Environmental protection based on the nanobiosensing of bacterial lipopolysaccharides (LPSs): material and method overview

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Lipopolysaccharide (LPS) or endotoxin control is critical for environmental and healthcare issues. LPSs are responsible for several infections, including septic and shock sepsis, and are found in water samples. Accurate and specific diagnosis of endotoxin is one of the most challenging issues in medical bacteriology. Enzyme-linked immunosorbent assay (ELISA), plating and culture-based methods, and Limulus amebocyte lysate (LAL) assay are the conventional techniques in quantifying LPS in research and medical laboratories. However, these methods have been restricted due to their disadvantages, such as low sensitivity and time-consuming and complicated procedures. Therefore, the development of new and advanced methods is demanding, particularly in the biological and medical fields. Biosensor technology is an innovative method that developed extensively in the past decade. Biosensors are classified based on the type of transducer and bioreceptor. So in this review, various types of biosensors, such as optical (fluorescence, SERS, FRET, and SPR), electrochemical, photoelectrochemical, and electrochemiluminescence, on the biosensing of LPS were investigated. Also, the critical role of advanced nanomaterials on the performance of the above-mentioned biosensors is discussed. In addition, the application of different labels on the efficient usage of biosensors for LPS is surveyed comprehensively. Also, various bio-elements (aptamer, DNA, miRNA, peptide, enzyme, antibody, etc.) on the structure of the LPS biosensor are investigated. Finally, bio-analytical parameters that affect the performance of LPS biosensors are surveyed.

1. Introduction

Gram-negative bacteria are described by an envelope that contains two membranes: an outer membrane (OM) that separates the cell from its environment and an inner membrane (IM) that surrounds cytoplasmic components.1,2 Gram-negative bacteria envelope surrounds periplasm that is an aqueous cellular compartment, which encloses the peptidoglycan cell wall. Therefore, OM encompasses a crucial role in the protection of Gram-negative bacteria against environmental treatments. Outstandingly, in distinction to many biological membranes, the OM of most Gram-negative microorganisms is not a lipid bilayer.3 Instead, it is an especially unbalanced bilayer that contains phospholipids within the inner leaflet and lipopolysaccharide (LPS) molecules in the outer leaflet.3 Consistent with previous studies, LPS is the endotoxin portion of the Gram-negative bacterial cell wall. LPS is found in high levels in clinical necrotizing enterocolitis (NEC) that acts as a pro-inflammatory stimulus in the gastrointestinal (GI) tract. LPS performs numerous functions in Gram-negative bacteria. The essential role of LPS is to help as a main structural part of the OM. Also, LPS is a crucial section of the cell wall in some Gram-negative bacteria.4 The results show that the LPS molecules transform OM into a permeable membrane that is effective against small molecules and bacteria that can overcome the phospholipid bilayer, rendering Gram-negative bacteria resistant to natural antibacterial agents of some compounds.5,6 LPS may also play an essential role in bacterial-host interactions by regulating the host immune system.7 LPS is the cause of a wide range of infections in humans, including sepsis, severe fever, and shock sepsis, and is found in different types of water, including groundwater, freshwater, and saline.8

2. Biological effect of LPS

LPS is a molecule that forms a part of the bacterial cell wall of Gram-negative bacteria and helps to stabilize the bacterial cell wall. The LPS is made up of three parts.9 (A) The O-side (O antigen) is the main site of immunospecificity, (B) a central polysaccharide component close to the lipid A matrix, which is
exposed to the extracellular milieu; and (C) lipid A is the real fever component of LPS. Lipid A is surrounded by the cell barrier of Gram-negative bacterium and is the most conserved part of the LPS structure.\textsuperscript{10–12} The other two components are outside, away from the bacterial cell wall. Lipid A aids as an anchor for the LPS component. LPS acts as an inner and outer portion of the external cell wall and internal membrane of Gram-negative bacterial cells.\textsuperscript{13} A representative design of the Gram-negative bacteria cell wall structure is presented in Fig. 1.

LPS provides a protecting and stabilizing mechanical maintenance to the cell and aids in protecting the integrity of the cell wall, and therefore, survival of the cell mainly in high level stress, such as dehydration. The pathogenicity of the LPS is almost entirely due to the region III component, lipid A (endotoxin), which in several texts is mentioned as catechin.\textsuperscript{14,15} The main pathogenicity of lipid A may primarily be obvious itself by the increase of alteration of metabolism in small doses and fever.\textsuperscript{16,17} Therefore, LPS is one of the target antigens for diagnosis and potential candidates for vaccine and drug development. Even though the name “endotoxin” is infrequently used to refer to any cell-associated bacterial toxin, in bacteriology, it is accurately reserved to refer to the LPS complex related to the outer membrane of Gram-negative microorganisms such as Pseudomonas, Bordetella pertussis, Escherichia coli, Salmonella, Haemophilus influenza, Shigella, Neisseria, and Vibrio cholera. Some important endotoxin (LPS) producing bacteria and related diseases are summarized in Table 1.

Based on Table 1, there are a variety of diseases associated with bacterial endotoxin. Therefore, rapid and specific diagnosis of endotoxin plays a critical role in controlling and treating the disease. In the following, some of the most important and widely used methods of endotoxin diagnosis are discussed. These severe effects instantly demand approaches for sensitive quantification such as endotoxin from pharmaceutical and biological products. Limulus amoebocyte lysate assay (LAL), rabbit pyrogen test, enzyme-linked immunosorbent assay (ELISA), and fluorescence-based methods are the most important and widely used techniques for the determination of LPS.\textsuperscript{35–37} To strengthen and increase the sensitivity and specificity of routine methods in recent years, various methods have been developed, of which nanotechnology-based methods are one of the most important. The present article aims to investigate the diagnostic methods of lipopolysaccharide, emphasizing biosensors developed in this field. This study also addresses the challenges of routine testing and the importance of developing biosensors. As mentioned in the introduction, endotoxin is one of the most important pathogens associated with Gram-negative bacteria, so that its accurate, specific, and rapid identification can play a crucial role in controlling and treating the disease. In addition, due to the exceptional properties of endotoxin, this biomolecule has been considered by researchers in pharmacy, so the expansion of advanced diagnostic methods will be desirable. In the review, routine diagnostic methods on endotoxin monitoring are introduced, and their strengths/weaknesses are discussed. In addition to the comprehensive introduction of biosensors as a specific and sensitive method for endotoxin detection, the most up-to-date developed biosensors in this field have been reviewed. For the complete nobility of the readers of this article, a table containing general information of the introduced LPS biosensors such as analytical features of used techniques and platforms have been considered appropriately. So in this review, various types of biosensors such as optical (fluorescence, SERS, FRET, and SPR), electrochemical, photoelectrochemical, and electrochemiluminescence were investigated. Also, the critical role of advanced nanomaterials on the performance of the above-mentioned biosensors is discussed. In addition, the application of different labels on the efficient usage of biosensors for LPS is surveyed comprehensively. Also, various bioelements (aptamer, DNA, miRNA, peptide, enzyme, antibody, etc.) on the structure of the LPS biosensor were investigated. Finally, bioanalytical parameters, which affect the performance of LPS biosensors are surveyed.

3. Conventional methods in the detection of endotoxin (LPS)

Culturing and plating techniques are the out-of-date and ancient identified conventional incidental methods that aided as the gold standard method for bacterial endotoxin detection.\textsuperscript{33–35} The critical limitation is that each microorganism needs its own supplements and also its culture media for optimum growth.\textsuperscript{36,37} Similarly, new fresh media should be considered for each microbe, and each microbe will develop positive or negative colonies over time.\textsuperscript{38,39} The limulus amoeba cell lysate (LAL) enzyme assay is usually the preferred gold standard for endotoxin detection.\textsuperscript{40,41} LAL is obtained from

Fig. 1  Schematic illustration of the Gram-negative bacteria cell wall structure.
amoebic cells (similar to human leukocytes) of the horseshoe crab family (horseshoe crab family), including the horseshoe crab family (East Asia) and the horseshoe crab family (Atlantic Ocean). The LAL test is used both in the industry and in the laboratory to measure bacterial endotoxin in various samples. The principle of this technique is based on the coagulation process that occurs in the blood lymph of the horseshoe crab (Limulus polyphemus) in the existence of LPS. Various types of LAL based on fluorescent and colorimetric methods have been established for the sensitive recognition of LPS. Even though these tests have presented hopeful detection limits and sensitivity, many of them need tedious and complex processes. LAL assays’ sensitivity depends on the processing method, the sample type, and the dilution factor. The enzyme-linked immunosorbent assay (ELISA) is an immunological assay frequently used to measure proteins, antibodies, antigens, and glycoproteins in biological samples. Some examples include pregnancy tests, diagnosis of HIV infection, and measurement of cytokines or soluble receptors in serum or cell supernatant. ELISA is another widely used test in bacteriology and endotoxin diagnosis. ELISA method is sensitive, robust, and reliable. Since LPS is a very heterogeneous class of substances, it is still not possible to develop antibodies with sufficient affinity and broad specificity, so this method is not in the market. Since large-scale commercial production and detection of endotoxin has become an absolute requirement, controlling endotoxin levels is important, primarily because it can cause some severe physiological responses. Therefore, it is very

| Bacterium                        | Role and diseases                                                                 | Ref. |
|----------------------------------|-----------------------------------------------------------------------------------|------|
| Pseudomonas aeruginosa           | Persistent infections, mainly in the genetic ailment cystic fibrosis, facilitating | 18   |
|                                  | biofilm formation, antibiotic resistance                                        |      |
| Escherichia coli and Bacteroides dorei | Neurodegeneration diseases, hemolytic uremic syndrome (HUS), diarrhea that may range from watery to bloody, stomach pains and cramps, loss of appetite or nausea | 19 and 20 |
|                                  | Vomiting, cholesystitis, cholangitis, neonatal meningitis                        |      |
| Haemophilus influenzae           | Meningitis, septicemia and pneumonia, Texas Children's Hospital (TCH) disease, meningitis and sepsis, necrotizing myositis and septic shock | 21–23 |
| Salmonella                       | Bacteremia and meningitis, enterocolitis, tachycardia, fever, hepateomegal, splenomegal, diarrhea, vomiting | 24 and 25 |
| Neisseria gonorrhoeae            | Ophthalmia neonorum endocervicitis, urethritis, systemic neonatal infection       | 25 and 26 |
| Vibrio cholera                   | Wound infection, watery diarrhea leading to serious dehydration. Gastroenteritis, septicaemia | 27   |
| Staphylococcus aureus            | Toxic shock syndrome, septic arthritis, pneumonia, endocarditis, pneumonia, boils, folliculitis, impetigo, cellulitis | 28 and 29 |
| Bordetella pertussis             | Respiratory tract infection, pertussis, diphtheria                               | 30   |

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Table 1  Endotoxin (LPS) producing bacteria and related disease

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Table 2  Analytical parameters of conventional methods in detection of LPS

| Method                | Sample          | Technique                  | LOD/sensitivity | Ref. |
|-----------------------|-----------------|----------------------------|-----------------|------|
| Cultivation           | —               | Culture & plating          | 1.5 CFU mL⁻¹    | 50   |
| LAL                   | Milk            | Chromogenic assay          | ~103 CFU mL⁻¹   | 45   |
| LAL                   | Beef            | Violet red bile agar overlay | 5067.6 ng g⁻¹  | 51   |
| LAL                   | Physiological   | Violet red bile agar overlay | 7.00–7.49/g⁻¹  | 52   |
| LAL                   | Milk            | —                          | 1 : 10⁴ to 1 : 10⁹ | 48   |
| LAL                   | Plasma          | —                          | 0.005 to 0.001 µg mL⁻¹ | 53   |
| ELISA                 | Complex mixtures| ELISA using poly-L-lysine  | 1 µg mL⁻¹       | 54   |
| ELISA                 | Murine          | Sandwich capture ELISA     | 1 ng mL⁻¹       | 55   |
| ELISA                 | Clinical        | ELISA-bacteriophage receptor protein | 0.05 EU mL⁻¹ up to 500 EU mL⁻¹ | 56   |
| ELISA                 | Human biofluid  | ELISA-high coating efficiency | ~0.2 µg       | 57   |
| Kit                   | Biological      | Endpoint chromogenic assay | 0.1 EU mL⁻¹    | 58   |
| Kinetic-QCL           | Clinical        | Endpoint chromogenic assay | 0.005 EU mL⁻¹  | 59   |
| Pyrosate kit          | Clinical        | Gel clot assay             | 1.0 EU mL⁻¹    | 60   |
| EndoLISA              | Biological      | Fluorescence               | 0.005 EU mL⁻¹  | 56   |

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important in pharmaceutical manufacturing, life sciences and medical research. The commercial excess of various endotoxin detection kits on the market underscores the demand and need for early detection, regulation, and monitoring of endotoxin levels in different sectors. Compared to the official United States Pharmacopeia (USP) rabbit pyrogen test, the LAL test has been shown to be not only more sensitive to endotoxin, but also easier, faster, and cheaper to perform. Commercially available kits are based on various principles. Each strategy has its own advantages over other strategies. Everything is sensitive, reliable, and usually recommended over the old and slow rabbit pyrogen test. Each method has its own lower bound for endotoxin detection and its own incubation time, depending on the kit used.

Some practical and frequently used methods and also commercial products in the quantification of endotoxin are summarized in Table 2.

All the above techniques have certain drawbacks, such as attachment of additional agent (BSA), the use of high amounts of the coating antigen, cross-reactive reactions, false-positive results, and the possibility of variation of antigenic sites by chemical treatment. Some critical advantages and limitations of conventional methods are summarized in Table 3.

Due to the high importance of endotoxin (LPS) in various diseases, the development of advanced methods for its accurate and rapid diagnosis is an essential aim of researchers. Due to its exceptional properties, nanotechnology-based biosensing is more attractive to scientists. Biosensors are among the most important types of advanced technologies that have been developed extensively in recent years. The most important and latest diagnostic method (biosensing) for the detection of endotoxin will be discussed in the following subsections.

4. Biosensors; modern methods for the recognition of LPS

A biosensor is an analytical instrument that contains a biological sensor element (bioreceptor) that is closely connected or integrated with a transducer. The first biosensor was developed for the recognition of glucose in 1962. Meanwhile, in 1956 Prof. Clark developed the first “real” biosensor (Clark electrode) towards detection of oxygen in biological samples. Professor Clark is known as the “father of biosensors”, but the term “biosensors” was coined by Karl in 1972. The technology converts biologically induced recognition events into a measurable signal (transduction), and analyses are acquired on screen after a series of processing. Biosensors are classified based on various subjects. As previously mentioned, the transducer is one of the crucial parts of the biosensor. Accordingly, biosensors are classified into three main subclasses, which include electrochemical, optical, and mechanical biosensors. Meanwhile, electrochemical and optical biosensors are very popular in medical diagnoses.

Electrochemical (EC) biosensors proposition advantages such as low background noise, high specificity of their biological recognition process, and better signal to noise ratios. Furthermore, measurement with electrochemical method measurement needs small sample volumes. Electrochemical recognition is extensively chosen for the transduction of biosensors due to its simplicity of construction, low cost, portability, and user-friendliness. The biosensor has a simple, single overall structure that features direct conversion, high bioselectivity, high sensitivity, miniaturization, electrical/optoelectronic readout, continuous monitoring, ease of use, and cost effectiveness. Electrochemical biosensors are categorized into voltammetric, potentiometric, conductometric, or impedimetric based on transducing methods. Voltammetry sensors apply an electric potential to the working electrode and measure the current by electrochemical reduction or oxidation of the analyte. The current response is typically acquired in a peak comparative to the analyte concentration. Moreover, voltammetry contributes significantly to the boom in the concept of chemically modified electrodes. Findings show numerous kinds of voltammetric biosensors effectively planned over wide surfaces of modifying elements and transducers. Potentiometric technique, one of the earliest and most influential methods, occupies a permanent position in sensory analysis. This analytical method is an intelligent instrument for

| Method | Advantages | Limitation | Ref. |
|--------|------------|------------|------|
| Cultivation | It evaluates living (cultureable) microorganisms, recognizes live cells in the sample, easily quantifies the cells in the sample, and achieves high sensitivity in the appropriate medium | Advanced skills are required for optimal results, unique dietary supplements are required, and unique nutritional media are required for optimal growth. Time and resource intensive, relies on phenotypic biochemical characterization | 61 and 62 |
| LAL | Acceptable sensitivity & specificity, cost effective | Time consuming, complicated procedures, serious ecological problems | 63 and 64 |
| ELISA | Rapid, cost saving, acceptable sensitivity, and specificity, flexibility | Difficult antibody pretreatment, cross reactive between the captured antibody and target, need for standard ELISA kit | 65 and 66 |
many practical applications because it can detect different ions of different concentrations and can be used in inexpensive measuring instruments. A potentiometric biosensor is well-defined as a tool combining a biological sensing component attached to a potential electrochemical transducer. Potentiometric biosensors generally rely on simpler species and biochemical reactions that result in electrochemical detection. The analytical signal produced by a potentiometric biosensor is an electrical potential. However, impedance is generated in a complete alternating current (AC) circuit with a voltage–current phase angle gap due to inductive and capacitive effects. In the case of impedometric biosensors, the impedance consists of capacitive and partial ohm resistance due to complex interactions with small amplitude voltage signals as a function of frequency. A piezoelectric sensor is one of the most important sensors that can be used in home applications, medical applications, and energy self-sufficiency sensors. So far, researchers have been able to produce a next-generation piezoelectric sensor that is highly efficient, robust, lightweight, and can be used as an energy self-sufficient sensor. Piezoelectric sensors convert mechanical energies such as pressure, force, pressure, and vibration into electrical signals.

Some of the advantages and disadvantages of different electrochemical transducers are summarized in Table 4.

To date, various types of electrochemical biosensors have been developed for the recognition of LPS. In this section, some EC-based biosensors were surveyed. Also, the role of different nanomaterials on their analytical performance was discussed.

### 4.1 Optical biosensors for detection of LPS

Another essential type of biosensor is the opto-sensor. Optical biosensors have shown valuable performance in discovering biological systems and promoting primary progress in drug discovery, clinical diagnostics, environmental monitoring, and food process control. Simplicity in their pretreatment and possible influence on the nature of target molecules and robustness, high sensitivity, reliability, and potential to be incorporated on a single chip are the critical advantages of optical biosensors. Optical biosensors are categorized into two main groups; labeling and label-free method. Biosensing based on surface plasmon resonance (SPR) and fluorescence is the most popular and extensively used method in research and medical fields, such as pathogen recognition.

Examination of optical biosensors shows that despite the many advantages over routine methods, they have limitations and disadvantages that researchers in future studies should consider. Here are some examples of these problems. Optical biosensors have a medium or low selectivity, the main reason for which can be found in the method used. Low reproducibility as well as poor stability are other challenges related to the development of optical biosensors that should be addressed. The development of portable and cellophane-based biosensors can improve their attractiveness and popularity. So, developing such devices should be the goal of future studies.

Interestingly, a smartphone-based biosensor was developed to detect LPS on a grating-coupled surface plasmon resonance. Fixed bio-devices provide POC detection for environmental and biomedical targets with attractive simplicity and portability benefits over distance and satisfactory analytical results (linear range; 570–730 ng mL⁻¹ and LOD = 32.5 ng mL⁻¹). Streptavidin-Horseradish peroxidase-modified hybridization chain reaction (HCRHPP) nanocomposites have been used as signal amplifiers or signal reporting elements for sensitive quantification of LPS. The planned genosensor quantitatively shows a handheld spectrophotometer with wide linear range and good LOD (1–150 ng mL⁻¹ and 50 pg mL⁻¹, respectively) for future clinical diagnosis, food industry, and environment. It opened up a new perspective on LPS detection in monitoring.

An interesting immunosensor based on the electrochemiluminescence (ECL) method was fabricated to determine LPS. Planned ECL peptide biosensor offered a novel path in evaluating LPS expression on the bacteria surface and showed

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**Table 4** Some of the advantages and disadvantages of different electrochemical transducers

| Type of detection method | Advantages                                                                 | Disadvantages                                                                 | Ref. |
|--------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|------|
| Potentiometric           | Simple assembly technique, mass production, cost-effective, simple        | Low selectivity, temperature-dependent system, impact solution changes,      | 80–82|
|                          | monitoring instrument/in field detection, fast operation, high            | enormous mistake caused by logarithmic response, need additional components  |      |
|                          | sensitivity towards targeted ions, easy management system for POC        | such as B.                                                                   |      |
|                          | measurement                                                               | For signal amplification as the potential depends on the concentration of    |      |
|                          |                                                                          | the analyte                                                                  |      |
| Voltammetric             | Real-time detection, simultaneous analysis of several samples             | Environmentally sensitive, time consuming, and temperature sensitive         | 83 and 84|
| Impedometric             | Small amplitude perturbation from steady state                             | The sensitivity of measurement depends on the technical accuracy of the      | 85 and 86|
|                          |                                                                          | equipment and on the operating techniques                                    |      |
| Piezoelectric            | High frequency response, high                                          | Poor spatial resolution, dynamic                                            | 87   |
|                          | sensitivity, high accuracy, high dynamic range                           | sensing only, charge leakages                                               |      |
huge potential in the clinical analysis of LPS in related diseases. This study (Fig. 2) shows a strong gold–sulfur bond between the gold electrode surface and the thiol group of the peptide. In the presence of LPS, the peptide on the ECL biosensor can effectively capture LPS and produce LPS/peptide/AuE. The proposed system showed a wide linear detection range of 1.0–500 ng mL\(^{-1}\) and a LOD of 0.3 ng mL\(^{-1}\).\(^\text{87}\)

Magnetic nanoparticles (MNPs) are useable in optical sensing. The MNPs may improve the refractive index alteration for refractive index sensing, or over with suitable coatings, be turned into fluorescent or plasmonic sensors.\(^\text{82,83}\) Iron oxide MNPs were employed as prospective therapy platforms, and due to their magnetic property, bacteria detection has drawn excessive consideration. These MNPs have generally been used as drug delivery, magnetic hyperthermia agents, and bioimaging contrast agents to identify and treat bacterial infections.\(^\text{84}\) Carbon nanotubes (CNTs) have appeared as one of the most intensively explored nanostructured materials.\(^\text{91,92}\) CNTs are hollow carbon buildings with a nanometer-scale diameter and a relatively more important length, and one or more walls.\(^\text{93,94}\) The advantage of CNTs over other nanomaterials lies in the extraordinary combination of optical, electrical, magnetic, mechanical, and chemical properties that offers great potential for a wide range of applications, including biosensors.\(^\text{95}\) Accordingly, several biosensors based on CNTs were developed for identifying pathogenic bacteria. For example, a single-walled carbon nanotube (SWCNT) based biosensor was fabricated to detect *Staphylococcus aureus*. The fixed tool detected *S. aureus* with a limit of detection (LOD) of 10\(^4\) CFU mL\(^{-1}\).\(^\text{96}\) Also, for rapid and sensitive detection of *Yersinia enterocolitica*, SWCNT was used appropriately. The concentration range for the SWCNT-based biosensor was 10\(^6\) to 10\(^4\) CFU mL\(^{-1}\), and the optimal limit of detection (LOD) of the SWCNT-based biosensor was determined to be 10\(^4\) CFU mL\(^{-1}\) of *Y. enterocolitica* in both clinical and phosphate buffer solution (PBS).\(^\text{97}\) Screen-printed carbon electrodes (SPCE) modified with polymers molecularly imprinted [PMI] were applied to detect *P. aeruginosa*’s LPS. The developed bio-system was able to selectively identify *P. aeruginosa*’s LPS from the similar *E. coli* endotoxin with good LOD (16.7 \(\mu\)g mL\(^{-1}\)).\(^\text{98}\) The human Toll-Like Receptor-4 (TLR-4) is a protein responsible for sensing the LPS of Gram-negative bacteria. The TLR-4 was immobilized on the micro gold electrode by binding a modified self-assembled monolayer (mSAM). The formation of TLR-4 protein dimers increased resistance to charge transfer from a solution-based redox probe in response to varying concentrations of its target. In this work, linear range and LOD were (10\(^4\) and 10\(^5\) cells per mL, 100 cells per mL), respectively.\(^\text{99}\)

A different type of optical biosensor was fabricated to detect Gram-negative LPS based on T4 bacteriophage. This work presented recombinant adhesive phage protein as a receptor molecule in biosensing technology for the first time. Obtained analytical properties were acceptable (linear range: 0–0.07 mg mL\(^{-1}\), LOD: 50 mg L\(^{-1}\)).\(^\text{100}\) Through presenting an LPS specific binding peptide to a usual aggregation-induced emission (AIE) fluorophore, 1-(4-carboxylbenzene)-1,2,2-triphenyl (CTPY), a robust, specific, and sensitive optical biosensor based on the fluorescent method was settled. Such bionanodevices with rapid clearance and highly specific detection based on LPS specific binding peptides hold significant potential in diverse biological and clinical applications. The developed platform can achieve LPS sensing in a wide linear range of 0.1 to 1 \(\mu\)M and good LOD (6.97 nM).\(^\text{101}\) Ultra-sensitive detection of LPS based on combined amplification of dual enzymes was designated recently. With the effective signal amplification, the bio-system revealed high sensitivity with wide range linearity (2.5–1000 pg mL\(^{-1}\)) and an acceptable LOD1 (pg mL\(^{-1}\)). In addition, advanced biosensors can clearly distinguish LPS from interference and have high specificity for LPS detection. This biosensor is also effectively used to measure LPS in actual food samples and has the potential to be applied to detect food safety.\(^\text{102}\)

In early 2001, an original theory termed “aggregation-induced emission (AIE)” was first recommended by Tang et al. AIE luminogens (AIEgens) display negligible or weak emission in dilute solution but are released intensely in the aggregate or solid state.\(^\text{103,104}\) AIEgens are categorized into two basic biomedical platforms, AIE NP probes and AIE molecular probes, which have been advanced for numerous biomedical applications.\(^\text{105,106}\) Their exclusive properties in terms of stability, brightness, biocompatibility, and therapeutic functions have increased the constant development of original designs.\(^\text{107,108}\) Until now, several AIE molecular probes have been established for monitoring bacterial labeling, cancer cell ablation, biological processes, and cellular organelle labelling with low...
background, high specificity, and tremendous photo stability. AIE fluorescent platform was planned to detect LPS, photodynamic antibacterial therapy, and bacterial imaging. Created photophic electrochemical biosensor, Fig. 3, presented good analytical output (linear range: 0–2.6 × 10^8 M and LOD: 2.6 × 10^8 M), which showed great potential for detecting endotoxin in biological and food samples.

Graphene has been used in designing different biosensors of several transduction styles because of its electrical conductivity, capacity to immobilize other molecules, large surface area, and high electron transfer rate. In addition, the conjugated arrangement of graphene can facilitate electron transfer between the transducer and the bioreceptor, resulting in high signal sensitivity for electrochemical biosensors. Moreover, graphene-based nanomaterial was employed as a quencher in the transducer to produce fluorescent biosensors. Findings indicated that reduced graphene oxide (rGO), graphene oxide (GO), and graphene (G) have a very high efficiency of fluorescent quenching. Several rGO nanocomposite-based electrochemical biosensors were developed in the past decade for monitoring food-borne pathogenic bacteria. A DNA aptamer genosensor was established for Streptococcus pneumonia detection based on the GO combination fluorescent method with exceptional LOD of 15 CFU mL^{-1}.

Peptide-assembled graphene oxide was employed for endotoxin detection. Engineered fluorescent biosensor, Fig. 4, showed potential in selective detection of LPS from different bacterial strains and LPS on the membrane of living E. coli. Also, synthesized CdTe quantum dots (QDs) conjugated with concanavalin A (Con A) were proposed as an original bio device for specific and selective quantification of LPS. Wide linearity and acceptable sensitivity were reported in this research.

Interestingly, a cell-based fluorescent optical biosensor was advanced to detect and recognize LPS, which is carried out in a 96-well microplate with high efficiency, which is user-friendly and nondestructive. This practical study combined the promoter sequence of the critical signaling pathway Enhanced Green Fluorescence Protein (EGFP) and gene ZC3H12A (encoding MCPIP1 protein) with building a recombinant plasmid, which was transferred into 293/hTLR4A-MD2-CD14 cells through lipid-mediated, DNA-transfection technique. LPS could bind to TLR4 and co-receptors-induced signaling pathways could result in green fluorescent protein expression. The developed biosensor showed suitable analytical results (linear range: 5–200 μg mL^{-1}, LOD: 0.075 μg mL^{-1}) applicable for endotoxin screening in food industries and medical approaches. Also, an aptamer-based impedance genosensor was established for the detection of negative bacteria LPS. In

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**Fig. 3** AIE fluorescent platform for the detection of lipopolysaccharide, bacterial imaging, and photodynamic antibacterial therapy.

**Fig. 4** Peptide-based biosensor for detection of LPS.
this report, amine-terminated single-stranded DNA (ssDNA) was used as a probe that displayed high affinity to LPS and was immobilized on a gold electrode via 3-mercaptopropionic acid (MPA) as a linker. The designed system showed acceptable analytical results (linear range: 0.001–1 ng mL\(^{-1}\), LOD: 1 pg mL\(^{-1}\)). A robust living cell-based optical transcriptional biosensor to detect LPS with a red fluorescent protein reporter system was fabricated properly. In the developed system, 293/hTLR4A-MD2-CD14pGL4.26-mcherry-NF-\(\kappa\)B cells were used as a recognition element. The engineered biosensor has great potential for use in bacteria sensitive identification (linear range: 0.01 to 100 ng mL\(^{-1}\) and LOD: 1 ng mL\(^{-1}\)), the LPS detection in food industries, biological products, and supporting the control of food-borne diseases. Highly sensitive recognition (linearity: 1–10\(^5\) ng mL\(^{-1}\), LOD: 1.73 ng mL\(^{-1}\)) of LPS using a genosensor based on hybridization chain reaction (HCR) was advanced recently. In the presented technique, two complementary stable species of biotinylated DNA hairpins concurred in solution up to the introduction of a recognition probe initiated an HCR cascade. The LPS react specifically with the conjugate DNA, which was captured by the ethanolamine aptamer attached to the reaction fit surface (Fig. 5).

Lipoteichoic acid (LTA) is a surface-binding amphipathic substance derived from Gram-positive bacteria and is a regulator of autolytic wall enzymes. It is generally released from bacterial cells after lysozyme-induced lysis from beta-lactam antibiotics, cationic peptides, and leukocytes. Original research directly detects bacteremia by using host–pathogen interactions of LTA from Gram-positive bacteria and LPS from Gram-negative bacteria. The developed optical biosensor was sensitive (LOD = 4 ng mL\(^{-1}\)), rapid, and achieved an accurate diagnosis of bacteremia at the POC (Fig. 6).

The optical waveguide biosensor offers the facility to recognize the kinetics of the bio-molecular interaction on an online source without the requisite for extrinsic labeling of the biomolecules. Accordingly, a waveguide-based optical biosensor was settled for the high-sensitive detection of Gram-negative bacteria LPS. Waveguide-based biosystem demonstrated specific and rapid operation in the identification of pathogen biomarkers from small samples of serum or plasma, agreeing for the timely and sensitive analysis (linearity: 3.13 \(\mu\)g mL\(^{-1}\) to 200 \(\mu\)g mL\(^{-1}\), LOD: 25 \(\mu\)g mL\(^{-1}\)) of infection at the POC. A mechanical QCM biosensor was fabricated to detect the interaction of low molecular weight chitosan and its \(N\)-acylated derivatives and chitoliposomes with endotoxin. This work determined the attachment and detachment rate quantities for LPS binding to chitosan. The affinity constants were calculated based on alterations in the oscillation frequency.

Due to its incredible chemical specificity and capacity to offer a fingerprint-like spectrum for complicated aqueous solutions, Raman spectroscopy (RS) has ended up as one of the maximum promising optical techniques. RS employs easy and reasonably-priced instrumentation, requiring minimum pattern preparation. Raman scattering now has no longer located extensive software with the organic count because of its inherently vulnerable signal. However, to date, techniques to decorate the sensitivity have been employed, namely, resonance Raman effects, which offers a 10\(^2\)–10\(^6\) enhancement, and surface-enhanced Raman spectroscopy (SERS), which ends up in as much as 10\(^8\) enhancements. It is generally accepted that the enhancement is due to the binding of the molecular...
vibrations of the analyte molecule on the surface of the nanostructure to the locally enhanced electromagnetic field. These fields are created on the surface of metal nanostructures by quasiparticle vibrations called surface polarities and are formed when electrons on the metal surface interact with photons from incident light.\textsuperscript{129}

The endotoxin launched within the side of the antibacterial system was monitored with the aid of the designed SERS detection strategy. The outcomes received with the aid of using SERS evaluation have been steady with the ones of the ELISA kit.\textsuperscript{130} An innovative work describes the use of SERS for the label-free quantitative nanoscale identification of the LPS adsorbed on the surface of 50 nm AuNPs. This SERS method was an efficient tool to detect LPS on the AuNP surface and the basis for the development of a novel specific and sensitive LPS-detection sensor based on the use of SERS and AuNPs.\textsuperscript{131} FRET or Förster resonance energy transfer is a flexible and sensitive device for qualitative and quantitative evaluation of organic interactions and processes.\textsuperscript{132} The access to a wide range of fluorescent materials, in conjunction with improved, easy-to-use, spectrometers and very state-of-the-art microscopes, have made FRET a completely exceptional methodology for biosensing.\textsuperscript{132} Fluorophores, which can be applied in FRET, now embody natural dyes, semiconductor quantum dots, fluorescent proteins, metallic chelates, several noble metals and different nanoparticles, and also polymers, basically fluorescent amino acids and organic cofactors.\textsuperscript{132,133} Recently, a fluorescent turn-on sensor for detecting micromolar levels of bacterial LPS has been industrialized. Polydiacetylene liposome surface modified with fabricated pantenalyse peptide and histidine have effectively displayed fluorescence signal only in the presence of LPS. A significant increase in the fluorescence signal was perceived at \textit{E. coli} concentrations as low as $4.91 \times 10^8$ CFU mL$^{-1}$ with liposomes at a concentration of 40.0 $\mu$M. The sensor worked on the principle of FRET.\textsuperscript{134}

As discussed, optical biosensors are one of the most important and widely used methods of detecting bacterial endotoxin. Due to several advantages, including high specificity, sensitivity, small size, and cost-effectiveness, their development has increased extensively in recent years. In addition, optical biosensors have high environmental compatibility and good migration capability. On the other hand, as shown in the table, optical biosensors have the appropriate analytical properties in detecting real samples. Despite the advantages of optical biosensors to achieve ideal platforms, some of their weaknesses, such as sensitivity to the environment such as pH should be addressed in future studies.

4.2 Developed electrochemical biosensors for detection of LPS

Recently a three-dimensional gold nanoparticles/ferrocene/liposome cluster (GFLC) was developed for electrochemical biosensing of LPS. In this cluster, gold nanoparticles, ferrocene, and liposome clusters act as signal amplification components,
signal output components, or molecular recognition components. Also, a sensitive DNA-based biosensor (genosensor) was developed for the rapid and selective detection of LPS of *E. coli*. This system was cost-effective and showed excessive application potential for food safety, environmental monitoring, and real-time diagnosis. Magnetic nanoparticles (MNPs) are imperative in sensing as they offer viable solutions to the continuing challenges related to analytical and non-specific effects. MNPs are applicable to facilitate electrochemical responses via blocking access to an original electrode or after coating to make them conduct. Also, an innovative immunosensor based on MNPs was engineered to determine *S. typhimurium* endotoxin in related samples. The created electrochemical biosensor was selective, specific, and has excellent potential in real-time detection of Gram-negative bacteria LPS. For sensing Gram-negative LPS, Cu²⁺-AuNPs aggregates were appropriately used in the electrochemical platform. The developed biosensor, Fig. 7, showed a high specificity toward LPS in the presence of other common interfering substances and was effortlessly renewed. Moreover, the invented biosensor presented a good practical application for LPS recognition in human serum samples with satisfactory analytical results (linear range: 0.05 pg mL⁻¹ to 10 pg mL⁻¹, LOD: 0.033 pg mL⁻¹).

A sensitive electrochemical platform was established for sensitive determination of LPS based on metal complex immobilized gold electrode. In this research work, electrochemical impedance spectroscopy (EIS) was applied to detect the interaction of nitrotriacetic acid (NTA)[Cu²⁺] complex with endotoxin. In this work, (0.0001–0.1 ng mL⁻¹) and (0.0001 ng mL⁻¹) were reported as linear range and LOD, respectively. A three-dimensional cells-in-gels-in-paper miniaturized electrochemical biosensor was fabricated for the rapid and sensitive detection of Gram-negative bacterium LPS. The proposed technique is applicable in food industries with high sensitivity (LOD = 3.5 × 10⁻⁹ ng mL⁻¹) and low cost construction. Intracellular carbon nanoelectrode was employed as an electrochemical sensor for ultra-sensitive detection (LOD = 1 ng mL⁻¹) of hydrogen peroxide generated intracellularly in response to smooth and soft LPS structures. This work introduces a novel approach for the detection of LPS using various biosensing techniques, each with their unique advantages and applications.

### Table 5: Developed optical biosensors for detection of endotoxin

| Bacterium                     | Technique                  | Method                  | Sample | NPs         | Linear range | LOD      | Ref. |
|-------------------------------|----------------------------|-------------------------|--------|-------------|--------------|----------|------|
| *E. coli*                     | Grating-coupled SPR       | Label-free              | Clinical | Metallic    | 570–730 nm   | 32.5 ng  | 85   |
| *E. coli*                     | UV-Vis spectrophotometry  | Colorimetric/           | Clinical | Nickel      | 0.07 mg mL⁻¹ | 50 mg L⁻¹| 100  |
| *S. typhosa, K. pneumonia, E. coli, P. aeruginosa* | Fluorescence               | Fluorescent/           | Food    | Gold        | 2.5–1000 pg mL⁻¹ | 1 pg mL⁻¹| 102  |
| *Serratia marcescens*         | UV-visible spectra        | Fluorescent/           | Culture  | Inorganic   | 2.6 × 10⁸ M  | 2.6 × 10⁸ M| 107  |
| *E. coli*                     | Fluorescence emission     | Fluorescence           | Clinical | GO          | 0 to 20 nM   | 130 pM   | 115  |
| *S. typhimurium and Staphylococcus* | Fluorescent               | Waveguide-based        | Serum    | Streptavidin | 1–10⁸ ng mL⁻¹ | 1.73 ng mL⁻¹| 136  |
| *S. typhimurium*              | Fluorescent, wave guide   | Waveguide-based optical | Clinical | Streptavidin-biotin | —             | 4 ng mL⁻¹| 137  |
| *P. aeruginosa*               | SERS                      | SERS spectra            | Biological | AgNPs     | 0.10–10.0 μmol L⁻¹ | 6.125 μg mL⁻¹| 125  |
| *E. coli* O35:B5              | SERS                      | Raman and SERS spectra | Biological | AuNPs     | 0.1–10 μg mL⁻¹ | 2.6 ± 0.1 ng mL⁻¹| 131  |
| *E. coli*                     | FRET                      | Fluorescence labels/   | Clinical | —          | 4.91 × 10⁸ CFU mL⁻¹| 40.0 μM| 134  |

*Abbreviation: (GFLC): gold nanoparticles/ferrocene/liposome cluster, (GE): graphite electrode, (SAW): surface acoustic wave resonator, (EIS): electrochemical impedance spectroscopy (HCR-HRP): streptavidin-horseradish peroxidase modified hybridization chain reaction, (SPCE): screen-printed carbon electrodes, [NTA]: nitrotriacetic acid complex, (AIE) aggregation induced emission, (CTPY): 1-(4-carboxylbenzene)-1,2,2-tri phenyl, (SCE): saturated calomel electrode, (QDs): CdTe quantum dots, (Ac-ChLM): N-3-hydroxytetradecanol chitosan, surface-enhanced Raman spectroscopy (SERS).
showed different and indirect methods in determining bacterial endotoxin. A peptide was used as the recognition molecule in the electrochemical impedance immunosensor to determine LPS. The developed biosystem was used for real-time detection of endotoxin in real serum samples with acceptable linear range (0.01 pg mL$^{-1}$ to 1.0 ng mL$^{-1}$) and LOD (2.0 fg mL$^{-1}$) (Fig. 8). A dual electrochemical and mechanical label free lectin platform was developed for highly sensitive detection (LOD = up to 50 cells per mL) of antimicrobial susceptibility and the quantification of bacterial LPS. In this method, a polythiophene interface containing glycosylated fusion quinone units is used to form a carbohydrate platform for immobilization of concanavalin A (Con A), and LPS binding is measured via an orthogonal crystal oscillator microbalance and perform an electrochemical read (EQCM). An impedimetric electrochemical biosensor was developed for the quantification of E. coli produced LPS. In the developed system (Fig. 9), concanavalin A (Con A) lectins have been used as a molecular recognition element due to their specific interaction with the carbohydrate groups of LPS. Con A recognizes sigma-bonded mannose as the “core oligosaccharides” of some serum and membrane glycoproteins. The proposed biosensor was constructed based on lectin-functionalized Au–graphene compounds and showed acceptable stability and reproducibility with satisfactory analytical properties (linear range = 7.03 × 10$^{-12}$ to 1.41 × 10$^{-7}$ pg L$^{-1}$ and LOD = 600 pg L$^{-1}$). Au and graphene nanoparticles have recently been recognized as efficient and most promising electrochemical and luminescence catalysts.
DNAzyme-assisted recycling and Ce-based metal–organic structures dual signal amplifiers for sensitive electrochemical detection of LPS were settled. In the planned biosensor, Ce-MOFs were decorated with AuNPs to achieve AuNPs/Ce-MOFs. In this report, AuNPs/Ce-MOFs acted as catalysts to catalyze the oxidation of ascorbic acid (AA) and nanocarrier to capture –SH terminated hairpin probes 2 (HP2) for acquiring HP2/AuNPs/Ce-MOFs signal probes. Projected aptasensor for LPS showed a wide linear range from 10 fg mL$^{-1}$ to 100 ng mL$^{-1}$ with a 3.3 fg mL$^{-1}$ LOD. An innovative electrochemical aptasensing platform based on GCE modified using GO and AuNPs was an assembly for the identification of $E. coli$ endotoxin. The obtained results revealed that the modified GCE has a satisfactory selectivity for LPS over other biomolecules and is positively used to investigate serum of healthy persons and patients. In this work, acceptable linear range (0.1–0.9 pg mL$^{-1}$) and LOD (30 fg mL$^{-1}$) were reported. An electrochemical impedimetric biosensor based on SAM mixture CramoLL lectin and cysteine-gold nanoparticles (cys-AuNPs) was proposed for bacterial LPS recognition. Findings revealed that LPS from $Serratia marcescens$, $Escherichia coli$, $Salmonella enterica$, and $Klebsiella pneumoniae$ are measurable by the settled system with good LOD (10 mM). A gold atomic cluster was applied as an electrochemical aptasensor for the recognition of LPS. The formed gold atomic clusters make Apt/AuAC/Au show an excellent property (LOD = 7.94 × 10$^{-21}$ M) for the LPS determination in related samples. Also, the designed biosensor demonstrated a simple and easy technique for detecting LPS on the nanoscale amount. To complete our discussion, Table 6 summarizes all EC biosensors for the detection of LPS in different samples and compares their analytical parameters.

Highlights of Table 6 include the following: (A) as demonstrated in Table 6, similar to optical biosensors, despite the presence of various endotoxin-producing bacteria, most studies have been performed on $E. coli$. Therefore, future studies should be aimed at detecting endotoxins in other bacteria. (B) In most of the studies summarized in the table, the impedimetric technique has been used mainly because of the simplicity of performing and diagnosis in real-time. (C) Good reducibility, high sensitivity, and specificity are critical properties in aptamer-based biosensors. Therefore, this kind of biosensing method has been considered by researchers to date. (D) Gold nanoparticles have been the most used in the development of LPS biosensors, and the results show that their use has increased the sensitivity and specificity of biosensors. Due to the unique properties of carbon-based nanoparticles, such as low cost and high conductivity, it is suggested that their use be further considered in future studies. (E) Analytical results of various studies indicated a linear relationship between μM to nM. Compared to routine methods, these results are acceptable, but their improvement in future studies seems crucial. According to the findings detailed in Table 6, biosensors based on AuNPs show extra sensitivity and specificity.

Electrochemiluminescence (ECL) based sensors combine electrochemistry and quantity of optical luminescence. In this method, when a potential is applied onto an electrode, the electrode surface is excited. Therefore, an electron transfer is done between molecules, and the resulting light is measured. ECL biosensors have been established to recognize chemical and bacteriological contaminants in food products. ECL biosensor was advanced for $Escherichia coli$ O157:H7 quantitative recognition based on nitrogen-doped graphene quantum dots (N-GQDs) and a polydopamine (PDA) surface imprinted polymer (SIP).

Magnetic resonance elastography (EG) is a valuable noninvasive analytical method of detecting abnormalities, such as liver fibrosis. The method generates tissue deformation by applying external or internal excitation, which causes displacements, and these displacements can be measured using modified MRE pulse sequences. Accordingly, EG as

Fig. 9 Representation of impedimetric lectin-based biosensors for bacterial LPS.
a flexible analytical method was applied for the detection of coagulation. The rapid detection of LPS is achieved by the EG analysis of endotoxin-induced limulus amebocyte lysate coagulation. This method is better than other methods using the same reagents in not only sensitivity but also detection time.\textsuperscript{335}

As mentioned before, various types of biosensors are being developed, among which researchers have given electrochemical and optical biosensors more attention due to their many advantages. In the following, the electrochemical and optical biosensors developed for endotoxin detection are discussed in more detail, respectively. Photoelectrochemical (PEC) biosensors are an imperative branch of electrochemical detection based on graphite-like carbon nitride decorated with NiO.\textsuperscript{12} Despite the unique features of PEC biosensors, according to the studies conducted in this study, to date, this type of platform for LPS detection has not been developed. Therefore, considering the exceptional advantages of PEC biosensors, their development should be considered in future studies.

### 5. The role of nanoparticles in biosensor development

As reviewed in the present study, various nanoparticles were applied in biosensor development, and some of the presented nanoparticles have been used extensively. The use of NPs, nanotubes, nanowires, etc., in biosensor diagnostic devices is considered in future studies. In this study, to date, this type of platform for LPS detection has not been developed. Therefore, considering the exceptional advantages of PEC biosensors, their development should be considered in future studies.

#### Table 6  Developed electrochemical biosensors for detection of endotoxin\textsuperscript{a}

| Bacterium          | Technique     | Method                              | Sample     | NPs                  | Linear range              | LOD               | Ref.  |
|--------------------|---------------|-------------------------------------|------------|----------------------|---------------------------|-------------------|-------|
| P. aeruginosa      | DPV, FT-IR spectra | Fluorescence emission spectra       | Food       | GFLC                 | 2 × 10^{-9} μg mL^{-1} to 0.51 × 10^{-10} μg mL^{-1} | 139               |
|                    |               | Labeled-aptasensor                   | Rat serum  | HCR-HRP              | 1 to 150 ng mL^{-1}        | 152               |
|                    |               | Immunosensor                         | Food and water | Magnetic             | 0.001–0.1 μg mL^{-1}      | 10^{2} CFU mL^{-1} | 141   |
| E. coli            | Aptsensor     |                                       | Serum      | Cu^{2+}-                 | 0.05 pg mL^{-1} to 10 pg mL^{-1} | 98                |
| S. typhimurium     | EIS, impedimetric | Labeled-aptasensor                   | Serum      | Cu^{2+}-NTA           | 0.0001–0.1 ng mL^{-1}     | 142               |
| P. aeruginosa      | CVs           | MIP                                 | Clinical   | Cu^{2+}-                 | 10^{4} and 10^{5} cells per 10^{3} cells per mL | 99                |
| S. typhimurium     | EIS           | Immunosensor/EDC/NHS                 | Clinical   | AuNPs                 | 0.033 pg mL^{-1} to 144 pg mL^{-1} | 145               |
| E. coli            | EIS           | Labeled, apsensors, DPV              | Serum      | AuNPs                 | 1.0 to 1 × 10^{1} pg mL^{-1} | 1.0 to 1 × 10^{6} g L^{-1} | 132   |
| S. enterica        | EIS           | EIS/CVs                             | Clinical   | Cu^{2+}-NTA           | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| E. coli, S. minnesota | CVs          | Electrochemical/ EIS                | Clinical   | Cu^{2+}-NTA           | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| E. coli            | Impedimetric  | EIS/immunosensor                     | Clinical   | AuNPs                 | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| E. coli            | Impedimetric  | Impedimetric/ labeled                | Clinical   | AuNPs/AlNPs           | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| Gram negative bacteria | CVs, EIS    | Genosensor/labeled                   | Serum      | AuNPs/AlNPs           | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| E. coli            | SWV           | Aptsensor/label free                 | Serum      | RGO/AlNPs            | 1 to 10^{1} to 1 × 10^{3} ng 3.5 × 10^{-3} ng mL^{-1} | 143               |
| Gram negative bacteria | UV-visible absorption spectrum, EIS, DPV | Aptsensor/label free | Serum      | Aptsensor/label free | 0.01 attomolar to 10 picomolar M | 150               |
| S. marcescens, E. coli, S. enterica, K. pneumoniae | Impedimetric, CVs | Aptsensor/EIS                          | Clinical   | Cys-Au                | 7.94 × 10^{-10} M to 9.15 M | 143               |

\textsuperscript{a} Abbeviation: (GFLC): gold nanoparticles/ferroin/sliposome cluster, (GE): graphite electrode, (SAW): surface acoustic wave resonator, (EIS): electrochemical impedance spectroscopy (HCR-HRP): streptavidin-horseradish peroxidase modified hybridization chain reaction, (SPCE): screen-printed carbon electrodes, (NTA): nitrilotriacetic acid complex, (AIE): aggregation induced emission, (CTPY): 1-(4-carboxylbenzene)-1,2,2-triphenyl, (SCE): saturated calomel electrode, (QDs): CdTe quantum dots, (Ac-ChLM): N-3-hydroxytetradecanoyl chitosan.
desired analyte are developing. Nanomaterials are generally used as transducer materials that are an important part of biosensor development. The advantages and disadvantages of different nanomaterial-based biosensors are presented in Table 7.

It has been determined that the usage of nanomaterials can also additionally cause extended biosensor overall performance along with extended sensitivities and occasional limit-of-detection of numerous orders of magnitudes. Nanostructured substances display extended surface-to-extent ratio, mechanical strength, chemical activity, electrocatalytic properties, and more advantageous diffusivity. Nanomaterials were anticipated to play a critical role in the high performance of a biosensor. To probe biomolecules along with bacteria, viruses, DNA, etc., the biocompatibility of nanomaterials has been a serious issue in designing a biosensor.

6. Discoveries of gaps and future outlook

Biosensors establish an interdisciplinary field that is presently one of the critical parts of investigation in analytical chemistry. Expending biosensors naturally reduces the need for sample preparation. The biosensor’s performance is typically and experimentally assessed based on its LOD, sensitivity, reproducibility, dynamic and linear ranges, or accuracy of the selectivity response and its response to interferences. Additional frequently compared factors include operational and storage stability, sensor reaction time, easy operation, and portability.

Ideally, the sensing surface should be reusable for numerous repeated quantities to be made. For various environmental, clinical, and food applications, the sensor should be capable of constantly monitoring the analyte online. Conversely, single-

Table 7 Advantages and disadvantages of different nanomaterial-based biosensors

| Nanomaterial | Advantages | Disadvantages | Ref. |
|--------------|------------|---------------|------|
| CNTs         | Extremely small and lightweight, plentiful resources, resistant to temperature changes, ability to cross cellular membranes and barriers, high chemical and mechanical stability, strong C–H bonds | Expensive nanotube production process, low yield, low hydrogen storage capacity, purification problems | 158 and 159 |
| GO           | Water dispersibility, polar functionalization, easy workability, low-cost | Lower electrical and thermal conductibility | 145, 160 and 161 |
| rGO          | High electrical and thermal conductibility, good control on functionalization, economical and facile technique | Hydrophobicity, difficult workability, and production methodology are important in their properties | 88 and 89 |
| MNPs         | Large surface-to-volume ratio, low cytotoxicity to biomass cell, ease of synthesis, capacity to bind several targeted compounds | High cost of synthesis processes and materials, mobility dependent on environment compatibilities | 162 and 163 |

Fig. 10 Schematic illustration of the PEC sensor.
use biosensors are acceptable for some main applications, such as personal blood glucose monitoring by diabetics. Therefore, future studies should be in line with developing an ideal biosensor with the mentioned features and capabilities. In addition to the above, the methodology is critical in the development of biosensors; for example: as described in the text, LPS are some intercellular components and cell-based biosensors play a critical role in their determination.

On the other hand, functionalized CNTs can successfully penetrate individual cells and cross biological barriers like cell membranes. This property and the release of CNTs from the cells and mechanism of internalization are of main interest for biological and in particular intracellular biosensing applications. Therefore, the use of CNTs in the development of future biosensors should be given more attention.

7. Conclusion

In this review, the up-to-date scientific literature dealing with biosensors for LPS detection was investigated. Different methods advanced by various studies to detect endotoxin are declared. The biosensors have different sample pretreatment requirements, other detection limits for the target organisms, and different degrees of automation evaluation, complexities, and requisite analysis times. Based on the surveyed literature, biosensors have verified the great potential for LPS analysis, but the following points should be considered in future studies. In conclusion, many of the established biosensing systems target Salmonella, E. coli 0157:H7. At the same time, some of the reported examples are not directed at the main imperative pathogens listed in Table 1. (B) For commercialization, one of the problems still facing the construction of biosensors for direct detection of LPS is the sensitivity of the analyses in the real sample. (C) Specificity is the critical issue in biosensor development and should be improved in future investigations; in other words, a robust biosensor should be able to detect target structures from similar structures in contaminated samples. (D) Simple and low-cost structure, easy to operate and easy interpretation of results, and fast and high sensitivity are the features of LPS biosensors that should be considered in their development. (E) Endotoxins are Gram-negative bacterial wall compounds, so the development of cell-based biosensors is of great importance. (F) As found in reviewing and comparing different studies, various factors play a critical role in constructing an ideal biosensor, the least of which include: the type of the used nanomaterial and techniques. Also, according to the results obtained in this study, the use of appropriate nanomaterials is one of the main factors in achieving improved analytical results. Finally, although biosensors have advantages over routine and older methods, future studies should be developed to address the barriers and weaknesses of biosensors so that researchers should consider the following points: simple and inexpensive structure is one of the strategic goals of biosensor development, so the use of advanced and expensive materials and tools will make the created biosensors not welcome. This may be one of the main reasons for the unsuccessful industrialization and commercialization of biosensors developed to date. Subsequently, according to studies, labeled biosensors, in addition to high cost, have a time-consuming and complex design process, so the development of label-free biosensors should be considered as much as possible. As shown in Table 4, vulnerabilities to temperature changes and the surrounding environment and pH are one of the main problems and limitations in the development of electrochemical biosensors, especially concerning physiological matrices, so eliminating this vulnerability should be highlighted in the future studies.

Conflicts of interest

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

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References

1 T. J. Silhavy, D. Kahne and S. Walker, The bacterial cell envelope, Cold Spring Harbor Perspect. Biol., 2010, 2(5), a000414.
2 Y. Kamio and H. Nikaido, Outer membrane of Salmonella typhimurium: accessibility of phospholipid head groups to phospholipase c and cyanogen bromide activated dextran in the external medium, Biochemistry, 1976, 15(12), 2561–2570.
3 A. T. Jan, Outer Membrane Vesicles (OMVs) of Gram-negative Bacteria: A Perspective Update, Front. Microbiol., 2017, 8, 1053.
4 M. P. Bos, V. Robert and J. Tommassen, Biogenesis of the gram-negative bacterial outer membrane, Annu. Rev. Microbiol., 2007, 61, 191–214.
5 G. Zhang, T. C. Meredith and D. Kahne, On the essentiality of lipopolysaccharide to Gram-negative bacteria, Curr. Opin. Microbiol., 2013, 16(6), 779–785.
6 H. Nikaido, Molecular basis of bacterial outer membrane permeability revisited, Microbiol. Mol. Biol. Rev., 2003, 67(4), 593–656.
7 S. M. Galloway and C. R. Raetz, A mutant of Escherichia coli defective in the first step of endotoxin biosynthesis, J. Biol. Chem., 1990, 265(11), 6394–6402.
8 E. R. Rojas, G. Billings, P. D. Odermatt, G. K. Auer, L. Zhu, A. Miguel, F. Chang, D. B. Weibel, J. A. Theriot and K. C. Huang, The outer membrane is an essential load-bearing element in Gram-negative bacteria, Nature, 2018, 559(7715), 617–621.
9 X. Su, L. Sutarlie and X. J. Loh, Sensors, Biosensors, and Analytical Technologies for Aquaculture Water Quality, Research, 2020, 2020, 8272705.
10 M. Pither, The structure of Lipid A and composition of the oligosaccharides of the lipopolysaccharides of the bacterial species: Veillonella parvula, Keele University, 2019.

11 G. Datta, B. J. Fuller and B. R. Davidson, Molecular mechanisms of liver ischemia reperfusion injury: insights from transgenic knockout models, World J. Gastroenterol., 2013, 19(11), 1683–1698.

12 F. El-Taboni, E. Caseley, M. Katsikogianni, L. Swanson, T. Swift and M. E. Romero-González, Fluorescence Spectroscopy Analysis of the Bacteria-Mineral Interface: Adsorption of Lipopolysaccharides to Silica and Alumina, Langmuir, 2020, 36(7), 1623–1632.

13 A. Emiola, J. George and S. S. Andrews, A Complete Pathway Model for Lipid A Biosynthesis in Escherichia coli, PLoS One, 2015, 10(4), e0121216.

14 A. P. Moran, M. M. Prendergast and B. J. Appelmelk, Molecular mimicry of host structures by bacterial lipopolysaccharides and its contribution to disease, FEMS Immunol. Med. Microbiol., 1996, 16(2), 105–115.

15 S. M. Huszczynski, J. S. Lam and C. M. Khursigara, The Role of Pseudomonas aeruginosaa lipopolysaccharide in bacterial pathogenesis and physiology, Pathogens, 2020, 9(1), 6.

16 P. N. A. Harris, P. A. Tambyah, D. C. Lye, Y. Mo, T. H. Lee, M. Yilmaz, T. H. Alenazi, Y. Arabi, M. Falcone, M. Bassetti, E. Righi, B. A. Rogers, S. Kanj, H. Bhally, J. Iredell, M. Mendelson, T. H. Boyles, D. Looke, S. Miyakis, G. Walls, M. Al Khamis, A. Zikri, A. Crowe, P. Ingram, N. Daneman, P. Griffin, E. Athan, P. Lorenc, P. Baker, L. Roberts, S. A. Beatson, A. Y. Peleg, T. Harris-Brown and D. L. Paterson, Effect of Piperacillin-Tazobactam vs. Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftiraxone Resistance: A Randomized Clinical Trial, JAMA, 2018, 320(10), 984–994.

17 K. Nesperova, E. R. Wyrsh, A. Valcek, I. Bitar, K. Chaw, P. Harris, J. Hrabak, I. Literak, S. P. Djordjevic and M. Dolejska, Escherichia coli Sequence Type 457 Is an Emerging Extended-Spectrum-β-Lactam-Resistant Lineage with Reservoirs in Wildlife and Food-Producing Animals, Antimicrob. Agents Chemother., 2020, 65(1), e01118–e01120.

18 M. Ibar-Bariain, A. Rodríguez-Gascón, A. Isla, M. Solínis and A. Canut-Blasco, Evaluation of the adequacy of the antimicrobial therapy of invasive Haemophilus influenzae infections: A pharmacokinetic/pharmacodynamic perspective, Enferm. Infec. Microbiol. Clin., 2021, 39(2), 65–71.

19 J. G. Vallejo, J. C. McNeil, K. G. Hultén, L. M. Sommer, J. J. Dunn and S. L. Kaplan, Invasive Haemophilus influenzae Disease at Texas Children's Hospital, 2011 to 2018, Pediatr. Infect. Dis. J., 2019, 38(9), 900–905.

20 F. Resman, T. Svensjö, C. Ünal, J. Cronqvist, H. Bronson, I. Odenholt and K. Riesbeck, Necrotizing myositis and septic shock caused by Haemophilus influenzae type f in a previously healthy man diagnosed with an IgG3 and a mannose-binding lectin deficiency, Scand. J. Infect. Dis., 2011, 43(11–12), 972–976.

21 J. J. Gilchrist and C. A. MacLennan, Invasive Nontyphoidal Salmonella Disease in Africa, EcoSal Plus, 2019, 8(2), 1–23.

22 R. A. Cheng, C. R. Eade and M. Wiedmann, Embracing Diversity: Differences in Virulence Mechanisms, Disease Severity, and Host Adaptations Contribute to the Success of Nontyphoidal Salmonella as a Foodborne Pathogen, Front. Microbiol., 2019, 10, 1368.

23 A. Lovett and J. A. Duncan, Human Immune Responses and the Natural History of Neisseria gonorrhoeae Infection, Front. Immunol., 2018, 9, 3187.

24 M. A. De Francesco, P. Stefanelli, A. Carannante, S. Corbellini, C. Giagulli, G. Lorenzin, M. Ronconi, E. Arici, M. Cadei, R. Campora and A. Caruso, Management of a Case of Peritonitis Due to Neisseria gonorrhoeae Infection Following Pelvic Inflammatory Disease (PID), Antibiotics, 2020, 9(4), 193.

25 I. Levade, A. I. Khan, F. Chowdhury, S. B. Calderwood, E. T. Ryan, J. B. Harris, R. C. LaRocque, T. R. Bhuiyan, F. Qadri and A. A. Weil, A Combination of Metagenomic and Cultivation Approaches Reveals Hypermutator Phenotypes within Vibrio cholerae-Infected Patients, mSystems, 2021, 6(4), e00889.

26 S. Y. Tong, J. S. Davis, E. Eichenberger, T. L. Holland and V. G. Fowler, Jr, Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management, Clin. Microbiol. Rev., 2015, 28(3), 603–661.

27 M. J. Rybak, J. Le, T. P. Lodise, D. P. Levine, J. S. Bradley, C. Liu, B. A. Mueller, M. P. Pai, A. Wong-Beringer, J. C. Rotschafer, K. A. Rodvold, H. D. Maples and B. M. Lomaestro, Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists, Am. J. Health-Syst. Pharm., 2020, 77(11), 835–864.

28 J. D. Cherry, The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection, Pediatrics, 2005, 115(5), 1422–1427.

29 M. Sakata, Y. Fukuma, M. Todokoro and M. Kunitake, Selective assay for endotoxin using poly(epsilon-lysine)-immobilized Cellulose and Limulus amoebocyte lysate (LAL), Anal. Biochem., 2009, 385(2), 368–370.

30 G. Solano, A. Gómez and G. León, Assessing endotoxins in equine-derived snake antivenoms: Comparison of the USP pyrogen test and the Limulus Amoebocyte Lysate assay (LAL), Toxicon, 2015, 105, 13–18.

31 P. Rajapaksha, A. Elbourne, S. Gangadoo, R. Brown, D. Cozzolino and J. Chapman, A review of methods for the detection of pathogenic microorganisms, Analyst, 2019, 144(2), 396–411.

32 L. Váradi, J. L. Luo, D. E. Hibbs, J. D. Perry, R. J. Anderson, S. Orenga and P. W. Groundwater, Methods for the detection and identification of pathogenic bacteria: past,
present, and future, *Chem. Soc. Rev.*, 2017, **46**(16), 4818–4832.

33 A. Mobed, B. Baradaran, M. de la Guardia, M. Agazadeh, M. Hasanzadeh, M. A. Rezaee, J. Mosafer, A. Mokhtarzadeh and M. R. Hamblin, Advances in detection of fastidious bacteria: from microscopic observation to molecular biosensors, *Trends Anal. Chem.*, 2019, **113**, 157–171.

34 A. Saravanan, P. S. Kumar, R. V. Hemavathy, S. Jeevanantham, R. Kamalesh, S. Sneha and P. R. Yaashikaa, Methods of detection of food-borne pathogens: a review, *Environ. Chem. Lett.*, 2020, **19**, 189–207.

35 C. Y. Park, S. H. Jung, J. P. Bak, S. S. Lee and D. K. Rhee, Comparison of the rabbit pyrogen test and Limulus amoebocyte lysate (LAL) assay for endotoxin in hepatitis B vaccines and the effect of aluminum hydroxide, *Biologicals*, 2005, **33**(3), 145–151.

36 J. Scudder and J. Y. Ye, Limulus amoebocyte lysate test via an open-microcavity optical biosensor, *Biomed. Opt..*, 2018, **23**(2), 1–6.

37 J. S. Lam, E. M. Anderson and Y. Hao, LPS quantitation procedures, *Pseudomonas Methods and Protocols*, Springer, 2014, pp. 375–402.

38 R. Blechova and D. Pivodova, Limulus amoebocyte lysate (LAL) test-An alternative method for detection of bacterial endotoxins, *Acta Vet. Brno*, 2001, **70**(3), 291–296.

39 R. J. Elin and J. Hosseini, Clinical utility of the Limulus amoebocyte lysate (LAL) test, *Prog. Clin. Biol. Res.*, 1985, **189**, 307–327.

40 J. C. Hurley, Endotoxemia: methods of detection and clinical correlates, *Clin. Microbiol. Rev.*, 1995, **8**(2), 268–292.

41 H. Grallert and S. Leopoldseder, *EndoLISA®: a novel and reliable method for endotoxin detection*, 2011.

42 R. Pennamareddy, K. Prabakar and J. Pandian, Sorting out of interference in detection of endotoxins in biotherapeutic drugs, *Indian J. Sci. Technol.*, 2009, **2**(11), 20–22.

43 J. L. Ding and B. Ho, Endotoxin detection—from limulus amoebocyte lysate to recombinant factor C, *Endotoxins: structure, function and recognition*, Springer, 2010, pp. 187–208.

44 M. M. Masri, M. S. T. Maidin and A. B. Ariff, Impact of single and two-phase dissolved oxygen tension control on bacillus thuringiensis cultivation and δ-endotoxin production, *Malays. Appl. Biol.*, 2021, **50**(1), 73–84.

45 A. Svensson and B. Hahn-Hägerdal, Comparison of a gelation and a chromogenic Limulus (LAL) assay for the detection of gram-negative bacteria, and the application of the latter assay to milk, *J. Dairy Res.*, 1987, **54**(2), 267–273.

46 J. M. Jay, S. Margitic, A. L. Shereda and H. V. Covington, Determining endotoxin content of ground beef by the Limulus amoebocyte lysate test as a rapid indicator of microbial quality, *Appl. Environ. Microbiol.*, 1979, **38**(5), 885–890.

47 J. M. Jay, Rapid estimation of microbial numbers in fresh ground beef by use of the Limulus test, *J. Food Prot.*, 1981, **44**(4), 275–278.

48 I. Hartman, G. Ziv and A. Saran, Application of the Limulus amoebocyte lysate test to the detection of gram-negative bacterial endotoxins in normal and mastitic milk, *Res. Vet. Sci.*, 1976, **20**(3), 342–343.

49 R. B. Reinhold and J. Fine, A technique for quantitative measurement of endotoxin in human plasma, *Proc. Soc. Exp. Biol. Med.*, 1971, **137**(1), 334–340.

50 M. M. Masri, M. S. T. Maidin and A. B. Ariff, Impact of single and two-phase dissolved oxygen tension control on bacillus thuringiensis cultivation and δ-endotoxin production, *Malays. Appl. Biol.*, 2021, **50**(1), 73–84.

51 D. Choi, R. Tsang and M. Ng, Sandwich capture ELISA by a murine monoclonal antibody against a genus-specific LPS epitope for the detection of different common serotypes of salmonellas, *J. Appl. Bacteriol.*, 1992, **72**(2), 134–138.

52 J. M. Jay, Rapid estimation of microbial numbers in fresh ground beef by use of the Limulus test, *J. Food Prot.*, 1981, **44**(4), 275–278.

53 F. C. Martinho, W. M. Chiesa, A. A. Zaia, C. C. Ferraz, J. F. Almeida, F. J. Souza-Filho and B. P. Gomes, Comparison of endotoxin levels in previous studies on primary endocardial infections, *J. Endod.*, 2011, **37**(2), 163–167.

54 C. Barro, A. Paul, F. Saleh, T. Chitnis and H. L. Weiner, Validation of Two Kinetic Assays for the Quantification of Endotoxin in Human Serum, *Front. Neurol.*, 2021, **12**, 1005.

55 T. N. Soe, Ultrafiltration Membrane Process for Pyrogen Removal in the Preparation of Water for Injection (WFI), *Inquiry*, 2006, 7(1), 13.

56 R. Wedmann and T. Uhlig, *Sensitive and flexible bacterial endotoxin testing with the EndoZyme® II Recombinant Factor C Assay using the Synergy™ HTX Microplate Reader*, 2017.

57 F. Mégraud, Advantages and disadvantages of current diagnostic tests for the detection of Helicobacter pylori, *Scand. J. Gastroenterol.*, 1996, **31**(suppl 215), 57–62.

58 M. Koskinen, G. Wellenberg, O. Sampimon, J. Holopainen, A. Rothkamp, L. Salmikivi, W. Van Haeringen, T. Lam and S. Pyörälä, Field comparison of real-time polymerase chain reaction and bacterial culture for identification of bovine mastitis bacteria, *J. Dairy Sci.*, 2010, **93**(12), 5707–5715.

59 L. R. Stromberg, H. M. Mendez and H. Mukundan, Detection methods for lipopolysaccharides: past and present. *Escherichia coli*-recent advances on physiology, pathogenesis and biotechnological applications, *InTech*, 2017, pp. 141–168.

60 S. L. Gaffin, N. Badsha, J. Brock-Utne, B. Vorster and J. Conradie, An ELISA procedure for detecting human anti-endotoxin antibodies in serum, *Ann. Clin. Biochem.*, 1982, **19**(3), 191–194.

61 V. Murugan and K. Sankaran, Bacterial lipid modification of ICP11 and a new ELISA system applicable for WSSV infection detection, *Mar. Biotechnol.*, 2018, **20**(3), 375–384.

62 G. Banik, Biosensor: Potential and Scope in Agriculture, *Chem. Sci. Rev. Lett.*, 2021, **10**(38), 116–122.
63 N. Arora, Recent advances in biosensors technology: a review, *Octa J. Biosci.*, 2013, 1(2), 147–150.
64 K. Srinivas, T. S. Rao and C. B. Kiranmayi, The emergence of biosensors: potentials and scope in food safety, *Everyman's Science*, 1962, 141, 141–144.
65 X.-d. Wang and O. S. Wolfbeis, Fiber-optic chemical sensors and biosensors (2013–2015), *Anal. Chem.*, 2016, 88(1), 203–227.
66 Q. Zhou, W. Zhang, M. Qiu and Y. Yu, Role of oxygen in copper-based catalysts for carbon dioxide electrochemical reduction, *Mater. Today Phys.*, 2021, 20, 100443.
67 R. Jain and A. Sinha, Graphene-zinc oxide nanorods nanocomposite based sensor for voltammetric quantification of tizanidine in solubilized system, *Appl. Surf. Sci.*, 2016, 369, 151–158.
68 J. Ding and W. Qin, Recent advances in potentiometric biosensors, *TrAC, Trends Anal. Chem.*, 2020, 124, 115803.
69 J. Lin, R. Wang, P. Jiao, Y. Li, Y. Li, M. Liao, Y. Yu and M. Wang, An impedance immunosensor based on low-cost microelectrodes and specific monoclonal antibodies for rapid detection of avian influenza virus H5N1 in chicken swabs, *Biosens. Bioelectron.*, 2015, 67, 546–552.
70 E. P. Randviir and C. E. Banks, Electrochemical impedance spectroscopy: an overview of bioanalytical applications, *Anal. Methods*, 2013, 5(5), 1098–1115.
71 R. Jain and A. Sinha, Graphene-zinc oxide nanorods nanocomposite based sensor for voltammetric quantification of tizanidine in solubilized system, *Appl. Surf. Sci.*, 2016, 369, 151–158.
72 S. Akhavan Alavi, M. Mohammadmehr and S. Ejtahed, Vibration analysis and control of micro porous beam integrated with FG-CNT distributed piezoelectric sensor and actuator, *Steel Compos. Struct.*, 2021, 41(4), 595–608.
73 N. Sriplai, R. Mangayil, A. Pammio, V. Santala, S. Tuukkanen and S. Pinitsoontorn, Enhancing piezoelectric properties of bacterial cellulose films by incorporation of MnFe2O4 nanoparticles, *Carbohydr. Polym.*, 2020, 231, 115730.
74 D. T. Luat, D. Van Thom, T. T. Thanh, P. Van Minh, T. Van Ke and P. Van Vinh, Mechanical analysis of bi-functionally graded sandwich nanobeams, *Adv. Nano Res.*, 2021, 11(1), 55–71.
75 B. Paczosa-Bator, L. Cabaj, M. Raš, B. Baš and R. Piech, Potentiometric sensor platform based on a carbon black modified electrodes, *Int. J. Electrochem. Sci.*, 2014, 9, 2816–2823.
76 E. I. Santos, M. C. B. Montenegro, C. Couto, A. N. Araújo, M. F. Pimentel and V. L. da Silva, Sequential injection analysis of chloride and nitrate in waters with improved accuracy using potentiometric detection, *Talanta*, 2004, 63(3), 721–727.
77 S. S. Hassan, H. Sayour and S. S. Al-Mehrezi, A novel planar miniaturized potentiometric sensor for flow injection analysis of nitrates in wastewaters, fertilizers and pharmaceuticals, *Anal. Chim. Acta*, 2007, 581(1), 13–18.
78 H. Karimi-Maleh, F. Karimi, S. Malekmohammadi, N. Zakariae, R. Esmaeili, S. Rostamnia, M. L. Yola, N. Atar, S. Movaghgharnezhad and S. Rajendran, An amplified voltammetric sensor based on platinum nanoparticle/polyoxometalate/two-dimensional hexagonal boron nitride nanosheets composite and ionic liquid for determination of N-hydroxysuccinimide in water samples, *J. Mol. Liq.*, 2020, 310, 113185.
79 S. Menon, S. Jesny and K. G. Kumar, A voltammetric sensor for acetaminophen based on electropolymerized–molecularly imprinted poly(o-aminophenol) modified gold electrode, *Talanta*, 2018, 179, 668–675.
80 R. Arshad, A. Rhouati, A. Hayat, M. H. Nawaz, M. A. Yameen, A. Mujahid and U. Latif, MIP-based impedimetric sensor for detecting dengue fever biomarker, *Appl. Biochem. Biotechnol.*, 2020, 191(4), 1384–1394.
81 S. Xiao, L. Chen, X. Xiong, Q. Zhang, J. Feng, S. Deng and L. Zhou, A new impedimetric sensor based on anionic intercalator for detection of lead ions with low cost and high sensitivity, *J. Electroanal. Chem.*, 2018, 827, 175–180.
82 C. Chi, X. Sun, N. Xue, T. Li and C. Liu, Recent progress in technologies for tactile sensors, *Sensors*, 2018, 18(4), 948.
83 C. Chen and J. Wang, Optical biosensors: an exhaustive and comprehensive review, *Analyst*, 2020, 145(5), 1605–1628.
84 X. Fan, I. M. White, S. I. Shopova, H. Zhu, J. D. Suter and Y. Sun, Sensitive optical biosensors for unlabeled targets: a review, *Anal. Chim. Acta*, 2008, 620(1–2), 8–26.
85 J. Zhang, I. Khan, Q. Zhang, X. Liu, J. Dostalek, B. Liedberg and Y. Wang, Lipopolysaccharides detection on a grating-coupled surface plasmon resonance smartphone biosensor, *Biosens. Bioelectron.*, 2018, 99, 312–317.
86 W. Xu, J. Tian, X. Shao, L. Zhu, K. Huang and Y. Luo, A rapid and visual aptasensor for lipopolysaccharides detection based on the bulb-like triplex turn-on switch coupled with HCR-HRP nanostructures, *Biosens. Bioelectron.*, 2017, 89, 795–801.
87 X. Fan, Z. Li, S. Wang, Y. Wang, L. Yu and X. Fan, An electrochemiluminescence sandwich biosensor for the detection of lipopolysaccharide, *Quim. Nova*, 2020, 43, 747–751.
88 L. Gloag, M. Mehdipour, D. Chen, R. D. Tilley and J. J. Gooding, Advances in the application of magnetic nanoparticles for sensing, *Adv. Mater.*, 2019, 31(48), 1904385.
89 J. Kudr, Y. Haddad, L. Richtera, Z. Heger, M. Cernak, V. Adam and O. Zitka, Magnetic nanoparticles: from design and synthesis to real world applications, *Nanomaterials*, 2017, 7(9), 243.
90 C. Xu, O. U. Akakuru, J. Zheng and A. Wu, Applications of iron oxide-based magnetic nanoparticles in the diagnosis and treatment of bacterial infections, *Front. Bioeng. Biotechnol.*, 2019, 7, 141.
91 C.-M. Tilmaciu and M. C. Morris, Carbon nanotube biosensors, *Front. Chem.*, 2015, 3, 59.
92 X.-M. Liu, Z. Dong Huang, S. Woon Oh, B. Zhang, P.-C. Ma, M. M. Yuen and J.-K. Kim, Carbon nanotube (CNT)-based composites as electrode material for rechargeable Li-ion batteries: a review, *Compos. Sci. Technol.*, 2012, 72(2), 121–144.
A. C. Hengartner, K. E. Klosterman, H. A. Bridgewater, V. Otieno, Q. Cheng, S. B. Anyona, C. Ouma, E. Raballah, D. J. Perkins, B. H. McMahon and H. Mukundan, Direct detection of bacteremia by exploiting host-pathogen interactions of lipoteichoic acid and lipopolysaccharide, Sci. Rep., 2019, 9(1), 6203.

123 J.-N. Yih, Y.-M. Chu, Y.-C. Mao, W.-H. Wang, F.-C. Chien, C.-Y. Lin, K.-L. Lee, P.-K. Wei and S.-J. Chen, Optical waveguide biosensors constructed with subwavelength gratings, Appl. Opt., 2006, 45(9), 1938–1942.

124 H. Hosseini-Toudeshky and F. A. Amjad, Sensor placement optimization for guided wave-based structural health monitoring, Struct. Monit. Maint., 2021, 8(2), 125–150.

125 A. Noormohamed, L. R. Stromberg, A. S. Anderson, Z. Karim, P. Dighe, P. Kempaiah and A. C. Hengartner, V. Gorbach, E. Kalmykova and S. Xiang, C. Ge, S. Li, L. Chen, L. Wang and Y. Xu, Determination of the parameters of binding between lipopolysaccharide and chitosan and its N-acetylated derivative using a gravimetric piezoquartz biosensor, Biophys. Chem., 2015, 198, 9–13.

126 M. Moskovitis, Surface-enhanced spectroscopy, Rev. Mod. Phys., 1985, 57(3), 783–826.

127 N. Valley, N. Greenelitch, R. P. Van Duyne and G. C. Schatz, A look at the origin and magnitude of the chemical contribution to the enhancement mechanism of surface-enhanced Raman spectroscopy (SERS): theory and experiment, J. Phys. Chem. Lett., 2013, 4(16), 2599–2604.

128 F. N. Kenry, L. Clark, S. R. Panikkanvalappil, B. Andreiuk and C. Andreou, Advances in Surface Enhanced Raman Spectroscopy for in Vivo Imaging in Oncology, Nanotheranostics, 2022, 6(1), 31.

129 X. Luo, Q. Qi, L. Zhang, R. Zeng, L. Su and D. Tang, Branched polyethylenimine-modified upconversion nanohybrid-mediated photoelectrochemical immunoassay with synergistic effect of dual-purpose copper ions, Anal. Chem., 2019, 91(6), 4149–4156.

130 L. Liu, F. He, Y. Yu and Y. Wang, Application of FRET biosensors in mechanobiology and mechanopharmaceutical screening, Front. Bioeng. Biotechnol., 2020, 8, 1299.

131 J. Wu, A. Zawistowski, M. Ehrmann, T. Yi and C. Schmuck, Peptide functionalized polydiacetylene liposomes act as a fluorescent turn-on sensor for bacterial lipopolysaccharide, J. Am. Chem. Soc., 2011, 133(25), 9720–9723.

132 J. Sun, P. Zhu, X. Wang, J. Ji, J. d. D. Habimana, J. Shao, H. Lei, Y. Zhang and X. Sun, Cell based-green fluorescent biosensor using cytotoxic pathway for bacterial lipopolysaccharide recognition, J. Agric. Food Chem., 2018, 66(26), 6869–6876.

133 P. Xie, L. Zhu, X. Shao, K. Huang, J. Tian and W. Xu, Highly sensitive detection of lipopolysaccharides using an aptasensor based on hybridization chain reaction, Sci. Rep., 2016, 6(1), 1–8.

134 J. Z. Kubicek-Sutherland, D. M. Vu, A. Noormohamed, H. M. Mendez, L. R. Stromberg, C. A. Pedersen, A. C. Hengartner, K. E. Klosterman, H. A. Bridgewater and V. Otieno, Direct detection of bacteremia by exploiting host-pathogen interactions of lipoteichoic acid and lipopolysaccharide, Sci. Rep., 2019, 9(1), 1–14.

135 M. A. Khadimallah, M. Hussain, K. M. Khedher, S. M. Bouzgarrou, A. F. Al Naim, M. N. Naeem, M. Taj, Z. Iqbal and A. Tounsi, Vibration of SWCNTs: Consistency and behavior of polynomial law index with Galerkin’s model, Adv. Nano Res., 2020, 9(4), 251–261.

136 J. Chen, A. Sheng, Y. Hu, D. Mao, L. Ning and J. Zhang, Modularization of three-dimensional gold nanoparticles/ferrocene/liposome cluster for electrochemical biosensor, Biosens. Bioelectron., 2019, 124, 115–121.

137 J. Zhang, R. Oueslati, C. Cheng, L. Zhao, J. Chen, R. Almeida and J. Wu, Rapid, highly sensitive detection of Gram-negative bacteria with lipopolysaccharide based disposable aptasensor, Biosens. Bioelectron., 2018, 112, 48–53.

138 S. Sannigrahi, S. K. Arumugasamy, J. Mathiyarasu and K. Suthindhiran, Magnetosome-anti-Salmonella antibody complex based biosensor for the detection of Salmonella typhimurium, Mater. Sci. Eng., C, 2020, 114, 111071.

139 M. Cho, L. Chun, M. Lin, W. Choe, J. Nam and Y. Lee, Sensitive electrochemical sensor for detection of lipopolysaccharide on metal complex immobilized gold electrode, Sens. Actuators, B, 2012, 174, 490–494.

140 H. Jiang, J. Yang, K. Wan, D. Jiang and C. Jin, Miniaturized paper-supported 3D cell-based electrochemical sensor for bacterial lipopolysaccharide detection, ACS Sens., 2020, 5(5), 1325–1335.

141 J. Hicks, N. Silman, S. Jackson, J. Aylott and F. Rawson, Mass transport of lipopolysaccharide induced H2O2 detected by an intracellular carbon nanoelectrode sensor, Bioelectrochemistry, 2020, 133, 107547.

142 X. Fan, Z. Li, S. Wang, L. Liu, P. Liu, F. Chen and X. Zheng, Electrochemical Impedance biosensor for the determination of lipopolysaccharide using peptidase as the recognition molecule, J. Braz. Chem. Soc., 2019, 30, 1762–1768.

143 F. Ma, A. Rehman, M. Sims and X. Zeng, Antimicrobial susceptibility assays based on the quantification of bacterial lipopolysaccharides via a label free lectin biosensor, Anal. Chem., 2015, 87(8), 4385–4393.
147 J. Qin, H. Sun, H. Hao, L. Jia, C. Yao, Q. Wang and H. Yang, Impedimetric Biosensor for the Detection of Bacterial Lipopolysaccharide Based on Lectin-functionalized Gold Nanoparticle–Graphene Composites, Sens. Mater., 2019, 31(9), 2917–2929.

148 W.-J. Shen, Y. Zhuo, Y.-Q. Chai and R. Yuan, Ce-based metal-organic frameworks and DNAzyme-assisted recycling as dual signal amplifiers for sensitive electrochemical detection of lipopolysaccharide, Biosens. Bioelectron., 2016, 83, 287–292.

149 M. Pourmadadi, J. S. Shayeh, M. Omidi, F. Yazdian, M. Alebouyeh and L. Tayebi, A glassy carbon electrode modified with reduced graphene oxide and gold nanoparticles for electrochemical aptasensing of lipopolysaccharides from Escherichia coli bacteria, Microchim. Acta, 2019, 186(12), 1–8.

150 M. D. Oliveira, C. A. Andrade, M. T. Correia, L. C. Coelho, P. R. Singh and X. Zeng, Impedimetric biosensor based on self-assembled hybrid cystein-gold nanoparticles and CramoLL lectin for bacterial lipopolysaccharide recognition, J. Colloid Interface Sci., 2011, 362(1), 194–201.

151 B. Posha, S. R. Nambar and N. Sandhyarani, Gold atomic cluster mediated electrochemical aptasensor for the detection of lipopolysaccharide, Biosens. Bioelectron., 2018, 101, 199–205.

152 S. Chen, X. Chen, L. Zhang, J. Gao and Q. Ma, Electrochemiluminescence Detection of Escherichia coli O157:H7 Based on a Novel Polydopamine Surface Imprinted Polymer Biosensor, ACS Appl. Mater. Interfaces, 2017, 9(6), 5430–5436.

153 V. Gaudin, Chapter 11 – Receptor-based electrochemical biosensors for the detection of contaminants in food products, in Electrochemical Biosensors, ed. A. A. Ensaifi, Elsevier, 2019, pp. 307–365.

154 L.-X. You, N.-J. Chen, L. Wang, J. Chen, S.-F. Qin, C. Rensing, Z.-Y. Lin and S.-G. Zhou, Electrochemiluminescence for the identification of electrochemically active bacteria, Biosens. Bioelectron., 2019, 137, 222–228.

155 H. Sun, P. Miao, Y. Tang, B. Wang, J. Qian and D. Wang, An elastography analytical method for the rapid detection of endotoxin, Analyst, 2015, 140(13), 4374–4378.

156 Z. Yang, Y. Wang and D. Zhang, An integrated multifunctional photoelectrochemical platform for simultaneous capture, detection, and inactivation of pathogenic bacteria, Sens. Actuators, B, 2018, 274, 228–234.

157 Y. Hou, L. Zhu, H. Hao, Z. Zhang, C. Ding, G. Zhang, J. Bi, S. Yan, G. Liu and H. Hou, A novel photoelectrochemical aptamer sensor based on rare-earth doped Bi2WO6 and Ag2S for the rapid detection of Vibrio parahaemolyticus, Microchem. J., 2021, 165, 106132.

158 S. Prolongo, R. Moriche, A. Jiménez-Suárez, M. Sánchez and A. Ureña, Advantages and disadvantages of the addition of graphene nanoplatelets to epoxy resins, Eur. Polym. J., 2014, 61, 206–214.

159 E. Frackowiak, K. Metenier, V. Bertagna and F. Beguin, Supercapacitor electrodes from multiwalled carbon nanotubes, Appl. Phys. Lett., 2000, 77(15), 2421–2423.

160 Y. Yim, H. Shin, S. M. Ahn and D.-H. Min, Graphene oxide-based fluorescent biosensors and their biomedical applications in diagnosis and drug discovery, Chem. Commun., 2021, 57(77), 9820–9833.

161 Y. Yim, H. Shin, S. M. Ahn and D.-H. Min, Graphene oxide-based fluorescent biosensors and their biomedical applications in diagnosis and drug discovery, Chem. Commun., 2021, 57(77), 9820–9833.

162 I. M. Obaidat, B. Issa and Y. Haik, Magnetic properties of magnetic nanoparticles for efficient hyperthermia, Nanomaterials, 2015, 5(1), 63–89.

163 A. G. Kolhatkar, A. C. Jamison, D. Litvinov, R. C. Willson and T. R. Lee, Tuning the magnetic properties of nanoparticles, Int. J. Mol. Sci., 2013, 14(8), 15977–16009.

164 S. Höfinger, M. Melle-Franco, T. Gallo, A. Cantelli, M. Calvaresi, J. A. Gomes and F. Zerbetto, A computational analysis of the insertion of carbon nanotubes into cellular membranes, Biomaterials, 2011, 32(29), 7079–7085.