gas chromatography (GC) and enzyme-linked immunosorbent assay (ELISA) (Bhardwaj et al., 2022; Cheng and Chuang, 2019). The main issue with these methods is that final product is merely analyzed and the production process is ignored which make the source identification difficult. Additionally, the sensitivity levels of these conventional methods are often insufficient for rapid and precise detection of trace amounts of toxins. For example:

- **HPLC and GC** typically detect toxins at sensitivity levels in the range of **ng/mL to μg/mL**, which can be too high to detect small quantities of foodborne toxins that may be present at lower concentrations.
- **ELISA**, another common method, can detect toxins at **ppb (parts per billion)** levels, which may not be sensitive enough for certain toxins, particularly those at low concentrations in food samples.

This lack of sensitivity limits the ability to identify contamination during the early stages of food production, thus hindering timely intervention. To implement the hazard analysis and critical control points (HACCP) system in food industries, determination and analysis of critical control points through the production line is essential. Hence, the demand for rapid, effective, and reliable methods for detecting FTs has increased (Bhardwaj et al., 2022; Malhotra et al., 2014).

The use of biosensors has increased rapidly in recent years for quantification and evaluation of target analytes, owing to their precise and accurate outcomes and rapid responsiveness (Zhang et al., 2024). The analytical device quantifies the interaction between the analyte and its specific biorecognition element by generating detection signals that are directly proportional to the analyte's concentration (Malhotra et al., 2014). Biosensors are mainly composed of three parts; receptor which contains the biological recognition element, transducer that transforms the biological response to the electrical, optical, mass or thermal signal, and finally detector which analyzes the received signals from transducer (Cheng and Chuang, 2019). Nanosensors are actually the biosensors using nanoscale components to detect the presence of specific analytes. The application of nanomaterials (NMs) in the structure of bioreceptor develops conducive functional groups which can enhance the surface-to-volume ratio and improve the electrical or optical responses (Thakur et al., 2022). Different types of NMs, such as metal nanoparticles (NPs) (e.g., gold, silver), carbon-based NMs (e.g., graphene, carbon nanotubes), and quantum dots (QDs), contribute uniquely to enhancing sensor sensitivity. Metal NPs, for example, can improve electrochemical responses by providing a large surface area for biomolecular interactions, while carbon NMs enhance the conductivity and stability of the sensor. QDs, with their unique optical properties, can enhance fluorescence signals for improved detection sensitivity. These NMs significantly improve the overall performance, making nanosensors more efficient for detecting low concentrations of analytes (Thakur et al., 2022).

The immunosensor (IS) is a new type of biosensor made by a specific complementary structure between antigen (AG) and antibody (Ab). Regular ISs usually consists of two parts: biological recognition and signal conversion. Biological recognition is the specific response of receptor surface AG-Ab in the sensor. Signal conversion is to sense the optical, spectroscopic or electrical parameter changes caused by specific binding. Due to the advantages of high analytical sensitivity, strong specificity, and easy use, ISs have been widely used in many fields e.g., clinical diagnosis, microbiological detection, environmental monitoring, and food analysis (Inbaraj and Chen, 2016). **NISs** are a new class of biosensors that combine the specificity of antibody-antigen interactions with the enhanced sensitivity of NMs. These sensors incorporate nanoscale components, such as NPs, to detect specific analytes. By leveraging the unique properties of NMs, such as their large surface area, high surface-to-volume ratio, and the ability to amplify detection signals, NISs offer significant improvements in both sensitivity and specificity. These features make them particularly well-suited for the rapid and precise detection of foodborne toxins, even at low concentrations (Thakur et al., 2022). Different types of NISs include:

1. **Electrochemical NISs**: These sensors use metal or carbon-based NPs to amplify electrochemical signals resulting from antigen-antibody binding, making them ideal for detecting bacterial toxins and mycotoxins.
2. **Optical NISs**: These sensors utilize the optical properties of NPs, such as gold NPs or QDs, to detect changes in light absorption, fluorescence, or scattering upon the binding of target analytes.
3. **Magnetic NISs**: Magnetic NPs concentrate the target analytes, and the resulting changes in magnetic properties are measured to detect the presence of toxins.
4. **Piezoelectric NISs**: These sensors measure changes in the resonant frequency of piezoelectric materials when an analyte binds, providing real-time detection of foodborne toxins.

Due to their high sensitivity, rapid response, and portability, NISs have been widely applied in the detection of foodborne toxins, offering a promising alternative to conventional methods.

This review is focused on the background, latest trends, challenges, and limitations of various NISs used in detection and analysis of FTs.

2. Foodborne toxins; an overview

Bacterial, fungal, and marine toxins, along with chemical toxicants are main FTs known as main cause of the foodborne illnesses spreading from farm to fork (Malhotra et al., 2014). Among all, bacterial and fungal toxins lead to a major economic loss to the food industry. Therefore, strict monitoring of their content and the design and application of emerging technologies for ultrasensitive and rapid detection and decontamination of these toxins in the food chain and environment is urgent.

Escherichia coli O157:H7 is one of the major human pathogens and causes illness by consuming contaminated raw food. It is a Shiga-like toxin (ST)-producing type of *E. coli*, and the attachment and biofilm formation of this bacterium varies in different water environments (Lee et al., 2015). *E. coli* containing genes encoding ST 1 and/or 2, such as *E. coli* O157:H7, cause hemolytic uremic syndrome and severe bloody diarrhea after consuming contaminated foods. ST-producing *E. coli* is associated with numerous foodborne outbreaks on leafy greens such as spinach and lettuce (Lee et al., 2016). Another bacterial toxin is Cholera toxin (CT) as an AB5 multimeric protein complex produced by *Vibrio cholerae* which causes life-threatening diarrheal disease (Demirci et al., 2020). Enterotoxins produced by *Staphylococcus aureus* are also associated with foodborne diseases with severe diarrhea, nausea, and vomiting (Yang et al., 2008). Botulinum toxin (BT) is known as another lethal neurotoxin protein that causes severe neuroparalytic disease. It is secreted by *Clostridium botulinum* and other related species commonly found in soil, water, plants, and the intestinal tracts of animals (Cheng and Chuang, 2019).

Fungal toxins, known as mycotoxins, are secondary metabolites of fungi that are mainly produced by *Aspergillus*, *Alternaria*, *Penicillium*, and *Fusarium* species. Mycotoxins are found in most of agricultural commodities including coffee, cereals, groundnuts, and pistachio. Climate variability in different regions and seasons strongly affects the fungal growth and mycotoxin production. Several factors including pH, temperature, chemical additives, water stress, gas composition, moisture, and also insect damage have distinct impact on the rate of mycotoxin production in food crops (Inbaraj and Chen, 2016). Among the various mycotoxins, some are known to be hazardous and immunotoxic to humans and animals e.g., aflatoxins (AFs), fumonisins (FUMs), ochratoxin A (OTA), zearalenone (ZEA), citrinin, patulin, T-2/HT-2 toxins, and deoxynivalenol (DON) (Richard, 2007; Zain, 2011). Inhaled, absorbed through the skin or ingested mycotoxins are mostly responsible for teratogenic, carcinogenic, and mutagenic effects in animals and humans. Mycotoxins have also considerable economical adverse effects on food crops due to the reduction of the yield of fiber. Globally, an estimated 6 billion individuals are at risk of consuming AF-contaminated food (Inbaraj and Chen, 2016). Recently, Food and Agricultural Organization (FAO) has indicated that nearly a quarter of food crops worldwide are affected by mycotoxin contamination, leading to considerable economic losses estimated at one billion metric tons annually (Oranusi et al., 2017). Consequently, the existence and use of fast, simple, uncomplicated, cheap, and high-sensitive detection methods seem necessary.

Various marine toxins (MTs) enter the human food chain through the feeding of toxic phytoplankton using aquatic species such as fish, crabs, shellfish, and oysters (Tian et al., 2021). MTs fall into eight categories based on their chemical structure, which include Okadaic acid (OA), Brevetoxins (BTX), Saxitoxin (STX), Azaspiracid toxins (AZT), Domoic acid (DA), Palytoxin (PLTX), Tetrodotoxin (TTX), and Ciguatoxins (CTX). Different studies have shown that eating foods contaminated with various MTs cause serious and dangerous disorders in the nervous, gastrointestinal and cardiovascular systems, and even be deadly to humans (Saravanakumar et al., 2022; Tian et al., 2021).

Chemical contaminants/toxicants are among the unwanted and harmful items that can be introduced into the food supply at different points in the production stages, processing, packaging, and storage, or may be absorbed from soil and water during agricultural growth. Chemical toxicants include a wide range of agricultural, industrial, sewage, pharmaceutical, and environmental sources such as pesticides, heavy metals, antibiotics, and preservatives that cause dangerous diseases, especially damage to the nervous system, which in most cases are irreversible (Kuswandi et al., 2017). Therefore, fast, simple, responsive and selective detection of chemical toxicants in food is greatly required.

Accordingly, NISs have attracted remarkable attention to address the consumers' demand for better quality and safe food products, owing to their unique affinity to contaminants compared to traditional methods such as TLC, HPLC, and GC combined with mass spectrometry (MS) (Felix and Angnes, 2018; Jin et al., 2021; Pérez-Fernández and de la Escosura Muñiz, 2022). Traditional methods are relatively expensive, labor-intensive, and time-consuming, which limits their application in the analysis of contaminants and residues in food, the environment, and point-of-care settings. In contrast, NISs offer several advantages, including rapid detection, high sensitivity, and the ability to simultaneously detect multiple toxins with minimal sample preparation, making them more effective and efficient for toxin detection in various settings.

3. Different approaches in development of nano-immunosensors

A sensor can be generally defined as a device that converts chemical information, from the concentration of a specific component in a sample to the analysis of the sample's overall composition, into data that is useful for analysis. Their detection is highly specific, rapid, practical, cost-effective, and sensitive allowing them to measure at a much lower level in contrast to the macroscale biosensors (Sharma et al., 2021; Srivastava et al., 2018).

A typical nanosensor is composed of three basic sections including bioreceptor, signal transducer and detector. The bioreceptor is a recognition molecule which has a biological origin and can detect the specific analyte within the sample. The sample could be a uniform or a heterogeneous mixture of gas, liquid or solid state. It contains specific functional molecules or organisms, which the biosensors can selectively detect them. The bioreceptor is unique for the analyte and could be a structural or functional protein e.g., antibodies (Abs), oligonucleotides including aptamers, enzymes, cells or any subcellular organells. Bioreceptors have high specificity, affinity, and selectivity for their particular analytes to quantify them at an acceptable level. Once the analyte is recognized by the receptor, a physicochemical change (such as an alteration in properties like pH, conductivity, or temperature) occurs. This change is then converted into a computable signal *via* a probe integrated or functionalized with NMs. Based on their certain signal transduction methods, nanobiosensors are classified into optical,

electrochemical, and mass detection biosensors. They convert the detection event into a computable signal that can be further processed to produce data. Finally, the detection component receives the signals from the transducer, which are then transferred to a microprocessor where they are enhanced and analyzed; the information is then converted to user friendly data and displayed (Rai et al., 2012; Srivastava et al., 2018).

Different approaches have been used in development of nanosensors based on the type of biorecptors (enzyme, AG/Ab, aptamers, DNA/nucleic acid, and living cells) or transducers (optical, electrical/electrochemical, and piezoelectric). It is important for a bioreceptor to selectively attach to the specific analyte of interest to hinder any interference by other components in the sample mixture.

3.1. Bio-signaling mechanisms

Based on the type of bio-signaling mechanism, biosensors can be classified into five main groups (Perumal and Hashim, 2014):

(I) **Enzymes** can specifically recognize their substrates through the lock and key and induced fit mechanism, and catalyze their transformation without forming any undesirable products. This unique feature of enzymes makes them very efficient tools for developing analytical devices. The immobilization of enzymes on the transducer is very important. A few considerations should be taken when immobilizing enzymes on the transducer: during reaction, the enzyme should be stable, the enzyme's active center should be protected from the reagent's interactions, and eliminating of the unattached enzymes should not be harmful to the attached enzymes. Enzyme immobilization can be conducted using covalent binding, cross-linking, entrapment, and adsorption (Leca-bouvier B.., 2010; Perumal and Hashim, 2014).

(II) **AG/Ab** as bioreceptor is applied in ISs. An Ab is a ''Y'' shaped immunoglobulin (Ig) that has two light chains (L) and two heavy chains (H) linked by disulfide bonds. Each chain is composed of a constant and variable region. The variable region of H and L chains interacts specifically to the target AG. ISs perform based on the interaction and formation of the specific AG-Ab complexes for the detection and quantification of biomarkers (Lara and Perez-Potti, 2018; Perumal and Hashim, 2014).

(III) **Aptamers** are short synthetic single stranded nucleotide sequences (DNA or RNA) with 10–30 kDa molecular weight (Mw) which can bind to small solutes, peptides and proteins, oligosaccharides, cells and viruses with high affinity. When these specialized nucleic acids bind to their designated targets, they experience a three-dimensional (3D) conformational shift. This allows them to capture their targets through interactions like hydrogen bonds, *van der Waals* forces, aromatic stacking, and salt bridges. Aptamers exhibit unique features for bioanalytical applications. In contrast to Abs, they have lower Mw, relatively more stability under different buffer conditions and high temperature, resistance to degradation, and easier to be synthesized. Aptamers are chemically synthesized in high purity by an automated procedure; thus they can be modified easily (Muhammad and Huang, 2021).

(IV) **DNA/nucleic acids** are utilized as the biological sensing element and could detect the specific single stranded DNA (ssDNA) of interest in the sample. A ssDNA is immobilized as a probe which the DNA base sequence is complementary to the target analyte. The recognition mechanism in this sensor is based on the highly specific affinity between the target nucleic acid strand and the immobilized ssDNA and to form a double stranded DNA (dsDNA). Based on the Watson-crick pairing, the two complementary ssDNA specifically bind and form a double-helical structure, which in turn with the hybridization of the two nucleic acid strand leads to production of a biochemical reaction. This reaction will allow the transducer to amplify the signal to an electrical signal. An important feature of DNA is that by modifying the ion concentration of the buffer, the nucleic acid strands can be denatured to reverse binding and be regenerated. Another important feature of these bioreceptors is that the nucleic acid is easily synthesized and highly specific for the target of interest (Hai et al., 2020; Perumal and Hashim, 2014).

(V) **Living cells** can also be utilized as the bioreceptor, to detect the condition of the intracellular and extracellular microenvironment, and create a response through the interaction between the stimulus and the cell. In contrast to enzyme-based biosensors, these sensors exhibit reduced sensitivity to interference caused by solutes, and tolerate a higher suboptimal pH and temperature values, and since there is no need for isolation of the active cells, they are cheaper. However, these biosensors have their limitations too. The natural microenvironmental requirements in which the cells can remain viable for an extended period to regulate the chemical and physical conditions of its environment specifies the limit of detection (LOD). Also, the cells stability is another limitation, which different conditions such as sterilization, durability, and biocompatibility affect it. Cell based biosensors have become an emerging tool in various sections of scientific research areas in the last decade. For instance, they are used for medical diagnosis, environmental monitoring, food quality control, chemical and pharmaceutical industry, and drug screening (Perumal and Hashim, 2014; Wang et al., 2010).

3.2. Types of transducers

The transducer is an integral component of the biosensor, playing a pivotal role in the signal detection process. With the recognition of the bioanalyte and the stimulation of the bioreceptor, the transducer produces sensory signals. Thus, a transducer could be described as a device that efficiently converts various types of physical, chemical, or biological responses into electrical signals, ensuring high sensitivity and minimal interference with the element being measured (Perumal and Hashim, 2014). Based on the transduction method, biosensors can be categorized into optical, electrical/electrochemical and piezoelectric transduced types (Shafiee et al., 2019).

(i) **Electrochemical** nanosensors are the oldest and the most widely used transducers. These transducers are based on the principle of electrochemistry. Upon the reaction between the analyte of interest and the bioreceptor, a current is generated by the reduction and oxidation reaction. In this reaction, ions or electrons are produced or consumed, which are measured by an electrochemical transducer. Thus, the correlation between the generated current and the quantity of activated bioreceptors exhibits the amount of the analyte. Electrochemical transducers have high sensitivity, low-LOD, robustness, and are cost effective. Based on their working principle, these transducers are classified into potentiometric, impedance, and amperometric subclasses (Conroy et al., 2009; Srivastava et al., 2018).

(ii) **Optical** nanosensors convert a chemical or biological reaction into a readable optical signal. They are based on sensing the change in the optical signal by identifying alterations in phase, intensity, time, polarity and wavelength of the light. In general, many diverse optical methods have been used in biosensors, which are based on absorbance, fluorescence spectroscopy, surface Plasmon resonance (SPR), interferometry, and surface-enhanced Raman scattering (SERS) (Srivastava et al., 2018). Different characteristics of the analyte can be measured utilizing these transduction methods. Optical biosensors can provide label free, real time and parallel detection (Perumal and Hashim, 2014). The detection of optical signal by nanosensors offers high

sensitivity; however, sensitivity is highly dependent on the detection mode of the optical phenomena (Nosheen et al., 2019).

(iii) **Piezoelectric** nanosensors are mass-sensitive. The piezoelectric material in these transducers produces an electrical signal in response to mechanical forces, which can be detected by the signal processing element of the biosensor (Shafiee et al., 2019). Piezoelectricity refers to the direct correlation between mechanical pressure and electrical voltage in certain crystalline materials. Piezoelectric biosensors operate on the principle that an oscillating crystal, typically quartz, resonates at a specific natural frequency. The biosensor's transducer, composed of this piezoelectric material, is coated with a biosensing layer that vibrates at a predetermined frequency. When an external electrical signal is applied, it governs this frequency. The presence of the target analyte alters the interaction with the sensor layer, causing a shift in the crystal's vibration frequency, which is then detected as a variation in the electrical current. These changes in the current is collated to the mass of the target analyte (Perumal and Hashim, 2014)

3.3. Nanomaterials in development of nanosensors

Various NMs, including metal NPs like gold and silver, carbon nanotubes (CNTs), and carbon QDs (CQDs), have been utilized in nanosensors. These NMs enhance the performance of nanosensors by increasing sensitivity through several mechanisms: they improve charge electron transfer, boost catalytic activity, increase the number of immobilized biomolecules, reduce background current, and enhance the signal-to-noise ratio (Inbaraj and Chen, 2016).

3.3.1. Metal nanoparticles

Gold NPs (AuNPs) are one of the frequently used NMs with highly versatility as an electrode modifier, catalytic label, nanozyme (NMs-based artificial enzyme that mimics the catalytic activity of natural enzymes), electron transfer regulator, and carrier of Abs through biosensing process (Campuzano et al., 2020). AuNPs are the most commonly used signal reinforcement labels for different ISs. The exclusive properties of AuNPs mostly refers to their size and shape. Their large surface area allows for a higher number of immobilized molecules, with optimal spacing and orientation, and provides excellent conductivity, which is crucial for maintaining the bioactivity of attached biomolecules. While other NMs also possess these properties and can be used for developing nanobiosensors, CNTs are particularly favored due to their unique structural, electrical, and mechanical properties, which make them highly effective in enhancing sensor performance (Campuzano et al., 2020; Farka et al., 2017). AuNPs can also be applied in combination with carbon-based NMs including CNTs in the development of nanostructured electrode surfaces to improve the affinity of nanosensors (Farka et al., 2017).

Iarossi et al. (2018) described a colorimetric IS to detect human IgG (the most common type of Ab in blood and other body fluids) based on AuNPs functionalized by Ab. It was revealed that Abs can be stably attached onto gold surfaces through a method activated by UV light, termed the photochemical immobilization technique (PIT). The initial phase involves the modification of AuNPs using polyclonal anti-human IgG, which is activated by UV light. The absorption of UV light by proximal aromatic amino acids results in the selective cleavage of certain disulfide bonds. The emergent reactive thiol groups then forming strong connections with the gold surface, creating robust attachment points. The use of polyclonal Abs, along with the multiple binding sites found on AGs, facilitates the interaction between AGs and Abs. This interaction, coupled with SPR among NPs, leads to their shift from a dispersed to an aggregated state, which in turn causes the suspension to change its color from red to purple (Fig. 1). These reactions are the basis of the colorimetric assay of human Ig in this research (Iarossi et al., 2018).

Thyroxine is the main hormone secreted by the thyroid gland. Mradula et al. (2020) synthetized an IS based on AuNPs labeled with Ab for the detection of thyroxine and consequently, the diagnosis of several thyroid disorders. AuNPs capped with cysteamine (C-AuNPs) were synthesized using the sodium borohydride reduction technique. Cysteamine, containing both amine and sulfur groups, serves dual functions: it stabilizes AuNPs and facilitates the attachment of Abs to the gold surface. The thyroxine Ab (anti-T4) was bound covalently to C-AuNPs using a coupling reaction involving EDC and NHS. These anti-T4/C-AuNP conjugates were then used to measure free thyroxine hormone levels in samples. The presence of the hormone caused only a change in SPR angle, leading to a lower absorbance at the peak wavelength of 528 nm, without shifting the wavelength. This indicates that AG-Ab complex formation on the C-AuNPs surface leads to a decrease in the stability of C-AuNPs. The method developed offers high-performance ISs with a linear detection range (LDR) from 0.52 to 65.1 pg/mL and a limit of detection (LOD) of 0.52 pg/mL, which refers to the lowest concentration of a substance that can be reliably detected (Mradula et al., 2020).

Estrone (E) is considered as the major postmenopausal estrogen produced by the ovaries and adrenal glands. Monerris et al. (2016) designed a straightforward and highly sensitive electrochemical IS (EI)

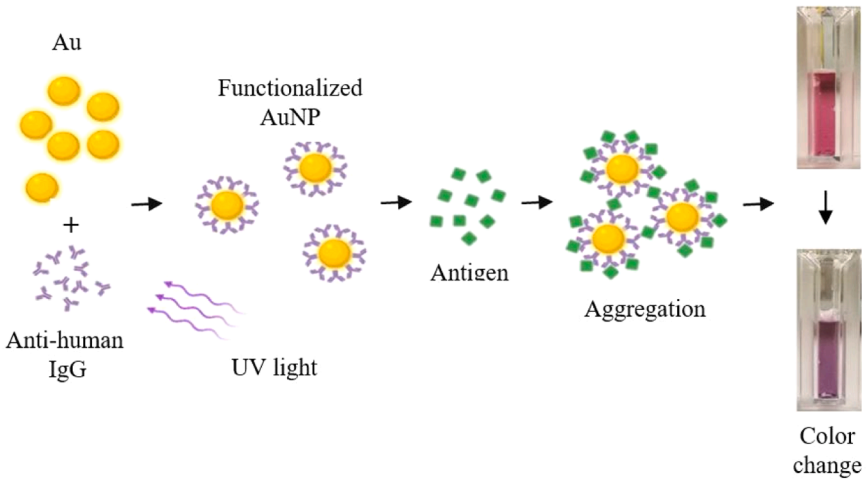

Fig. 1. Illustrative representation of the detection mechanism used in nano-immunosensors: Antibodies are securely attached in an upright position to gold nanoparticles *via* a process known as photochemical immobilization. This orientation facilitates multiple binding sites on the antigens to act as connectors, resulting in the clustering of nanoparticles. This clustering is critical for signal generation and amplification in biosensing applications (Iarossi et al., 2018).

for measuring E levels in water samples without the need for sample pre-treatment, for AG and Ab labeling. The detection mechanism of this IS relies on the fact that E serves as a co-substrate for horseradish peroxidase (HRP). In this study, for constructing the EI, the anti-E monoclonal Ab (mAbE) was immobilized on a glassy carbon electrode (GCE) modified with AuNPs electro-synthesized on a 1 naphthylamine polymer (pNap) film (GCE-pNap-AuNPs). This composite structure exhibited unique characteristics due to the size effects of AuNPs and the exceptional properties of the polymer. In fact, the pNap provided an extensive specific surface area and a dense matrix to incorporate AuNPs, leading to improved stability of GCE-pNap-AuNPs (Monerris et al., 2016). Water samples were augmented with established concentrations of E, followed by a period of incubation on GCE-pNap-AuNPs-mAbE. Subsequently, EI was placed in an electrochemical cell comprising citrate buffer solutions (pH = 5.00), specific concentrations of HRP, pyrocatechol (H2Q) and H2O2. The E and H2Q, as enzyme cosubstrates, react with HRP. The HRP, in the presence of H2O2, catalyzes the oxidation of E and also, H2Q to a given product and benzoquinone (Q), respectively.

Square wave voltammetry (SWV) was used to carry out the back electro-chemical conversion of Q to H2Q on the modified electrode surface (GCE-pNap-AuNPs-mAbE) (Fig. 2). The electrochemical response was directly related to the amount of H2Q but inversely related to the concentration of E in water samples. It can be concluded that the maximum electrochemical response is achieved in the absence of E at the electrode surface for a specific H2Q level. This EI exhibited a very high sensitivity to determine trace levels of E in water samples, in comparison with other conventional techniques. The IS exhibited a LDR between 8×10^2 and 2×10^4 pg /mL and LOD = 0.061 pg/ mL. The recovery rates were exceptionally satisfactory. Experiments were also performed to investigate the cross-reactivity of E and other structurally similar hormones, including estriol, progesterone and 17β-estradiol. EI exhibited high selectivity for detecting E even in the presence of other hormones. Therefore, this EI can be considered as an attractive tool for E determination in water samples (Monerris et al., 2016).

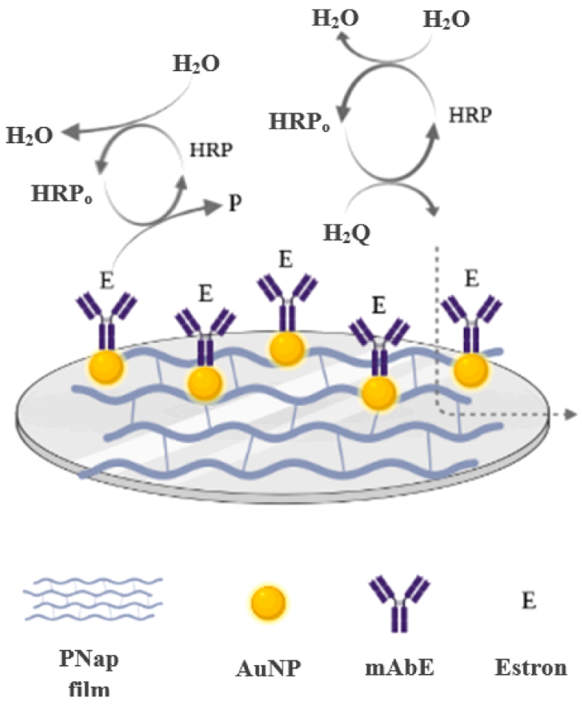

Fig. 2. Schematic illustration of an electrochemical immunosensor developed for the detection of estrone in water samples. The sensor incorporates a glassy carbon electrode modified with gold nanoparticles and a polymer film, enhancing sensitivity and stability. The immunosensor enables the accurate detection of trace levels of estrone through a specific antigen-antibody interaction (Monerris et al., 2016).

Silver NPs (AgNPs) are the other commercially produced NPs. They can be oxidized easily which offers an improved electrochemical activity in comparison with AuNPs, making them suitable candidates for application in nanosensors. However, their applications in ISs are limited due to their difficulty to functionalize, significantly lower stability, and limited biocompatibility compared to AuNPs. It should also be noted that the mentioned weaknesses can be fixed by some modifications in the methods of stabilization, functionalization, and synthesis (Farka et al., 2017).

3.3.2. *Carbon nanomaterials*

CNTs were initially introduced by Iijima (1991). CNTs are commonly graphite sheets turned into nanotubes which can be in both forms of single-walled (SWCNTs) and multi-walled CNTs (MWCNTs). SWCNTs are formed by rolling a sheet of graphene into a cylindrical tube which are approximately 1 −100 μm in length and 0.4–2 nm in diameter, based on the synthesis method. MWCNTs consist of cylinders of wrapped graphene sheets with diameters ranging from 1 to 10 nm, depending on the number of sheets. Distinctive in their electronic characteristics, CNTs can be either conductive or semi-conductive, a trait determined by their unique chiral angles and the circumferences of the tubes (Wang et al., 2024). The chiral nature is identified as chiral, zigzag, or armchair, contingent on the nanotube's axial alignment (Zhang et al., 2023).

The predominant techniques for fabricating CNTs encompasses chemical vapor deposition (CVD) (Kumar and Ando, 2010), laser ablation (Alamro et al., 2021) and arc discharge (Sari et al., 2018). The pioneering method to synthesize CNTs was through carbon-arc discharge, which, contingent on the chosen catalyst, can produce either SWCNTs or MWCNTs with an impressive yield rate of nearly 90 %, while also allowing for meticulous control over the tube dimensions. This method is favored for mass production due to its high yield and consistent quality. The CVD, reliant on catalysts as well, yields finer-diameter CNTs. Though the output is less, the resultant CNTs are substantially purer, which streamlines the cleaning process. The cleanest CNTs are obtained *via* laser ablation, which comes at a steeper cost and lower yield. All these methods result in a heterogeneous mix of conductive and semi-conductive CNTs (Norizan et al., 2020).

In the realm of ISs, CNTs are prized for their singular physical and chemical attributes, such as their expansive surface-to-volume ratio, exceptional electrical conductance, and expedited kinetics at the electrode interface (Norizan et al., 2020; Wang et al., 2024). Functionalization of CNTs is achievable through either covalent or noncovalent bonds with diverse chemical entities, thus ensuring a high degree of compatibility for the attachment of biological molecules (Norizan et al., 2020). The inherent conductivity of CNTs is also instrumental in promoting electron transference, which in turn augments the current that can be measured (Dubey et al., 2021). Additionally, the chemical tailoring of CNTs can be optimized to improve their dissolution in solvents and their compatibility with biological systems (Murjani et al., 2022).

CNTs have also been used to develop NISs. Troponin T is recognized as a diagnostic marker for myocardial infarction and minor cardiac cell damage. Gomes-Filho et al. (2013) synthetized a NIS by CNTs for the detection of cardiac Troponin T (cTnT). Carboxylated CNTs were chemically bonded to the electrode's surface *via* polyethyleneimine (PEI). The modified nanostructured surface was utilized to adhere anti-cTnT mAbs (Fig. 3). The IS had a low LOD = 0.033 ng/mL and a LDR from 0.1 to 10 ng/mL for cTnT, which is crucial for diagnosing acute myocardial infarction. The fabricated IS demonstrated acceptable reproducibility and repeatability, with coefficients of variation of 2.6 % and 3.7 %, respectively.

In another study, Liu et al. (2012) fabricated an EI using a chemical method to organize CNTs in a

vertical alignment on carbon-based surfaces. For this purpose, a

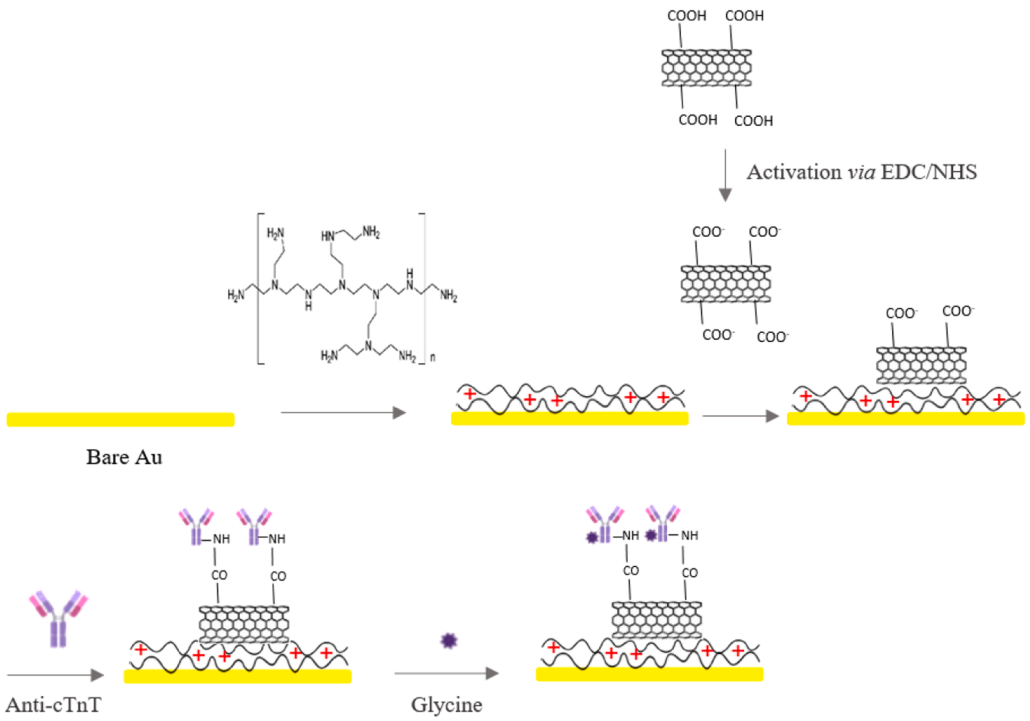

Fig. 3. The immunosensor developed for detecting cardiac Troponin T (cTnT), a critical biomarker for diagnosing myocardial infarction. This sensor employs carbon nanotubes functionalized with polyethyleneimine to enhance electron transfer and immobilize antibodies effectively, allowing sensitive detection of cTnT in biological samples (Gomes-Filho et al., 2013).

glassy carbon substrate was covalently functionalized with a mixed layer of 4-aminophenyl and phenyl. SWCNTs were chemically bonded in a vertical orientation to the electrode surface, facilitated by the formation of amide bonds between the amine groups on the altered substrate and the carboxylic groups at the terminus of SWCNTs. Then, Ferrocenedimethylamine (FDMA) was bonded to the opposite end of SWCNTs through amide linkages, which was then succeeded by the coupling of an epitope, specifically the endosulfan hapten, along with a bound Ab, to FDMA. The binding or unbinding of Ab to the detection surface results in alterations to the electrochemical behavior of ferrocene. The electrodes were subjected to environmental water samples augmented with endosulfan (the unbound target analyte) and analyzed by SWV method. The developed EI successfully detected endosulfan within a sensitivity range of 0.01 −20 ppb (Liu et al., 2012). A-fetoprotein (AFP) is a tumor marker for diagnosing hepatocellular carcinoma and Chlorpyrifos is an organophosphate pesticide that is used to control soil-borne insect pests on a variety of food and feed crops. Development of an IS based on CNT/manganese dioxide electrochemical tags for sensitive detection of AFP and fabrication of a novel amperometric IS based on CN-thionine-chitosan nanocomposite for identifying chlorpyrifos residues are other examples of research conducted in this field (Sun et al., 2012; Tu et al., 2015).

CQDs, are tiny fluorescent semiconductor crystals, typically sized between 1 and 10 nm. These nanocrystals are versatile, finding use in a range of technologies including light-emitting devices, photodetectors, solar cells, field- effect transistors, memory elements, and various biomedical applications such as luminescent labels, sensors, and imaging tools (Arshad et al., 2022). CQDs are unique for their size-dependent photoluminescence, broad excitation ranges, and more defined emission peaks when compared to traditional organic dyes (Manikandan and Min, 2023; Kechagias et al., 2023). The color of the emitted light from CQDs can be fine-tuned by altering the size of the dots, which is controlled by the synthesis temperature or growth period. By selecting suitable semiconductor materials and sizes, CQDs can be engineered to emit light across a spectrum from 380 to 2000 nm (Manikandan and Min, 2023). Advanced techniques allow for the creation of color-coded multiplexing by embedding different-sized CQDs into polymer beads at specific ratios (Bonilla et al., 2016).

For analytical purposes, CQDs are often designed with a core-shell structure, where the core crystal is encased in another semiconductor layer to enhance and protect its optical features. High-quality CQDs with optimal quantum yields and uniform sizes are typically produced at elevated temperatures using organic solvents (Manikandan and Min, 2023). To make these inherently hydrophobic CQDs water-soluble, the surface ligands must be altered. The two main strategies for this transformation are encapsulation within amphiphilic polymers and ligand exchange (Jańczewski et al., 2011). Ligand exchange frequently involves the use of mercapto-based ligands due to their strong affinity for the CQD surface (Zhu et al., 2021). When conjugated with Abs, CQDs form stable complexes that emit a strong analytical signal, making them exceptionally sensitive fluorescent markers for use in ISs (Qiu et al., 2022; Zhu et al., 2021).

CQD was used by Zhang et al. (2015) to design an electrochemiluminescence (ECL) IS. This sensor, featuring a platinum electrode modified with Au/SiO_2 core-shell NPs, was intended for the sensitive detection of 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is one of the predominant forms of oxidative lesions caused by free radical, and is commonly employed as an indicator for oxidative stress and also, carcinogenicity. In their research, rabbit anti-8-OHdG Ab was covalently attached to CQDs on the surface of Au/SiO_2 core-shell NPs (Fig. 4). Through signal amplification of Au/SiO_2 core-shell NPs, 8-fold increase of ECL signals was obtained. Under optimal conditions, a good LDR between 0.2 and 200 ng/mL and a low LOD = 0.085 ng/mL were achieved for the detection of 8-OHdG. Interference experiments exhibited that the ECL intensity of 8-OHdG was 8–18 times greater than that of ascorbic acid, uric acid, and guanine, indicating its acceptable selectivity for detection of 8-OHdG. The ECL IS had long-term stability with a relative standard deviation of 8.5 % even after 16 cycles of continuous potential scanning. The result obtained from analytical detection of 8-OHdG in real samples was satisfactory. Therefore, the described ECL IS

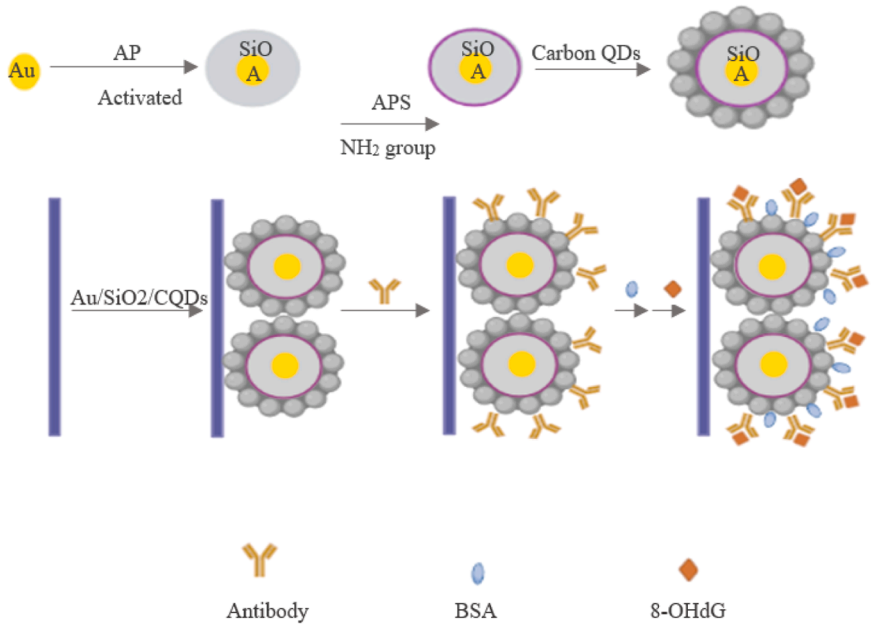

Fig. 4. The fabrication process of an electrochemiluminescence (ECL) immunosensor designed for the sensitive detection of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker for oxidative stress. This sensor uses gold/silica core-shell nanoparticles to amplify the ECL signal, allowing for precise detection of 8-OHdG with high sensitivity and specificity (Zhang et al., 2016).

demonstrated excellent performance with repeatability, stability, high sensitivity, and specificity, making it a powerful tool for monitoring 8-OHdG in clinical samples (Zhang et al., 2016).

3.4. Fundamentals of developing nano-immunosensors with an emphasis on antibodies

There are several aspects to be considered in developing NISs, such as other diagnostic tools they need to be responsive, specific, fast and user-friendly. On the other hand, in most cases, we face a multi-causal condition or we simply need to detect the main cause of the disease among several possible factors. So, multiplexing analysis is a growing demand to be met. The development is based on four fundamental parts: (i) the immobilization process, the type of binding to the immobilization surface (physical or covalent), and the orientation of immobilization; (ii) the mechanism of electronical signal amplification, (amplification by redox mediators, multiple redox indicators, or nano-molecules); (iii) developing the ability of multiplexing analysis; and (iv) integration of the product to develop an analytical instrument (recently have done by flow-through technology). As a general fact, the cost and size of the commercial product is also of great importance, especially when NISs are designed as a home test diagnostic kit (Wan et al., 2013; Zumpano et al., 2021).

Food safety is of great importance, so an appropriate IS should have special characteristics to detect FTs: (i) Rapid identification of toxins. Some food products have short shelf lives, so a rapid sensor is required to monitor them before consumption. On the other hand, when there are several cases of foodborne diseases, administration of proper antimicrobial agent is relied on a rapid diagnosis. (ii) Ability to accurately detect small amount of toxin in different food samples. Usually there are very low concentration of toxins in the food samples, therefore ISs need to have sufficient sensitivity and specificity to identify and differentiate them from the natural compositions of the food sample. Therefore, selecting an Ab designed for a high-specific epitope is recommended. Many toxins have identical antigens which make them difficult to discriminate. (iii) The Ab has to bind to the target with adequate strength (high-affinity) to have a robust diagnostic signal. There may be several candidate Abs to select for ISs. In this case we can use primary techniques such as enzyme-linked immunosorbent assay (ELISA) to check the above criteria. At the next stage, the potential Abs with the favorable characteristics can be further assessed by sensor-based analysis to know the best applicant with high sensitivity, specificity and target affinity. Finally, the selected Ab will be applied in the platform (Byrne et al., 2009).

When selecting antibodies for detecting various foodborne toxins, several criteria must be considered to ensure the effectiveness of NISs including specificity, sensitivity, stability, production feasibility and compatibility with detection platform. For bacterial toxins such as Staphylococcal enterotoxins or Clostridium botulinum toxins, high-affinity monoclonal antibodies (mAbs) are preferred due to their ability to target specific toxin epitopes accurately. For mycotoxins like aflatoxins or ochratoxin A, polyclonal antibodies can be used, although recombinant antibodies (rAbs) offer enhanced specificity and sensitivity. For chemical contaminants such as pesticides or heavy metals, the selected antibodies should exhibit strong binding affinity to the target molecules despite their small size and potential structural similarities with other compounds. The use of rAbs or engineered fragments such as single-chain variable fragments (scFvs) can improve detection accuracy and reduce cross-reactivity. These criteria ensure that the selected antibodies contribute to the overall reliability and efficiency of NISs in various food safety applications (Byrne et al., 2009; Sharma et al., 2016). These criteria ensure that the selected antibodies provide accurate, reliable, and reproducible results across different food matrices.

Different techniques are used to develop ISs including application of new NMs, specially combined and hybrid ones such as decorated–GN/GO/rGO MeNPs, QDs and multi MeNPs. They have been successfully used both in sandwich and label-free configurations. Using NMs for signal amplification has been done through disposable systems in which the sensitive part of the sensor can be produced economically at large scale (Zumpano et al., 2021). There are several examples of the recent promising studies on the novel nanosensors. For instance, sandwiched immune-complexes with AuNPs was shown to be a rapid biosensor for detecting BT in emergency situations (Cheng and Chuang, 2019). Using magnetic NPs (Fe_3O_4) and conjugated Ab was also effective for the detection of *E. coli* (Srinivasan et al., 2020).

Abs are a group of immunological proteins made in the body in

response to the exposure to an external material. The substrate may be a pathogen or an allergen. The Mw of the stimulating molecules is > 1.5 kDa and they contain an Ag. This Ag is responsible for triggering later immune responses. Abs also known as Igs are classified in five groups including IgA, IgD, IgE, IgG and IgM. They have a similar Y-shaped structure, but they are different in the number of the arms. They have also different numbers and positions of disulfide bridges and glycosylation. They attach to AG by the AG binding site and induce following immune reactions. IgG with Mw = 150 kDa is a mAb which is commonly used for ISs. Its structure contains two H and two L chains with connecting bridges of disulfide. The chains contain a constant and a variable region. Each IgG have two identical AG binding sites consisted of variable segments of L and H chains.

Two groups of Abs are widely used for diagnostic purposes including monoclonal and polyclonal Abs. The mAbs are generated during an expensive process in which similar cells are cultured using hybridoma technology. They only bind to a single specific site. Polyclonal Abs are specified with their general affinity for the Ag and attaching to its various binding sites with different affinities. They are more easily isolated; at first, some animals are immunized and polyclonal Abs are then obtained from their serum samples. However, it is preferred to use mAbs in immunologic tests, as they have beneficial characteristics such as higher affinity and specificity (Rinken, 2015).

Recombinant Abs (rAbs) have been developed in the last two decades when Plückthun and Skerra used bacterial vector to produce fragment variable (Fv) and AG-binding fragment (Fab) with full function and correct structure. Afterwards, Ab fragments have been generated *via* a wide range of systems including mammalian, insect, yeast, and plant (S. Sharma et al., 2016). The rAbs are available in different forms; (i) the single-chain Fv or scFv containing a flexible peptide (Gly4Ser)3 attached to augment the stability of the molecule; (ii) Variants of ScFvs including diabodies, domain specific Abs (dAb), and minibodies (e.g., scFv–CH3 dimers); (iii) bispecific Abs (bsAb) containing two L and two H chains, originated from two different Abs; (iv) Fab fragment containing the full section of AG binding part and F (ab')2 with two connected Fab fragments; (v) dimeric Ab containing two Abs with a peptidal connection (Cabezas et al., 2010), as shown in Fig. 5. There are also other formats of rAbs found in the literature. Application of rAbs may improve the characteristics of NISs in different ways. They are of small size, with a strong design and easy to manipulate which make them favorable to reach a satisfying immobilization on the sensor surface. However their application in the field of ISs needs more robust studies (Sharma et al., 2016).

By developing ISs, application of mAbs and rAbs compared with polyclonal Abs help to improve the ability of the device to detect toxins. For instance, an IS has been developed to detect 0.1 μg/mL of *Staphylococcal enterotoxin B* (SEB). However the rabbit polyclonal Ab was captured on the sensor surface, restricting its ability to bind to the free SEB (Byrne et al., 2009). Inspection of AFs produced by *Aspergillus* spp. is another instance. AFs B1, B2, G1, G2 and M1 are the most important ones inducing great dangers to the consumers. Polyclonal conjugated rabbit Abs have been used to detect AFB1. The authors then generated recombinant murine scFvs against AFB1 with phage display plan. There are other examples of rAbs to detect important AFs; incorporating monomeric and dimeric scFv rAbs to diagnose 390 and 12,000 ppb and 190 and 24,000 ppb of AFB1, respectively. The mAbs from marine source have also been used as part of a sensitive system to detect AFB1 and ochratoxin (Byrne et al., 2009). In the structure of NISs both polyclonal and monoclonal Abs may be applied. For instance, a novel NIS to detect BT had a monoclonal anti-BoNT/A IgG Ab to capture Ab for protein quantification; monoclonal mouse anti-SNAP-25 IgG was used for the purpose of capturing and as a probe Ab to diagnose toxin activity, and a polyclonal mouse anti-BoNT/A IgG, as a probe Ab (Cheng and Chuang, 2019).

4. Detection of foodborne toxins *via* nano-immunosensors

NISs facilitate the high sensitive and specific detection of a broad

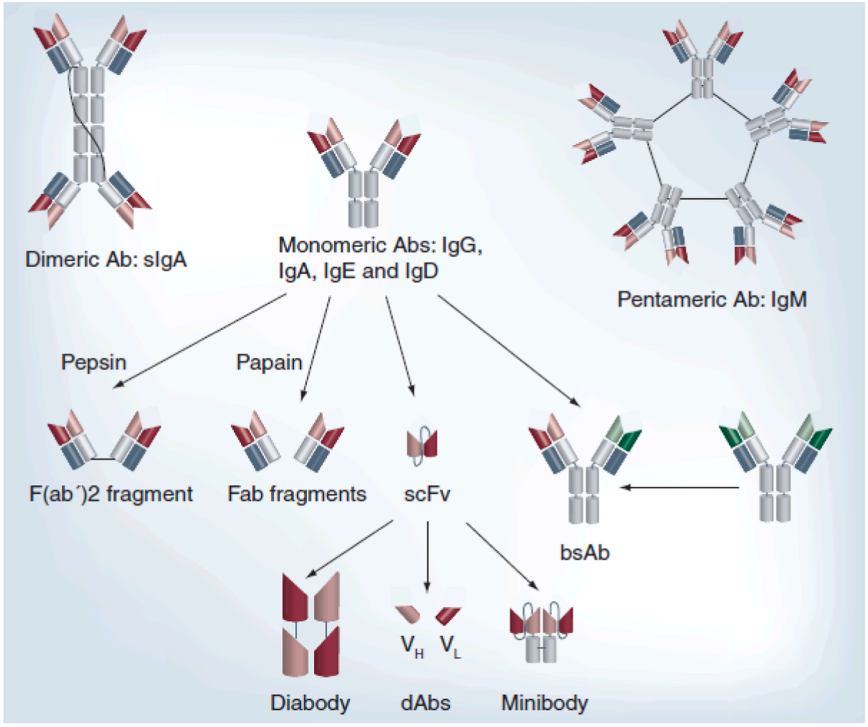

Fig. 5. Configurations of five human antibodies, including Secretory Immunoglobulin A (sIgA), Immunoglobulin G (IgG), Immunoglobulin A (IgA), Immunoglobulin E (IgE), Immunoglobulin D (IgD), and Immunoglobulin M (IgM). Additionally, various altered antibody structures generated through molecular biology methods are shown, such as F(ab')2 segments, Fab segments, single-chain variable fragments (scFv), diabodies, domain antibodies (dAbs), minibodies, and bispecific antibodies (bsAbs). These configurations illustrate the diversity of antibody formats used in nano-immunosensor development (Cabezas et al., 2010).

spectrum of toxins through complex mixtures with minimal treatment in a short period of time (Inbaraj and Chen, 2016).

4.1. Bacterial pathogens and their toxins

4.1.1. Bacterial pathogens

A microgravimetric quartz crystal microbalance (qCM) DNA sensor for *E. coli* O157:H7 detection was designed by NPs amplification approach. Accordingly, a thiolated ssDNA probe was formed as a self-assembly monolayer on the surface of the gold electrode for specific binding to *E. coli* O157:H7 eaeA gene. This thiolated ssDNA probe can be hybridized with complementary target DNA, leading to a mass alteration and hence a frequency change in qCM. The frequency change was enhanced by streptavidin labeled Fe_3O_4 NPs. The sensor detected 10–12 M synthesized biotinylated oligonucleotides and *E. coli* O157:H7 cells were observed from 2.67×10^2 to 2.67×10^6 CFU/mL between frequency change and logarithmic number (Mao et al., 2006). Similarly, a qCM IS was designed for identifying *E. coli* O157:H7. Here, Protein A and *E. coli* O157:H7 Abs were self-assembled on the gold electrode of an AT-cut piezoelectric qCM to construct IS. Then, streptavidin-conjugated NPs and biotinylated Abs were employed for signal amplification to improve the sensitivity of IS. The results presented that the detection sensitivity was enhanced by decreasing LOD from 10^7 to 10^2 CFU/mL in *E. coli* O157:H7 population with the binding of the immuno-magnetic NPs (MNPs) conjugates (Liu et al., 2007).

The detection of *S. typhimurium* with qCM IS using protein A for Ab immobilization was determined in another study. The simultaneous measurements of resonant frequency and the motional resistance corresponded to the concentration of *S. typhimurium* cells, which was within the range of 10^5–10^8 and 10^6–10^8 cells/mL, respectively, during the direct detection in the chicken flesh sample. Besides, LOD was decreased to 10^2 cells/mL in the measurements of the motional resistance (Su and Li, 2005). Through a copper-enhanced AuNPs label and anodic stripping voltammetry, an electrochemical metallo-IS for *S. typhi* has been fabricated. The results exhibited that the anodic stripping peak current had a LOD = 98.9 CFU/mL and *S. typhi* concentrations from 1.30×10^2 to 2.6×10^3 CFU/mL with a linear logarithmic correlation. This study also demonstrated that the highly sensitive and specific strategy of copper-enhanced AuNPs with electrochemical stripping examination could be used to detect bacterial cells in human serum (Dungchai et al., 2008).

The detection of magnetically tagged *L. monocytogenes* and the measurement of the rate of Ab-linked MNPs attached to bacteria were developed. The superparamagnetic Fe_3O_4 particles conjugated with Abs were added to the bacterial culture solution. When the magnetic dipole moments are aligned with a pulsed magnetic field, a superconducting quantum interference device for magnetic flux detection was used to examine the magnetic relaxation signal. This sensitive IS does not need to immobilize specific bacteria or wash away unbound MNPs by enhancing accuracy without any material loss; current LOD was 5.6×10^6 *L. monocytogenes* cells/mL (Grossman et al., 2004). Another study demonstrated the fabrication of a disposable EI for detection of *V. parahaemolyticus* using a screen-printed carbon electrode covered with agarose/nano-gold membrane and HRP-conjugated Ab of *V. parahaemolyticus*. The LOD was 7.4×10^4 CFU/mL and the detectable range was a linear calibration from 10^5 to 10^9 CFU/mL with a sigmoidal curve technique under the optimal conditions of EI analyzed by cyclic voltammetry and a laser scanning confocal microscope (Zhao etal., 2007).

4.1.2. Bacterial toxins

To detect CT, a 3D gel complex using oleogelators have been developed in NMs to stabilize the biochemical structure (Demirci et al., 2020). An EI with liposomic magnification was designed with encapsulated potassium ferrocyanide and ganglioside liposome for specific recognition labels. This IS made with a mAb of anti-CT B subunit connected to poly (3,4-ethylenedioxythiophene) covered on Nafion-reinforced MWCNTs caste film on a GCE. Under the detection with a sandwich-type assay utilizing electronic transducers, CT was initially attached to the anti–CT Ab before being conjugated with ganglioside-functionalized liposomes. Adsorptive stripping SWV was used to analyze the potassium ferrocyanide compounds released from liposomes attached to the electrode. LOD of CT was 10^{-16} g/mL, with a LDR from 10^{-14} to 10^{-7} g /mL (Viswanathan et al., 2006). A thiolated-lactose derivative that self-assembled on AuNPs of 16 nm diameter was designed in another rseearch. When the thiolated-lactose derivative binds to CT B-subunit, the aggregation of NPs was induced. The shift in color from red to deep purple was detected with the colorimetric bioassay, and LOD of CT B-subunit was 3 μg/mL (54 nM) (Schofield et al., 2007).

Besides, an optical CNT IS for the detection of SEB was designed. Anti-SEB Abs were electrostatically adsorbed on the surface of CNTs, and Ab–nanotube complex was subsequently bonded onto a polycarbonate film, followed by the binding of HRP-labeled secondary Ab and detecting its fluorescence. The introduction of CNTs and sandwich-type assay boosted the sensitivity of IS by 6–8-fold, decreasing LOD of SEB to 0.1 ng/mL with a LDR = 0.1–100 ng/mL (Yang et al., 2008). Also, a chromatic sensor with Gal-α1,4-Gal glycopolydiacetylene as NPs were developed to detect ST-producing *E. coli* O157:H7. The colorimeter was capable of measuring the color of NPs using various optical analytical techniques (Lee et al., 2020). Under UV–VIS spectroscopy, a colorimetric change happened from purple to brown when ST bound to NPs. This highly rapid and sensitive method can provide LOD = 1200 unit of *E. coli*/μL with a linear range from 1200 to 7200 unit/μL (Nagy et al., 2008). SPR imaging has also been applied to identify ST because of its quick and label-free screening. Multiple Abs were spotted one by one on the same elevated biochip with 50-nm gold film using a programmed microarrayer. The signal difference of SPR imaging between immobilizing Abs and IgG control was used to detect ST. In a sandwich framework, AuNPs were implemented to enhance the imaging signals of mAbs and improve LOD from ng/mL to pg/mL level (Wang et al., 2020).

Finally, the sandwiched NISs were developed on fluorescent probe particles (FBPs) and consisted of AuNPs, polyclonal and monoclonal Abs, and botulinum neurotoxin. The potency of BT was examined by coating synaptosomal-associated protein on FBPs. When the protein was disrupted by active botulinum, Abs conjugated AuNPs adhered to the probe particles. LOD for purified BT in whole milk and bovine serum samples ranged from 0.01 to 500 ng/mL (Cheng and Chuang, 2019).

4.1.3. Multiplex detection of bacterial strains and toxins

The development of multiplexing techniques to simultaneously detect various bacterial pathogens and toxins has become mainly promising. As an example, CT, ricin, ST 1, and SEB was detected by sandwich ISs. For the multiplexed fluoro-immunoassay, Abs and bio-inorganic conjugates were produced with highly luminous semiconductor nanocrystals containing QDs with cadmium selenide-zinc sulfide (CdSe-ZnS) coreshell. Even though this high-throughput approach can measure all four toxins in a single sample to eliminate the several isolations and incubation stages necessary in any standard immunoassay, cross-reactivity was found to be a concern. Antibodies may bind non-specifically to other components in the sample, leading to false positives or inaccurate results. Nonetheless, this problem may be overcome by carefully optimizing test conditions and selecting Ab reagent to achieve accuracy and durability (Goldman et al., 2004). Optimization may include adjusting factors such as antibody concentrations, incubation times, and buffer compositions to minimize non-specific binding and improve the accuracy of detection (Goldman et al., 2004). In another study, *E. coli O157:H7, Salmonella enterica* serovar *typhimurium*, and SEB were detected by the enzymatic bio-nanotransduction system. Magnetic beads were functionalized with primary Abs, attached to DNA templates for producing nano-signals. Immuno--magnetic trapping was proceeded by *in vitro* transcription of DNA

templates tethered to target molecules, resulting in RNA nano-signals that were specific to each bacterium or the toxin in the sample. The association between nano-signal characteristics and target levels was established using a conventional enzyme-linked oligonucleotide fluorescence technique for RNA nano-signals. LOD was 2.4×10^3 CFU/mL for *E. coli* O157:H7, 1.9×10^4 CFU/mL for *S. enterica*, and 0.11 ng/mL for SEB in milk and buffer samples (Branen et al., 2007).

A summary of different NISs for detection of bacterial strains and toxins is provided in Table 1.

4.2. Mycotoxins

Numerous NISs have been recently developed for the rapid and ultrasensitive detection and screening of mycotoxins in food products taking advantage of NMs to progress the assay in terms of sensitivity and selectivity. For instance, An and Jang (2018) developed a label-free optical liquid crystal-based IS to detect AFB1. This IS had a high specificity with LOD = 100 pg/mL. Interestingly, the results could be monitored with naked eyes through a polarized microscope without any lab-based devices. Lu et al. (2016) detected FUM B1 (FB1) and DON mycotoxins by using an EI. Under optimized conditions, LOD and LDR were 4.2 ppb and 0.2–4.5 ppm for FB1, respectively; while for DON, LOD and LDR were 8.6 ppb and 0.05–1 ppm, respectively. The developed IS was able to specifically detect the target mycotoxins more than other toxins with high sensitivity and low matrix interference in corn samples. Myndrul et al. (2021) used polyacrylonitrile /zinc oxide nanofibers for the detection of AFB1 by a photoluminescence label-free IS. It detected AFB1 with LOD = 39 pg/mL, while the LDR was between 0.1 and 20 ng/mL.

Azri et al. (2018) reported an electro-IS for the detection of AFB1 based on indirect competitive ELISA. The designed IS exhibited a LOD = 0.3 pg/mL with a LDR = 0.0001–10 ng/mL in peanut samples. Abdallah et al. (2019) fabricated and characterized an ultrasensitive label-free EI which successfully identified AFB1 with a LOD = 50 fg/mL in a LDR of 50 fg/mL to 5 ng/mL. Nirbhaya et al. (2021) used a metal-free nanostructured thionine/graphitic carbon nitride (g-C3N4)/indium tin oxide (ITO) coated glass for the development of an ultrasensing EI platform. It detected AFB1 with a LDR = 1 fg/mL to 1 ng/mL and LOD = 0.328 fg/mL. Likewise, Lu and Gunasekaran (2019) detected FB1 with LOD = 97 pg/mL and DON with LOD = 35 pg/mL simultaneously by a dual-channel ITO-microfluidic EI in ground corn samples. The corresponding LDR was 0.3–140 and 0.2–60 ppb for FB1 and DON, respectively.

Guo et al. (2021) designed and characterized a magnetic

Table 1
Nano-immunosensors (NISs) for the detection of different bacterial strains and toxins. This table provides detailed information on the target bacterial strain or toxin, the nanomaterial used, the detection method and recognition element, the detection limit, and the working concentration range; Each entry includes references for further reading.

Target	Nanomaterial	Detection method and recognition element	Detection limit/working concentration range	Reference
E. coli O157:H7	A quartz crystal microbalance (qCM) DNA sensor in magnetic nanoparticles (MNPs)	A thiolated single-stranded DNA probe immobilized on qCM conjugated with streptavidin in MNPs	2.67×10^2; 2.67×10^2 to 2.67×10^6 CFU/mL	(Mao et al., 2006)
	A qCM IS in MNPs	Protein A and *E. coli* Abs self-assembling on the gold electrode of an AT-cut piezoelectric qCM	10^2; 10^5 to 10^7 CFU/mL	(Liu et al., 2007)
Salmonella typhimurium	A qCM IS	IS with protein A for Ab immobilization in the simultaneous measurements of the resonant frequency and motional resistance	10^2; 10^5 to 10^8 (resonant frequency) and 10^6–10^8 cells/mL (motional resistance)	(Su and Li, 2005)
Salmonella typhi	An electrochemical metallo-IS in gold NPs (AuNPs)	A metallo-IS based on a copper-enhanced AuNPs label and anodic stripping voltammetry	98.9; 1.30×10^2 to 2.6×10^3 CFU/mL	(Dungchai et al., 2008)
Listeria monocytogenes	50-nm-diameter superparamagnetic magnetite particles conjugated with Abs	The magnetic flux detection with a high-transition temperature superconducting quantum interference device	5.6×10^6 CFU/mL	(Grossman et al., 2004)
Vibrio parahaemolyticus	AuNPs	A screen-printed carbon electrode covered with agarose/nano-gold membrane and horseradish peroxidase (HRP) conjugated Ab	7.374×10^4; 10^5 to 10^9 CFU/mL	(Zhao et al., 2007)
E. coli O157:H7, *Salmonella enterica* serovar *typhimurium*, and staphylococcal enterotoxin B (SEB)	MNPs	Enzymatic bio-nanotransduction on DNA-Abs conjugated on MNPs	*E. coli* 2.4×10^3, *S. enterica* 1.9×10^4 CFU/mL, and SEB 0.11 ng/mL in milk and buffer	(Branen et al., 2007)
Cholera toxin (CT)	Carbon nanotubes (CNTs)	mAb of anti-CT B subunit linked to poly(3,4-ethylenedioxythiophene) covered on Nafion-reinforced multiwalled CNT caste film on a glassy carbon electrode	10^{-16}; 10^{-14} to 10^{-7} g/mL	(Viswanathan et al., 2006)
	AuNPs	Thiolated lactose coated AuNPs by UV–Vis spectroscopy	3 μg/mL	(Schofield et al., 2007)
SEB	CNTs	Ab with HRP-labeled secondary Ab coated on CNTs under fluorescence detection	0.1; 0.1–100 ng/mL	(Yang et al., 2008)
Shiga toxin	Gal-α1,4-Gal glycopolydiacetylene NPs	A chromatic sensor with Gal-α1,4-Gal glycopolydiacetylene as NPs under UV–VIS spectroscopy	1200; 1200–7200 unit/μL	(Nagy et al., 2008)
	AuNPs	SPR imaging signals of mAbs amplified by AuNPs in a sandwich platform	1 pg/mL; 200–1000 mg/mL	(Wang et al., 2020)
Botulinum toxin (BT)	AuNPs	The sandwiched nano-ISs consist of AuNPs, polyclonal Ab, and BT on fluorescent probe particles with bead-based IS	10 pg/mL; 0.01–500 ng/mL	(Cheng and Chuang, 2019)
CT, ricin, Shiga-like toxin, and SEB	Quantum dots (QDs)	Abs with CdSe-ZnS on QDs under the fluoro-immunoassay	No data	(Goldman et al., 2004)
BT type A	Complex sample matrices by amplified luminescent proximity homogeneous assay linked immunosorbent assay (AlphaLISA)	An Ab specific to BT type A, anchored on an AlphaLISA bead, conjugated with biotin in proximity to streptavidin-coated donor beads	0.1 ng/mL	(Zhang et al., 2022)

separation-based NIS coupled with a nano-affinity for DON. In this study, CdSe/ZnS QD nanobeads coupled with maltose-binding protein and graphene oxide (GO) and linked with MNPs (Fe_3O_4)/protein G were applied for fluorescent reporter and immuno-magnetic adsorbent, respectively. The optimized NIS detected DON with a LDR = 0.3–3000 ng/mL and LOD = 0.50, 1.0, and 3.0 ng/mL. Jiang et al. (2020) developed a chemiluminescent IS coupled with SPR and AgNPs compared to traditional HPLC and ELISA methods for the detection of mycotoxins in red yeast rice samples. The LOD at the signals were 0.39 pg/mL for citrinin, 0.44 pg/mL for AFB1, and 0.83 pg/mL for OTA with a LDR between 0.001 and 1 ng/mL. The proposed AgNPs modified NISs indicated an acceptable accuracy for simultaneous detection of mycotoxins in rice samples. In another study, AFB1, OTA, ZEA and DON were detected simultaneously in corn and wheat samples using the SPR technique with indirect competitive ISs (Wei et al., 2019). LOD was about 0.59, 1.27, 7.07 and 3.26 ng/mL for AFB1, OTA, ZEA and DON, respectively. Used SPR sensor chip in this study increased the sensitivity of the method significantly.

Li et al. (2018) developed an IS based on SERS technique for simultaneously detection of AFB1, OTA, and ZEA in corn, rice and wheat samples. Accordingly, labeled AuNPs with 5,5-dithiobis(succinimidyl-2-nitrobenzoate) were considered as Raman reporter. This IS detected AFB1, OTA, and ZEA with LOD = 0.061–0.066, 0.26–0.29, and 0.53–0.57 μg/kg, respectively on a single gold chip under optimum condition. In another study, Wu et al. (2022) designed and characterized a sensitive, smart, and rapid microarray based on a smartphone and indirect competitive IS. It was able to simultaneously detected OTA, DON, FB1, and ZEA mycotoxins within 30 min with LOD = 6, 14, 66, and 5 pg/mL, respectively. LDR was 0.08–4860 for OTA, 0.09–3240 for DON, 0.09–3240 for FB1, and 0.05–3240 ng/mL for ZEA. Nabok et al. (2021) fabricated ISs based on an optical planar waveguide for the detection of ZEA; LOD was 0.01 ng/mL with a LDR up to 1000 ng/mL.

Yan et al. (2019) used an EI based on mimotope-peptide for ultrasensitive detection of DON in corn and wheat samples. Optimized EI indicated a dynamic detection range (DDR) between 0.1 and 10, 000 pg/mL and LOD = 0.07 pg/mL. Similarly, Hou et al. (2019) developed an ultrasensitive competitive EI based on phage displayed mimotope-peptide for detection of OTA in corn and beer samples. The LOD of the optimized IS was 2.04 fg/mL, with a DDR = 7.17–548.76 fg/mL. Valera et al. (2019) designed an IS based on electrochemical nanoprobe for detection of DON in wheat samples. Nanoprobes (AbDON) was labeled with CdS NPs. LOD was 342.4 μg/kg, with a LDR from 610 to 6210 μg/kg. Székács et al. (2021) applied a direct-competitive IS based on optical waveguide light-mode spectroscopy for detection of ZEA in corn samples. A remarkable LOD = 0.002 pg/mL was found for ZEA with a LDR between 0.01 and 1 pg/mL.

To summarize, as various studies have shown, ISs are the ideal,

Table 2
Immunosensor applications for simultaneous detection of mycotoxins in food matrices. This table outlines various immunosensors designed to detect multiple mycotoxins in different food samples. It includes details on the technique used, nanomaterial involved, limit of detection, linear detection range, and the specific food matrix tested.

Target	Technique	Nanomaterial	Limit of detection	Linear range	Product	Ref.
Non-competitive immunoassays						
AFB1	Electrochemical	Cysteine/AuNPs/Carbon nanotubes (CNTs)	0.79 pg/g	0.1–20 pg/g	Corn flour	(Costa et al., 2017)
		Dimanganese trioxide (Mn_2O_3)/ Indium tin oxide (ITO)	0.54 pg/mL	1 pg/mL to 10 μg/mL	Corn	(Singh et al., 2021)
Competitive immunoassays						
AFB1, ZEA, OTA	Lateral flow	AuNPs	0.10, 0.42, and 0.19 μg/kg for AFB1, ZEA, and OTA in corn. 0.12, 0.43, and 0.21 μg/kg for AFB1, ZEA, and OTA in rice. 0.13, 0.46, and 0.24 μg/kg for AFB1, ZEA, and OTA in peanut.	0.1–7.0, 0.42–35.5, 0.19–10.1 μg/kg for AFB1, ZEA, OTA in corn. 0.12–7.2, 0.43–35.5, 0.21–10.2 μg/kg for AFB1, ZEA, and OTA in rice. 0.13–7.2, 0.46–35.7, and 0.24–10.3 μg/kg for AFB1, ZEA, and OTA in peanut.	Corn/rice/ peanut	(Chen et al., 2016)
ZEA, DON	Lateral flow	Quantum Dots (QDs)	40 μg/kg for ZEA and 400 μg/kg for DON	-	Corn/ wheat	(Goryacheva et al., 2020)
AFB1	Electrochemical	Au nanodots/rGO nanosheets/ ITO	6.9 pg/mL	-	Peanut	(Althagafi et al., 2019)
		AuNPs/ poly (3,4ethylenedioxythiophene)/ graphene oxide	0.989 μA ng/mL	0.5–20 ng/mL	Corn	(Sharma et al., 2018)
		AuNPs/poly4-aminobenzoic acid/graphene	0.001 ng/mL	0.01–25 ng/mL	Vegetable oil	(Shi et al., 2020)
		Ferrocene /Multi-walled CNTs	0.159 pg/mL	10^{-3} ~2×10^4 ng/mL	Peanuts/ rice/corn	(Zhang et al., 2019)
AFM1		Single-walled CNTs	0.02 μg/L	0.01 μg/L to 1 μg/L	Milk	(Abera et al., 2019)
DON, T−2, FB1	Fluorescence polarization	-	242.0 μg/kg for DON, 17.8 μg/kg for T−2, and 331.5 μg/kg for FB1	447.5–3780 μg/kg for DON, 74.3–7014 μg/kg for T−2, and 587.0–6265 μg/kg for FB1	Corn	(Li et al., 2016a, 2016b)
DON, ZEA, T−2, FB1	Chemi-luminescence	-	0.0036, 0.0048, 0.0039, and 0.0017 ng/mL for DON, ZEA, T−2, and FB1.	0.01–0.1 ng/mL for four mycotoxin		(Li et al., 2016a, 2016b)
AFB1, ZEA, FB1, DON, OTA, T−2	Surface enhanced Raman scattering (SERS)	-	0.00096 ng/mL for AFB1, 0.0062 ng/mL for ZEA, 0.00026 ng/mL for FB1, 0.00011 ng/mL for DON, 0.0157 ng/mL for OTA, and 0.0086 ng/mL for T−2	0.0014–0.33 ng/mL for AFB1, 0.015–3.7 ng/mL for ZEA, 0.41–100 ng/mL for FB1, 0.14–33.3 ng/mL for DON, 0.027–6.7 ng/mL for OTA, and 0.014–3.3 ng/mL for T−2		(Zhang et al., 2020)

ultrasensitive and rapid tools for detecting a variety of contaminants, especially mycotoxins in the food chain and the environment. These systems are capable of detecting multiple mycotoxins simultaneously, even in complex food matrices, making them highly effective for comprehensive food safety monitoring. Their ability to perform multiplex detection ensures efficiency and accuracy in identifying various contaminants within a single test. Therefore, ISs can provide a potential application for the ultrasensitive detection of various toxicants in the food chain and environment with the minimum LOD. Table 2 represents a summary of NIS applications for simultaneous detection of mycotoxins in food matrices.

4.3. Marine toxins

The maximum presence levels of MTs have been established and announced by the EU (Regulation (EC) No 853/2004). A specific standard has been defined for each of these toxins. For example, the maximum presence of OA in the edible tissue of marine creatures such as fish is 160 μg/kg (Saravanakumar et al., 2022; Tian et al., 2021). There are several common methods for detecting these toxins, such as HPLC, ultra-performance liquid chromatography (UPLC), capillary electrophoresis (CE), nuclear magnetic resonance (NMR), MS, ELISA, and protein phosphatase inhibition assay (PPIA). Although they are accepted methods, they are complex, expensive, and time-consuming (Wu and Khan, 2020). ISs can be the most attractive methods for detecting MTs due to their highly precise molecular identification without the requirement for prior sample concentration and pretreatment (Wu and Khan, 2020). Efforts have been made on the development of ISs based on fluorescence, colorimetric, and other methods; nevertheless, the best candidate is EIs owing to their simplicity, cheapness, high sensitivity, and affluence of miniaturization. In immunoassay methods, biocompatible NMs complexes are of significant attention for the active immobilization and recognition of AG molecules in an extremely sensitive and discriminatory IS platform when detecting MTs (Wang et al., 2022).

Although the use of ISs to detect MTs is attractive and has been widely studied in recent years and recommended for use in diagnostic labs, application of NMs in these methods is new and there are fewer studies in this regard (Wang et al., 2022; Ye et al., 2019). As an example, Antunes et al. (2018) invented an EI based on graphene nanoplatelets (with outstanding electrochemical characterization) that were dropped on the superficial of field-effect transistors (FET) creating Gr-FET composite. Next, the anti-OA Ab was blended and cross-linked with Gr-FET. In the presence of OA, it was arrested via an immobilized Ab blocking the electric signal. This EI exhibited an extensive LDR = 0.05–300 ng/mL and LOD = 0.05 ng/mL, in comparison with ELISA. Reverté et al. (2017) described an innovative good wave-guide IS for TTX recognition in pufferfish. Initially, TTX was conjugated with jeffamine-keyhole limpet hemocyanin (KLH) creating a TTX composite. Next, TTX composites were cross-linked with BSA and restrained on planar waveguide nanoarray. Then, Ab fixed to free TTX in place of immobilized TTX, once added free TTX to the solution. Consequently, the fluorescence signal of Ab immobilized on wave-guide nanoarray would be decreased. In this study, the applied NIS could distinguish TTX in a LDR = 0.5–3.29 lg/g.

In another study, Talamini et al. (2018) designed a direct EI to detect Microcystin-LR (hepatotoxins formed *via* cyanobacteria) in seawater. They used liquid crystal (*E*)-1-decyl-4-[4-decyloxyphenyl) diazinyl] pyridinium bromide (Br-Py) as a redox probe and AuNPs stabilized in bovine serum albumin (BSA). By using N-hydroxysuccinimide (NHS) and N-(3-dimethylaminnopropyl)-N-ethyl-carbodiimide hydrochloride (EDC) on an AuNP-BSA/BrPy film, the microcystin-LR Ab (anti-MC-LR) was covalently immobilized. Finally, NIS showed a linear retort to Microcystin-LR concentrations of 0.05–500 ng/mL with LOD = 0.05 ng/mL. In some cases, toxins are secondarily produced in canned seafood, and their rapid and simple detection is important to prevent disease in the consumer. One of the most dangerous ones is BT, which causes neuroparalytic disease. NISs can be applied for rapid, straightforward, and precise identification of BT and several valuable studies have been performed in this regard. For example, NISs were created *via* establishing sandwiched immune-complexes containing toxic proteins, AuNPs, and Abs on fluorescent probe units for detection of BT (Cheng and Chuang, 2019). Table 3 shows some selected investigations that applied NISs to detect MTs.

4.4. Chemical toxicants

There is excessive potential in the employment of NISs for the fast identification of pesticide traces in foods and surroundings. Kumar et al. (2020) reviewed the contemporary status and perspectives of NISs for the detection of pesticides/herbicides. Their results showed that carbon and metal-based NMs are a desirable choice for ISs. Liu et al. (2014) applied a NIS based on patterned CNTs for the detection of paraoxon and endosulfan with high sensitivity. In their study, the developed NIS array demonstrated high selectivity (the ability to accurately distinguish the target pesticides from other substances in the mixture), specificity (ensuring exclusive identification of paraoxon and endosulfan, reducing false positives), repeatability (the capacity to produce consistent results under the same conditions across multiple trials), stability (maintaining performance characteristics over time under varying environmental conditions), and reproducibility (delivering consistent results across different settings, operators, and equipment) for pesticide detection. Some examples of CNT-based nano-sensors already commercially available or under development include:

1. **CNT-based gas sensors**: These are used for detecting various gases such as ammonia, methane, and volatile organic compounds (VOCs). These sensors are already available for industrial and environmental monitoring applications, benefiting from the high sensitivity and reliability of CNTs.
2. **Nano-sensors for environmental and water quality monitoring**: Some commercial sensors incorporate CNTs for detecting pollutants like heavy metals or pesticides in water or air, similar to the CNT-based NIS described by Liu et al. (2014). These sensors are part of ongoing efforts to monitor environmental contaminants, though not all may be explicitly designed for paraoxon or endosulfan.
3. **Wearable CNT-based biosensors**: These sensors are being developed for healthcare applications, allowing the detection of biomolecules and environmental contaminants. They benefit from the same qualities observed in Liu et al. (2014), such as repeatability, stability, and selectivity, making them suitable for a range of uses.

While CNT-based pesticide detection sensors like the one described in the study may still be in the prototype or research phase, CNTs are already being utilized in various commercial sensor products. As technology advances, the application of CNT-based sensors for pesticide detection, including paraoxon and endosulfan, may become more widespread (Liu et al., 2014).

Drug residues, especially antibiotics residues, are one of the main problems in environmental and food pollution. In the past few years, application of ISs, especially NISs, for the rapid, accurate, easy, and low-cost detection of drug residues compared to other methods has been recommended. For instance, Pollap and Kochana (2019) offered the current achievements of EIs and NISs in the detection and determination of antibiotics in food and environmental samples. El Hassani et al. (2019) reported a new EI for screening tetracycline in honey *via* an entirely combined electrochemical Bio-MEMS. This NIS was extremely sensitive with LOD = 1.2 pg/mL and specific in the existence of interferents.

The most important industrial and environmental toxicants are cases such as heavy metals, dioxins, and polychlorinated biphenyls which can be monitored by NISs. In a study, Kuang et al. (2013) described the

Table 3
Selected applications of nano-immunosensors (NISs) to detect marine toxins. This table highlights the application of nano-immunosensors in detecting various marine toxins, providing detailed information on the specific toxins targeted, the types of samples analyzed, the detection methods employed, the types of nanomaterials used, as well as the linear range and limit of detection (LOD) for each sensor.

Target	Sample	Detection method	Nanomaterials	Linear range/ LOD	Ref.
Okadaic Acid	Mussel	Electrochemical NIS (E. NIS)	Nanomaterial-modified screen-printed electrodes/ SPEs	0.18 ng/mL	(Nelis et al., 2021)
	Seawater		Graphene nanoplatelets	0.05–300 ng/mL	(Antunes et al., 2018)
Brevetoxins	Mollusk extracts: *Musculista senhousia, Sinonovacula constricta, and Tegillarca granosa*		AuNPs-decorated amine-terminated poly (amidoamine)/ AuNPs-PAADs	0.03–8 ng/mL	(Tang et al., 2011)
Brevetoxin B	Musculista senhousia		Mesoporous carbon-enriched palladium nanostructure/MSC-PdNS	0.01–10 ng/mL (ppb)	(Lin et al., 2015)
	Mollusk extracts: non-toxic *Musculista senhousia, Tegillarca granosa,* and *Sinonovacula constricta*	Magneto-controlled E. NIS	Guanine-functionalized graphene nanoribbons	1.0 pg/mL–10 ng/mL	(Tang et al., 2012)
Domoic acid	Shellfish	E. NIS	Gold nanostars (GNST), gold nanospheres (GNP) and carbon black (CB)	5–58 mg DA/kg	(Nelis et al., 2020)
	Mussel		Nanomaterial-modified screen-printed electrodes/SPEs	1.9 ng/mL	(Nelis et al., 2021)
Saxitoxin	Seawater and shellfish		Palladium-doped graphitic carbon nitride nano-sheets (g-C3N4-PdNPs)	1.2 pg/mL	(Jin et al., 2019)
Tetrodotoxin	Puffer fish		NIS array platforms based on self-assembled dithiols	0.5–3.29 lg/g	(Reverté et al., 2017)
			AuNPs	2–1250 ng/mL	(Shen et al., 2021)
Ciguatoxins	Fish	Amperometric NIS	Multiwalled carbon nanotube (MWCNT)-modified carbon electrodes	0.001 μg/kg	(Campàs et al., 2022)

utilization of a strip NIS approach, which employs probes consisting of AuNPs in varying sizes, for the identification of lead ions in potable water. Accordingly, the test samples exhibited a recovery rate between 96 % and 103 %, and the detection of the lead amount required approximately 15 min. Chobtang et al. (2011) reviewed the requirement and potential of biosensors (especially ISs and NISs) as simple and efficient methods to detect dioxins and dioxin-like polychlorinated biphenyls in some foods e.g., meat, milk, and egg. Food additives

Table 4
Selected studies on the application of nano-immunosensors (NISs) to detect chemical toxicants. This table highlights the use of nano-immunosensors in detecting various chemical toxicants, providing detailed information on the specific toxicants targeted, the types of samples analyzed, the detection methods employed, the nanomaterials used, and the linear range and limit of detection (LOD) for each sensor.

Target	Sample	Detection method	Nanomaterials	Linear range/LOD	Ref.
Pesticides: endosulfan and paraoxon	Four samples of environmental water: field water from a farm and lake water from a nearby lake	A multianalyte E. NIS	Carbon nanotubes (CNTs)	For endosulfan: 0.05–100 ppb For paraoxon: 2–2500 ppb	(Liu et al., 2014)
Drug residues: sulfamethoxazole	Milk, eggs, honey	E. NIS	CeO_2/chitosan nanocomposite-modified electrodes	5×10^{-7} - 5×10^{-4} mg/mL	(Cai et al., 2012)
Drug residues: ampicillin	Milk, tap water, orange juice		Molybdenum disulfide nanoparticles ($nMoS_2NPs$)	0.0325–64 μg/mL	(Yadav et al., 2021)
Drug residues: maduramicin	Egg		Au/Pt NPs	0.1 ng/mL - 50 ng/mL	(Hu et al., 2019)
Heavy metals: lead ions	Drinking water	Strip NIS	Two heterogeneously-sized AuNPs probes	2 ng/mL	(Kuang et al., 2013)
Heavy metals: mercury (II) ions	Facial cream, foundation	Electro chemiluminescent NIS	AuNPs	0.01–50 ng/mL	(Zhang et al., 2014)
Melamine	Raw milk	A novel NIS	Chitosan-prussian blue-graphene nanocomposite and AuNPs	0.3 – 1000 ng/mL	(Dong et al., 2016)
	Liquid milk, milk powder	A competitive E. NIS	AuNPs	1×10^{-6} - 1 μM	(Ren et al., 2020)
Acrylamide	Drinking water, coffee, potato chip	E. NIS	Chitosan/SnO_2-SiC hollow sphere nanochains/AuNPs	For drinking water: 187 ng/kg - 104 μg/kg For coffee and potato chip: negative	(Wu et al., 2019)
	Coffee, cocoa, prune juice		AuNPs, CNTs	0.01–35.00 μg/mL	(Lau et al., 2019)
Polycyclic aromatic hydrocarbons (PAHs): Benzo [*a*] pyrene	Grain- and oil-related foods		-	0.1–100 ng/mL	(Wang et al., 2016)
	Tap water, river water	Photo-electrochemical NIS	AuNPs	0.315 pM - 3.15 nM	(Kang et al., 2011)

including preservatives, dyes, sweeteners, and antioxidants; emerging chemical toxicants like melanin; process-related ingredients such as acrylamide, furans, and polycyclic aromatic hydrocarbons (PAH) are other chemical toxicants that can be identified and quantified by NISs in food and environmental samples due to their adverse effects on consumer health, especially in high and low doses (in long-term) (Kuswandi et al., 2017). Table 4 presents some selected investigations that applied NISs to detect chemical toxicants.

5. Pros and cons of using nano-immunosensors

Nowadays, researchers are mostly focused on the development of NISs due to the detection at low concentration, and more durability and stability for small analyte molecules. The main advantages of NISs over the conventional detection methods are being easy-to-use, rapid, cost-effective, sensitive, specific, portable, and quantitative method for single or multiple monitoring of toxins on a single tool (Rai et al., 2015). The use of NMs in ISs has presented an attractive platform for jointing the biorecognition element with the transducer for signal augmentation in ISs. Significant advancements have been made in the structure of NISs, including an increased volume ratio and surface area, as well as a more effective surface for immobilizing biomolecules with optimal orientation, spatial arrangement, sufficient adsorption, and improved electron-transfer kinetics. Furthermore, the physically improved structure and arrangements of NISs can boost AG-Ab binding functionality as well as enhancing the sensitivity of ISs (Hong et al., 2022; Inbaraj and Chen, 2016). It should also be added that some factors e.g., the time of AG-Ab binding reaction, concentration of AG, and Abs, pH, the washing step, ionic strength, and temperature have significant effects on the sensitivity of ISs.

To achieve an optimal antigen-antibody (AG-Ab) reaction, it is crucial to reach equilibrium where the reaction achieves maximum sensitivity. During the washing step, it's important to account for the partial dissociation of the AG-Ab complex due to the removal of unbound antibodies. This step can result in the loss of low-affinity antibodies, which may affect the overall sensitivity and specificity of the assay. In the context of human and environmental exposure to metallic NMs (NPs), it's essential to consider their potential toxicological effects. These NPs can interact with biological systems and the environment, leading to exposure risks. Understanding their behavior, bioavailability, and potential for bioaccumulation is critical to assess safety and mitigate any adverse effects (Hong et al., 2022).

Apart from the mentioned advantages, there are some limitations or challenges which need to be overcome to commercialize NISs for the analysis of FTs. The major challenge is to use the sustainable and convenient NMs which can improve the durability of ISs and stability of the immobilizing matrix. An additional issue about using NISs relates to their disposal after measurement of FTs (Inbaraj and Chen, 2016; M. Rai et al., 2015). Consequently, numerous investigators are concentrating primarily on enhancing the analytical efficiency of NISs and ensuring their safe disposal post-utilization.

6. Conclusion and future perspective

This review highlights the recent advancements, current trends, and challenges in the rapidly evolving field of NISs, particularly through the integration of NPs. NPs' diverse properties—electronic, magnetic, optical, catalytic, and mechanical—combined with the recognition capabilities of biomaterials like Abs, have led to significant improvements in sensor performance. NISs, when paired with microfluidics and MEMS technologies, offer a cost-effective, rapid, and user-friendly solution for detecting substances ranging from biomarkers to environmental pollutants. However, real-world performance remains unpredictable, and extensive testing is essential before large-scale commercialization.

Future research should focus on improving the reproducibility and scalability of NISs, addressing nanoscale heterogeneity, and ensuring stable immobilization of antibodies. Integration with portable devices for in-field food safety monitoring and enhancing sensor sensitivity and specificity are key areas for development. Additionally, progress in multiplexing capabilities, reducing cross-reactivity, and advancing data analysis systems is crucial for improving detection accuracy. Researchers should also explore the development of new NMs and consider the relevance of ultra-low LOD in practical applications.

Overall, the review emphasizes the potential of NMs, especially in detecting foodborne toxins like AFB1, and the advancements in opto-electrochemical biosensing. With the growing integration of microfluidic devices and NISs into portable, everyday devices, food safety monitoring could become more accessible to the public, paving the way for more reliable and widespread use of NISs.

CRediT authorship contribution statement

Akbari-Alavijeh Safoura: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **Shaddel Rezvan:** Data curation, Investigation, Methodology, Writing – original draft. **Lee Chi-Ching:** Data curation, Investigation, Methodology, Writing – original draft. **Pourjafar Hadi:** Data curation, Investigation, Methodology, Writing – original draft. **Ansari Fereshteh:** Data curation, Investigation, Methodology, Writing – original draft. **Sani Mahmoud Alizadeh:** Data curation, Investigation, Methodology, Writing – original draft. **Ajili Najmeh:** Data curation, Investigation, Methodology, Writing – original draft. **Assadpour Elham:** Formal analysis, Validation, Writing – review & editing. **Zhang Fuyuan:** Formal analysis, Supervision, Validation, Writing – review & editing. **Jafari Seid Mahdi:** Writing – review & editing, Validation, Supervision, Project administration.

Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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