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Review

Molecularly Imprinted Polymer-based Sensors for Lipopolysaccharide Detection in Food Safety Systems: A Review

Zakiah Dzulummah, Fitri Khoerunnisa*, Asep Kadarohman*

Department of Chemistry, Faculty of Mathematics and Science Education, Universitas Pendidikan Indonesia
Jalan Dr. Setiabudi 229 Bandung 40154 Indonesia

Corresponding author: fitri@upi.edu; kadar@upi.edu

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ABSTRACT. The conventional methods for detecting lipopolysaccharide (LPS) in food safety systems, such as the Limulus Amebocyte Lysate (LAL) assay and enzyme-linked immunosorbent assay (ELISA), still face several limitations, including time-consuming procedures, the requirement for specialized laboratory facilities, and limited applicability for on-site monitoring. Therefore, the development of alternative detection approaches that are rapid, selective, stable, and cost-effective is highly required. This review article provides a comprehensive overview of the recent advances in Molecularly Imprinted Polymer (MIP)-based sensors for LPS detection in food safety applications. A structured narrative review approach was conducted through literature searches in Scopus, ScienceDirect, and Google Scholar databases, covering publications from 2012 to 2026. The discussion focuses on the fundamental imprinting strategies for LPS recognition, MIP synthesis approaches, material characterization techniques, sensor platforms, and the relationship between structural properties and sensing performance of MIP-based LPS sensors. The reviewed studies demonstrate that integrating MIPs with various transducer platforms enables the development of LPS sensors with high selectivity, low detection limits, and rapid response, including applications in complex food matrices. MIP-based LPS sensors represent a promising and strategic approach for advancing rapid and reliable monitoring systems to enhance food safety.

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INTRODUCTION

The issue of food safety becomes a significant global challenge because it directly affects public health, economic stability, and the sustainability of food systems. The World Health Organization (WHO) reports that about 600 million people get sick and 420,000 die each year due to unsafe food consumption, with children under the age of five being the most vulnerable group (WHO, 2022). In Indonesia, the Food and Drug Supervisory

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Agency (BPOM) recorded at least 128 extraordinary incidents related to foodborne diseases, with more than 18,000 people exposed in 2011 (Muna and Khariri, 2020). Data from the Indonesian Ministry of Health show that the death rate due to food poisoning increased sharply by more than 130% in the period 2012 – 2014 (Lubis *et al.*, 2020). However, the actual number of cases is estimated to be much higher due to many unreported incidents (Muna and Khariri, 2020). This condition underscores the need for fast and accurate biological contaminant detection methods to strengthen food safety.

Foodborne disease is defined as a disease transmitted through the consumption of food or beverages contaminated with biological agents (bacteria, viruses, parasites) or chemical and radiological hazards (Bintsis, 2017). One of the main causes of foodborne illness is contamination by Gram-negative bacteria that produce lipopolysaccharides (LPS), which are the main components of the outer cell wall. LPS is known as a potent endotoxin that can induce an excessive immune response and septic shock in humans (Raetz and Whitfield, 2002). LPS is highly toxic even at very low concentrations and remains stable after bacteria have died, making it a leading indicator of Gram-negative bacterial contamination in the food chain. Although high temperatures and high pressure can kill bacteria, LPS cannot be eliminated or destroyed by bacterial death (Kosikowska-Adamus *et al.*, 2024). In addition, the presence of LPS in food products indicates contamination by Gram-negative bacteria such as Escherichia coli and Salmonella enterica, which often cause disease outbreaks in various countries (Belbruno, 2019). Early detection of LPS is important because this molecule triggers an immune and inflammatory response that can cause disease and death in humans (Jiang *et al.*, 2020).

Various conventional methods for LPS detection, such as the Limulus Amebocyte Lysate (LAL) assay and Enzyme-Linked Immunosorbent Assay (ELISA), have been widely used. Although they achieve good accuracy, these methods have limitations, including long analysis times, complex laboratory requirements, and high operational costs (Cesewski and Johnson, 2020). The development of functional material-based sensors is a promising alternative, as it allows real-time detection at low cost and high portability. One approach to developing sensor systems is the use of molecularly imprinted polymer (MIP) technology.

MIP technology offers a promising approach for use as a synthetic receptor (antibody mimic) in sensor development. MIP is formed through the polymerization of functional monomers around *the template* molecule, which, after release, leaves a complementary cavity specific to the molecular target. This allows selective recognition of targets, with the advantage of better chemical and physical stability than that of biological receptors. In the context of food safety, MIP has begun to be applied as chemical and biological contaminant recognition elements in sensors (Arreguin-Campos *et al.*, 2021). MIP is a synthetic polymer with a specific binding site for the target molecule, formed via molecular imprinting with functional monomers, crosslinkers, and template molecules. After polymerization and template removal, the MIP leaves a cavity that complements the shape, size, and distribution of the target molecule's functional groups. This structure allows MIPs to work like artificial antibodies with high chemical and thermal stability and resistance to extreme environmental conditions (Ayerdurai *et al.*, 2023).

MIP offers advantages in stability, reusability, and ease of synthesis at a relatively lower cost. In the context of food safety, MIP has been used to detect various contaminants, including pesticides, mycotoxins, antibiotics, and heavy metal residues. The integration of MIP into LPS sensors for food safety not only improves the speed, sensitivity, and selectivity of detection but also supports the transformation of food monitoring systems into more responsive and adaptive systems for real conditions across industries and the environment. The development of MIP-based sensors has great potential to improve food security and broadly protect consumers, taking into account the globalization of food supply chains and the increasing need for food safety assurance (Piletsky *et al.*, 2020). The use of MIP for biological *biomarker* detection, such as LPS, is still a relatively new and emerging field.

To date, several review articles have summarized and analyzed lipopolysaccharide (endotoxin) detection sensors (Das *et al.*, 2014; Su and Ding, 2015; Mobed and Hasanzadeh, 2022), making significant contributions to this field. However, reviews on the development of MIP-based detection systems combined with biosensors for detecting lipopolysaccharides (endotoxins) have been reported only infrequently, particularly in food safety applications. A number of studies on MIP-based sensors for LPS detection have been conducted, warranting further investigation. This review examines the latest developments in MIP-based sensors, particularly those targeting LPS as an indicator of Gram-negative bacterial contamination, and their applications in food safety systems. The scope of the review includes: (a) the principles and mechanisms of MIP work in sensors, (b) MIP printing strategies for LPS detection, (c) various transduction platforms, including MIP for LPS recognition, capture, and enrichment as a biosensing support approach, and (d) the performance of MIP-based sensors on

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different types of real matrices. This review is expected to provide insights for researchers and sensor developers to strengthen food safety monitoring systems through MIP technology.

This review article employs a narrative approach with a structured methodology to identify and analyze the development of MIP-based materials and sensors for the recognition and detection of LPS and other Gram-negative bacterial endotoxins (Figure 1). The literature was obtained from three scientific databases: Scopus, ScienceDirect, and Google Scholar. The search was conducted using a combination of keywords and Boolean operators, namely molecularly imprinted polymer or molecular imprinting, lipopolysaccharide or endotoxin, detection or sensor, and food safety. The literature reviewed includes publications from 2012 – 2026. The initial search yielded 3 articles from Scopus, 88 articles from ScienceDirect, and 71 articles from Google Scholar. After the removal of 41 duplicate articles, 121 articles were selected based on titles and abstracts. Furthermore, 38 articles were evaluated in full text, and 20 met the inclusion criteria for thematic analysis.

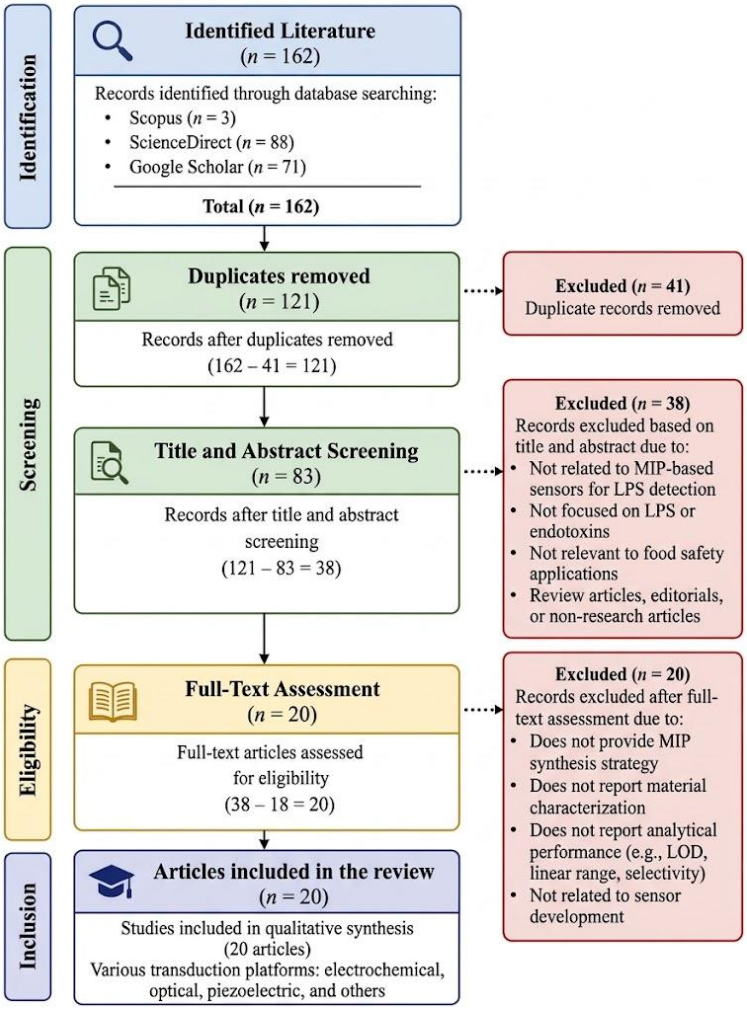


Figure 1. Literature selection flowchart.

Articles are considered for use as review material if they meet the criteria: (i) discuss MIPs designed for the introduction of LPS/endotoxins or Gram-negative bacteria through LPS targets; (ii) report on MIP synthesis strategies or designs; (iii) provide information on characterization, binding/rebinding, or analytical performance; and/or (iv) integrate MIP with transduction platforms for detection. Platforms covered include electrochemistry, optics, fluorescence, piezoelectric/photonics, and other transduction approaches relevant to MIP–LPS. Studies on MIP used only for capture, scavenging, or non-sensing applications are still considered supporting literature if they provide important information on the mechanism of LPS recognition or on material design.

Articles that are not related to MIP–LPS, do not provide information on imprinting strategies or material characteristics, nor do they provide relevant information regarding the introduction or performance of MIPs, are excluded. Identical articles from multiple databases are identified as duplicates and deleted. Selection is carried out by filtering titles, abstracts, and keywords, followed by full-text evaluation. The data obtained were analyzed

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thematically by template type, functional monomer, crosslinker, synthesis method, supporting material, transducer platform, recognition mechanism, characterization, analytical parameters, application to real matrices, and sensor limitations.

LIPOPOLYSACCHARIDES

Lipopolysaccharides (LPS) are the outermost part of the membrane of gram-negative bacteria (Figure 2), such as *Pseudomonas, Bordetella pertussis, Haemophilus influenzae, Shigella, Neisseria, Escherichia coli, Salmonella, Enterobacter, Proteus*, and pathogens such as *Vibrio cholerae, Yersinia pestis, Brucella abortus* (Raetz and Whitfield, 2002; Das *et al.*, 2014; Caroff and Novikov, 2020; Mobed and Hasanzadeh, 2022). Lipopolysaccharides are biomolecules consisting of long chains of polysaccharide groups that are covalently bound to lipids. These long chains form a layer of gelatin attached to the surface of the bacteria, which keeps the bacteria's outside moist and negatively charged (Wassenaar and Zimmermann, 2018).

Basically, LPS can be released during bacterial reproduction through cell division or when bacteria die, including as a result of heat treatment or antibiotic use. The release of large LPS into the host's bloodstream can trigger an inflammatory response that ends in septic shock, multi-organ failure, and even death. On the other hand, at low concentrations, lipopolysaccharides act as immunomodulators, stimulating the host immune response (Caroff and Novikov, 2020). This highly contrasting biological response dualism makes LPS a key molecule that is not only clinically relevant, but also crucial in the context of food safety.

The presence of LPS has been linked to a variety of health disorders, including liver damage, chronic inflammation of the gastrointestinal tract, neurodegenerative disorders, as well as diabetes, which is largely mediated by chronic inflammatory mechanisms. Although the human gastrointestinal tract naturally contains lipopolysaccharide-producing Gram-negative bacteria as part of the normal microbiota, exposure to exogenous LPS in certain amounts can pose health risks (Wassenaar and Zimmermann, 2018). LPS molecules remain stable even after the bacteria have died, making them a more persistent and representative indicator than the detection of intact bacterial cells.

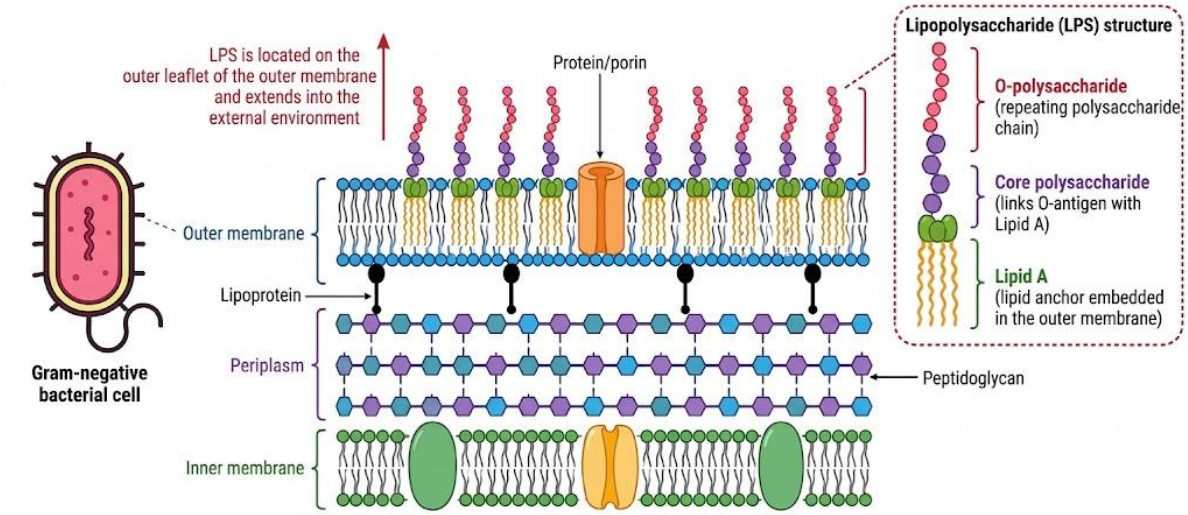


Figure 2. Schematic representation of the cell wall structure of Gram-negative bacteria with three main layers. Adapted from Mobed and Hasanzadeh (2022), with copyright 2022 the authors, under a CC-BY-NC 4.0 license.

Structure of Lipopolysaccharides

Lipopolysaccharides (LPS) are complex glycolipid macromolecules that are the main components of the outer membrane of Gram-negative bacteria and play important roles in both the structural stability of cells and bacterial pathogenicity. Structurally, LPS is composed of three main covalently connected domains, namely lipid A, core oligosaccharides, and O-antigen polysaccharide chains (Figure 3). Each domain has distinct chemical characteristics, conservation levels, and biological functions, which collectively determine the immunological and biological properties of LPS (Bertani and Ruiz, 2018).

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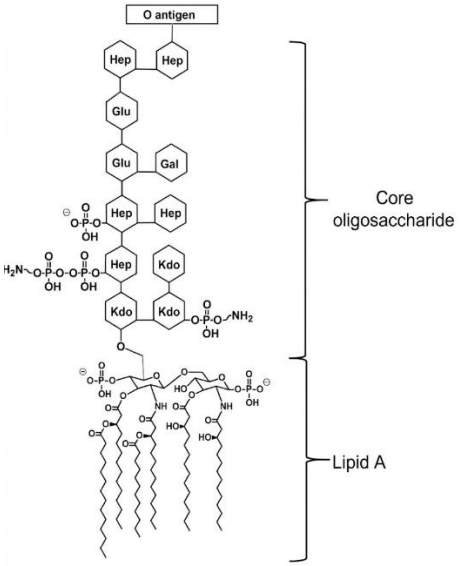


Figure 3. Molecular structure of lipopolysaccharides. Reprinted from Bertani and Ruiz (2018), with copyright (2018) American Society for Microbiology, under a CC-BY 4.0 license.

Lipid A

Lipid A is the most conserved and biologically active part of the LPS molecule. This domain serves as an anchor that anchors LPS to the lipid layer of the outer membrane of Gram-negative bacteria. Chemically, lipid A is composed of a skeleton of β-(1′→6)-diplucosamine disaccharides that are phosphorylated at the 1 and 4′ positions, hydrophilic and negatively charged. This skeleton is then modified by the attachment of hydrophobic acyl chains via amide and ester bonds (Caroff and Novikov, 2020). Lipid A generally contains six acyl chains (hexa-acylation), whereas in *Salmonella,* seven acyl chains can be found. Variations in the length, saturation, and number of acyl chains greatly influence lipid A's potential toxicity and its ability to activate the immune system. The unique structure of lipid A enables specific recognition by innate immune receptors, such as the Toll-like receptor 4 (TLR4)–MD-2 complex, thereby triggering a cascade of inflammatory signals. Therefore, almost all of the endotoxic activity of LPS, including pyrogenic effects, septic shock, and metabolic changes, is directly associated with the lipid A domains (Bertani and Ruiz, 2018).

Core Oligosaccharides

Core oligosaccharides are hydrophilic domains that connect lipid A with O-specific polysaccharide chains. This structure is composed of non-repeating monosaccharides in the tens of units, which can be arranged linearly or branched. Typical components of core oligosaccharides include 3-deoxy-D-manno-octosonate (Kdo), heptose residues, and various hexoses, which often undergo chemical modifications such as phosphorylation or substitution with phosphoethanolamines (Caroff and Novikov, 2020).

Structurally, the core oligosaccharides are divided into two subdomains, namely the inner nucleus and the outer nucleus. The inner nucleus binds directly to lipid A and is more conserved among bacterial species, primarily because of its key role in maintaining outer membrane stability. In contrast, the outer nucleus exhibits greater variation and serves as a binding site for O antigens. Although the specific biological function of the core oligosaccharides is not yet fully known, this domain plays a role in maintaining the structural integrity of LPS and contributes to bacterial resistance to environmental stresses and antimicrobial agents (Wassenaar and Zimmermann, 2018; Caroff and Novikov, 2020).

O-Antigen

The O-antigen is the most distal and most variable part of the LPS molecule and is directly exposed to the external environment of the bacterial cell. This domain is composed of long hydrophilic polysaccharide chains consisting of repeating oligosaccharide units, with each unit generally containing one to eight monosaccharides. The O-antigen chain binds to the cell surface, forming a layer that serves as the primary interface between the bacterium and its environment (Caroff and Novikov, 2020).

The variability of O-antigen structures is very high, including differences in monosaccharide types, stereochemical configurations, glycosidic bond types, and the presence of substituents such as acetyl groups,

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phosphates, glycerols, or ribitols. This complexity results in structural diversity that far exceeds that of other biomolecules, such that each O-antigen structure can be considered a unique molecular fingerprint. In the genus *Salmonella*, more than 1,000 immunochemical variants of O-antigen have been identified. O-antigen variations enable bacteria to evade recognition by the host immune system and contribute to differences in virulence among strains (Bertani and Ruiz, 2018).

Functions and Mechanisms of Lipopolysaccharide Toxicity

LPS molecules play an important role in protecting bacterial cells, maintaining the mechanical stability of the outer membrane, and preserving the integrity of the cell wall, especially under extreme environmental conditions such as dehydration or exposure to toxic substances. LPS molecules form a selective barrier layer, which allows nutrients to enter while inhibiting the penetration of harmful molecules (Wassenaar and Zimmermann, 2018). LPS is also a key component of the outer membrane of Gram-negative bacteria, playing an important role in maintaining the stability and integrity of the cell wall, especially under environmental stress. Nevertheless, from a host perspective, LPS is recognized as a major endotoxin and a key virulence factor of Gram-negative bacteria. Although high-temperature and high-pressure treatment can kill bacteria, LPS does not degrade or become inactivated after bacterial cells die; instead, it is released into the environment as highly chemically stable molecules (Su and Ding, 2015; Jiang *et al.*, 2020). Therefore, the presence of LPS remains a threat even after sterilization.

Interestingly, LPS integrated into the bacterial outer membrane is relatively non-toxic but becomes highly dangerous when released into the environment or the host's body. Exposure of immune cells to lipid A directly triggers an excessive inflammatory response, characterized by clinical symptoms such as fever, asthma, cough, dyspnea, diarrhea, and shock in severe cases (Zuo *et al.*, 2014; Neagu *et al.*, 2024). The high mortality rate associated with endotoxin shock makes LPS a serious clinical problem, especially in patients with weak or immunosuppressive conditions.

Biologically, LPS toxicity is almost entirely attributed to the lipid A domain, which serves as an LPS anchor on the outer membrane of Gram-negative bacteria. Lipid A is able to activate the innate immune system through interaction with immune receptors such as Toll-like receptors (TLRs), which further trigger the production of inflammatory mediators and prostaglandins, as well as transmit signals to the central nervous system to increase body temperature (fever). Meanwhile, the polysaccharide component of LPS is relatively less toxic and primarily serves structural and immunogenic functions (Zuo *et al.*, 2014).

The mechanism of LPS toxicity is presented in Figure 4. LPS, which is released from Gram-negative bacteria such as Escherichia coli, becomes a highly biologically active, toxic entity. LPS that enters the circulatory system binds to LPS-binding protein (LBP), a liver-produced protein secreted into blood plasma. The LBP-LPS complex can play a dual role. When LPS is small in number, LBP-LPS can increase LPS solubility, but when LPS concentrations are high, LBP-LPS is able to facilitate LPS transfer to the main receptor units (CD14/Cluster of Differentiation 14 and TLR4-MD2/ Toll-Like Receptor 4- Myeloid Differentiation factor 2) that are responsible for the introduction of LPS from Gram-negative bacteria and initiating an inflammatory response. Under some conditions, LPS can also activate TLR4 directly without having to form an LBP-LPS complex. LPS binding to the TLR4–MD2 complex triggers receptor activation and intracellular adapter recruitment, especially in the MyD88 (Myeloid differentiation primary response 88) pathway and other signal-carrying proteins such as IRAKs (Interleukin-1 Receptor-Associated Kinases), TRAF6 (Tumor Necrosis Factor Receptor-Associated Factor 6), NIK (NF-κB-Inducing Kinase), and IKKs (IκB Kinases/Complex Kinase Inhibitor of κB). The activation of the innate immune system by LPS triggers the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and platelet-activating factor, which can cause endotoxemia, characterized by changes in cell and organ function, metabolic disorders, increased body temperature, changes in hemodynamics, and septic shock, and can develop into systemic inflammatory response syndrome (SIRS). The condition has been reported as a leading cause of death in a variety of severe diseases, including acute respiratory syndrome, cancer, extensive burns, and acute peritonitis (Raetz and Whitfield, 2002; Maeshima and Fernandez, 2013; Su and Ding, 2015; Fang *et al.*, 2025).

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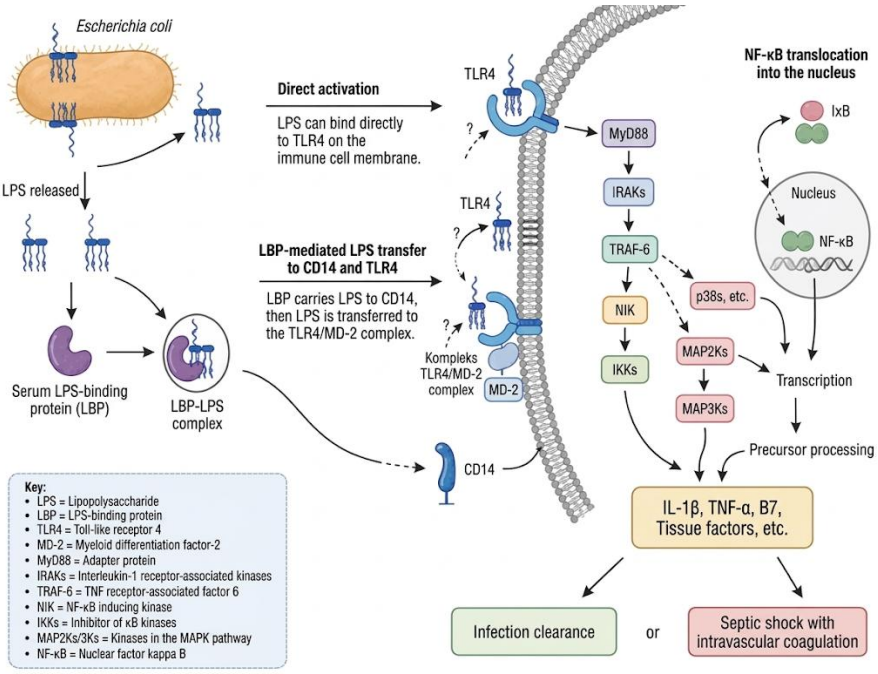


Figure 4. The mechanism of reaction of lipopolysaccharide toxicity in humans. Adapted from Raetz and Whitfield (2002), with copyright 2002 Annual Reviews.

Lipopolysaccharides as Biosensing Targets

In the context of food and biological product safety, LPS is of critical concern due to its high chemical stability. In contrast to bacterial cells, which can be eliminated by thermal sterilization or high-pressure treatment, LPS cannot be effectively destroyed by conventional methods. Therefore, the absence of live bacteria does not guarantee product safety, and LPS testing of the final product remains necessary even if the microorganism has been declared dead (Jiang *et al.*, 2020). This condition makes LPS a more representative biomarker for assessing biological risk than direct bacterial detection does.

The presence of LPS indicates contamination of pathogenic Gram-negative bacteria such as *Escherichia coli*, *Salmonella*, *Pseudomonas*, *Shigella*, and *Vibrio cholerae*. LPS can be released not only during bacterial cell death, but also during cell growth and division, and easily accumulates in various industrial environments and systems. Exposure to LPS affects health disorders, including acute and chronic respiratory distress, in the work environment, such as the agricultural, textile, and waste treatment sectors, and is a major issue in the food, pharmaceutical, and medical device industries (Turner, 2013; Das *et al.*, 2014).

Conventional methods such as Limulus Amebocyte Lysate (LAL) and ELISA have long been used as standard methods of LPS detection due to their high sensitivity and selectivity. However, these methods still have limitations, including the need for relatively expensive biological reagents, analytical procedures that require complex preparation and incubation steps, relatively long test times, and reliance on specialized laboratory facilities. In addition, the performance of both methods can be affected by the complexity of the sample matrix, variation in LPS structure among bacterial species, and potential interference from non-target components, which can compromise the accuracy of the analysis results. This has led to the development of biosensors as an alternative approach that offers fast, sensitive, and portable detection. Various biosensor platforms have been developed to detect LPS, with improved performance through the utilization of nanofunctional materials. Along with these developments, LPS is considered one of the strategic biosensing targets, and the integration of biosensors with synthetic receptors such as molecularly imprinted polymers (MIP) offers a great opportunity to produce selective, stable, and applicable LPS detection systems in strengthening food safety and public health systems (Stoica *et al.*, 2021; Neagu *et al.*, 2024).

LIPOPOLYSACCHARIDE DETECTION METHODS

Limulus Amebocyte Lysate (LAL)

The Limulus Amebocyte Lysate (LAL) method is widely recognized as the primary standard for detecting LPS, especially in the quality control of pharmaceutical, biological, and food products. This method uses

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hemolymph from the horseshoe crab (Limulus polyphemus), in which immune cells (amebocytes) undergo rapid coagulation upon exposure to LPS. Biologically, this mechanism serves as a natural defense system to prevent the spread of pathogens in the animal. The principle of LAL analysis is based on the activation of an enzymatic cascade triggered by LPS through Factor C, followed by subsequent protease activation, culminating in the cleavage of the coagulogens into coagulants that form a gel or produce an optical signal. The LAL method has replaced rabbit pyrogenic assays in many applications due to its high sensitivity and relative ease of application (Das *et al.*, 2014; Gorman and Golovanov, 2022).

Various LAL formats have been developed, including gel-clot, turbidimetric, and chromogenic assays, which allow qualitative to quantitative detection of LPS with low detection limits (Figure 5). Turbidimetric and chromogenic assays generally offer higher sensitivity and accuracy than gel-clot, so they are widely used in routine industrial testing. However, the performance of LAL is greatly influenced by the sample type, preparation method, dilution factors, and reaction conditions, so analysis on complex matrices often requires careful optimization (Su and Ding, 2015; Mobed and Hasanzadeh, 2022). In addition, LAL is susceptible to interference, particularly from β-(1,3)-glucans that can activate alternative coagulation pathways, as well as to low endotoxin recovery (LER) (Gorman and Golovanov, 2022).

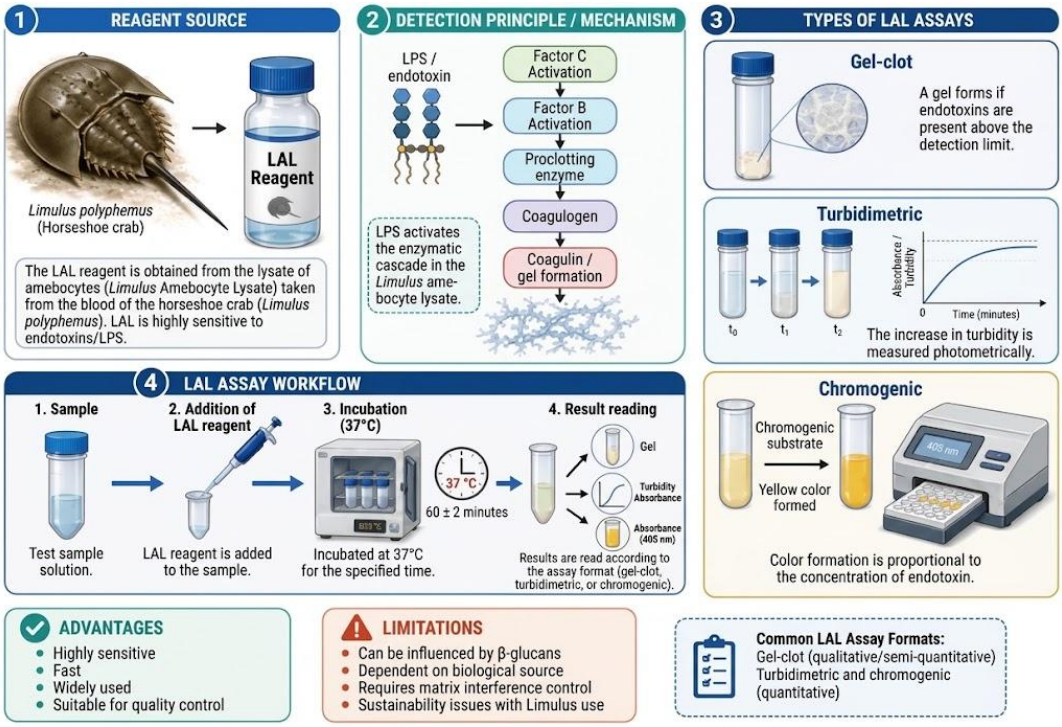


Figure 5. LPS detection method with Limulus Amebocyte Lysate.

The limitations of LPS that cannot be eliminated through conventional sterilization processes mean that its presence must be monitored in the final product even after the bacteria have died (Jiang *et al.*, 2020). Therefore, although LAL remains an important reference standard, there is a need for faster, more selective, and more robust detection methods suitable for a wide range of applications and less susceptible to matrix interference. The development of LPS biosensors is seen as a complement and strategic alternative to LAL, to strengthen food safety monitoring systems, biological products, and medical devices through more adaptive and sustainable endotoxin detection.

Enzyme-Linked Immunosorbent Assay (ELISA)

The Enzyme-Linked Immunosorbent Assay is a widely used immunochemical method for detecting and quantifying LPS in food, environmental, pharmaceutical, and biological product samples. The ELISA principle is based on antigen–antibody-specific interactions, in which LPS or its structural fragments (especially lipid A or the O-antigen) are recognized by specific antibodies and visualized via enzymatic reactions that generate colorimetric signals, fluorescence, or chemiluminescence. Various ELISA formats have been developed for LPS analysis, including *direct, indirect, competitive,* and *sandwich* ELISA. ELISA *sandwiches* are most widely used because

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they offer higher sensitivity and selectivity. A number of studies report that ELISA can detect LPS in the range of pg/mL to ng/mL, making this method an important reference for monitoring LPS in controlled laboratories. However, the application of ELISA for LPS detection still faces some limitations (Figure 6).

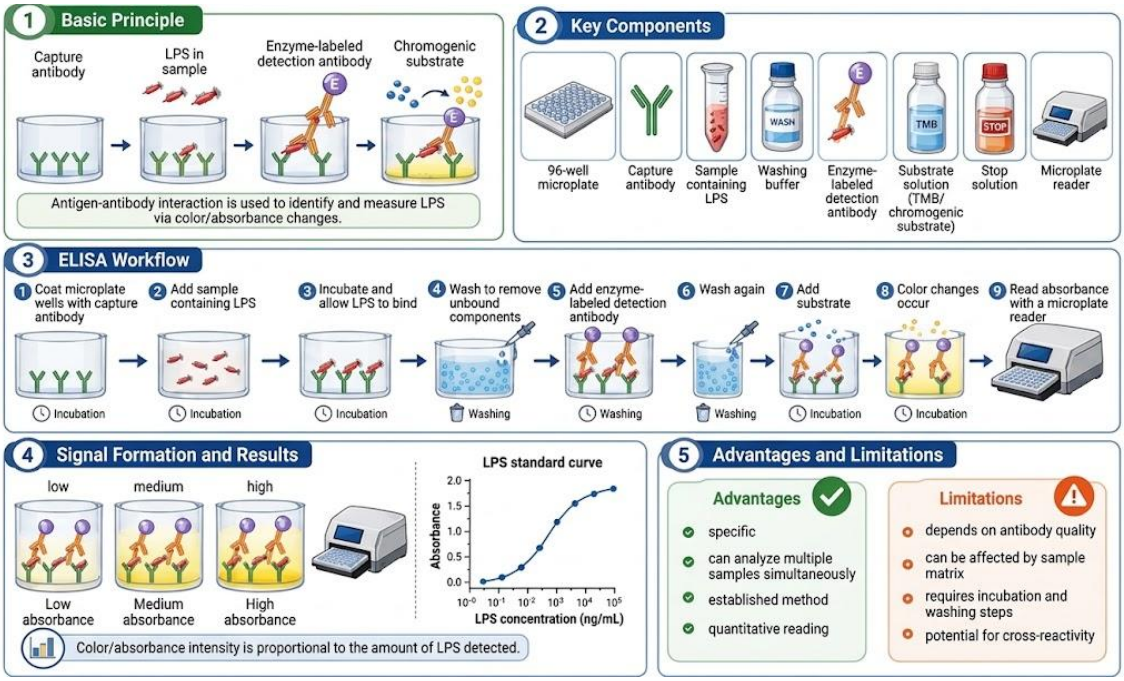


Figure 6. LPS detection method with ELISA.

The structural diversity of LPS between Gram-negative bacterial species can affect antibody affinity, potentially lowering detection accuracy and universality. ELISA is susceptible to matrix interference in complex samples and relies on biological reagents that are relatively expensive, less stable, and require a fairly long analysis time with multiple stages of washing. These limitations restrict the use of ELISA for rapid, on-site detection, so in many studies this method is more often used as a benchmark for evaluating alternative detection approaches. Therefore, although ELISA continues to play an important role in LPS analysis, its limitations have spurred the development of faster, more stable, and adaptive LPS biosensors for food safety and public health applications (Das *et al.*, 2014; Su and Ding, 2015; Mobed and Hasanzadeh, 2022). Table 1 compares detection methods using LAL and ELISA.

Table 1. Comparison of LAL and ELISA detection methods.

Method	Sample	Technique	LOD/ Sensitivity	References
LAL assay	LPS Standard	LAL chromogenic	~0.03 EU/mL (≈ 3 – 6 g/mL)	(Unger *et al.*, 2014)
LAL assay	Pharmaceutical and Biological Products	Chromogenic and turbidimetric LAL	0.01 – 0.1 EU/mL	(Dubczak *et al.*, 2021)
LAL assay	Pharmaceutical and Medical Products	Chromogenic and fluorogenic LAL	~ 0.005 EU/mL	(Gorman *et al.*, 2025)
ELISA	Medical Products	ELISA-bacteriophage receptor protein	0.05 – 500 EU/mL	(Wedmann *et al.*, 2017)
ELISA	Pure LPS	Sandwich-ELISA	1.0 ng/mL	(Choi *et al.*, 1992)
ELISA	Milk	ELISA	100 – 200 ng/mL	(Kerr *et al.*, 2001)

Biosensor Technology

A biosensor is an analytical device that integrates two main components, namely a biological identifier element (bioreceptor) and a physicochemical transducer, to detect an analyte selectively and sensitively. The

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biological identifier element recognizes a specific target through a biological interaction, while the transducer converts the binding event into a measurable signal, such as an electrical or optical signal. These signals are then processed and amplified to produce quantitative or semi-quantitative information that can be interpreted directly. Biosensors are widely applied in various fields, including medical diagnostics, environmental monitoring, food safety, the defense industry, and bioprocess control. The main advantage of biosensors over conventional analytical methods is their ability to provide fast, accurate, real-time results and potential for on-site use or in point-of-care testing systems. The working principle of biosensors is generally based on specific interactions between the bioreceptor and the target analyte, which triggers biochemical or biophysical changes. These changes are then translated by the transducer into electrical, optical, or other measurable signals. Based on transducer type, biosensors for LPS detection are differentiated into electrochemical, optical, piezoelectric, and magnetic biosensors (Figure 7) (Mobed and Hasanzadeh, 2022; Li *et al.*, 2024a; Li *et al.*, 2024b; Erdem *et al.*, 2025). A comparison of detection methods across different types of biosensors is presented in Table 2.

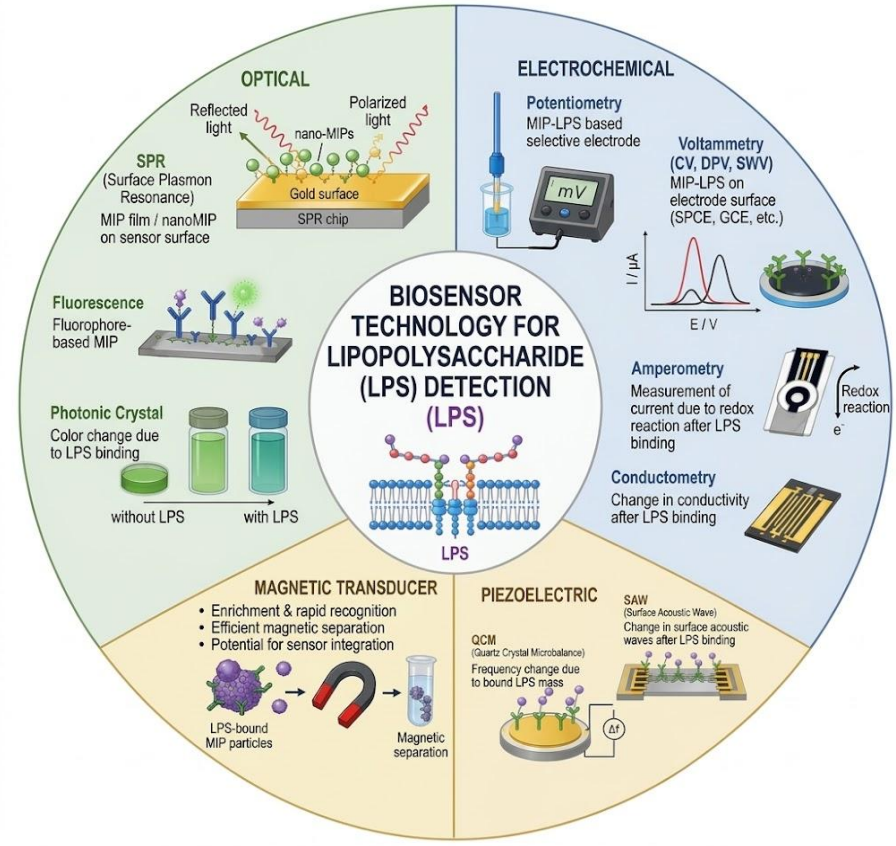


Figure 7. Types of transducers in LPS detection biosensors.

Table 2. Comparison of detection methods of different types of biosensor transducers.

Types of Biosensors	Target Analysis	Method	Measurement Parameters	Ref.
Electrochemistry	LPS *Escherichia coli O26:B6*	Cyclic Voltammetry (CV) and Electrochemical Impedance Spectroscopy (EIS)	a. LOD: 4.93 × 10-21 g/mL b. Linear Range: 5 × 10^{-21} to 5 × 10^{-14} g/mL c. Real Sample Validation: human serum and rat urine at 2.5 × 10-15 g/mL	(Kosikowska-Adamus *et al.*, 2024)
Electrochemistry	*Bacterial Endotoxin / LPS*	Differential Pulse Voltammetry (DPV) and CV	a. LOD: 40 fg/mL; LOQ: ~133 fg/mL b. Linear Range: 0.0001 to 100 ng/mL (R^2 = 0.996) c. Fruit Juice Application: Recovery 94.53% to 106.4% with low RSD (< 8.67%)	(Shen *et al.*, 2026)

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Types of Biosensors	Target Analysis	Method	Measurement Parameters	Ref.
Electrochemistry- Optics	Lipopolysaccharides	Dual-mode Electrochemical Optical SPR (EC-FO-SPR)	a. LOD SPR: 0.049 ng/mL b. LOD CV: 0.032 ng/mL c. Linearities: R2 = 0.989 (SPR); 0.998 (CV) d. Selectivity: Very high against sucrose, fructose, and phospholipids	(Stuttgart *et al.*, 2025)
Electrochemical- Piezoelectric	LPS in Live Bacteria (E. coli W1485)	Electrochemical and Quartz Crystal Microbalance (EQCM)	a. Application: Measure real-time release & unbinding of LPS cell walls due to exposure to antibiotics (ciprofloxacin, ceftriaxone, tetracycline) b. Parameter: τ (relaxation time) linear thd dose (τ ciprofloxacin = 11.2 – 23.6 minutes)	(And *et al.*, 2015)
Optics	Lipopolysaccharides	Flouresensi	a. LOD: 41 pM (~410 pg/mL) b. Reaction Time: Very fast (< 1 minute)	(Blink *et al.*, 2022)
Optics	LPS *E. coli and* LPS *P. aeruginosa*	Photonic Crystal Hydrogel Sensor	a. LOD: 0.87 ± 0.17 ng/mL (*E. coli* LPS); 1.22 ± 0.20 ng/mL (*P. aeruginosa* LPS) b. Linear Range: 10 to 1000 ng/mL c. Ka (Association Constant): 6.02×10^3 M^{-1}	(Murtaza *et al.*, 2020)
Piezoelectric	Endotoxin / LPS	Quartz Crystal Microbalance (MCQ)	a. LOD: 0.005 EU/mL b. Linear Range: 0.005 to 10 EU/mL c. Regeneration: Reusable after cleaning with Piranha d. Application: successfully detects endotoxins in blood plasma and Qingkailing herbal injection samples	(Over *et al.*, 2017)
Piezoelectric	Endotoxin / LPS	Surface Acoustic Wave (SAW)	a. LOD: 0.05ng/mL b. Linear range: 0.05 – 10ng/mL c. Phase signal gain 1.5 times higher than static method	(Stuttgart *et al.*, 2023)
Magnetic	Lipopolysaccharides	Giant Magnetoimpedance (GMI)	a. LOD: 1.8 pg/mL (Sensor); 13.1 pg/mL (*Portable)* b. LOQ: 10 pg/mL c. Linearity: R2 = 0.9867 (portable) d. RSD: 1.05% at 10 ng/mL	(Stuttgart *et al.*, 2026)

Optical Biosensor

Optical biosensors are among the most widely used biosensors in biomedical research, drug discovery, clinical diagnostics, environmental monitoring, and food process control. These biosensors work by detecting changes in optical properties, such as light intensity, wavelength, or refractive index, that arise from interactions between analytes and identifying elements on the sensor surface. The main advantages of optical biosensors include high sensitivity, reliability, minimal sample preparation, and the ability to integrate into microsystems or chip-scale systems. In addition, optical biosensors can be developed using two main approaches: labeled and unlabeled methods. Among the various optical techniques, surface plasmon resonance (SPR), fluorescence, and photonics are widely used, especially for detecting target pathogens and biomolecules (Mobed and Hasanzadeh, 2022).

Despite their many advantages, optical biosensors also face several limitations. Some of them have relatively low selectivity, suboptimal reproducibility, and limited long-term stability, especially under complex environmental conditions. Therefore, the development of more portable, stable, and flexible substrate-based optical biosensors is the focus of future research. In the context of imprinting-based biosensors, SPR, fluorescence, and photonics technologies have been used to detect LPS. The use of synthetic monomers such as N-methacryloyl-L-histidine methyl ester (MAH) allows the formation of a recognition site that resembles natural antibodies, but with much better chemical and physical stability (Rajpal and Mishra, 2022).

More recent developments have led to the integration of electrochemical and optical transduction into a single platform. Stuttgart *et al.* (2025) developed a dual-mode electrochemical fiber-optic surface plasmon resonance

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(EC-FO-SPR) system for sensitive, real-time LPS detection. In this system, the gold-plated optical fibers function simultaneously as a Probe SPR and a working electrode, enabling both optical and electrochemical signals to be obtained from the same interface. The sensor surface is modified by Reduced Graphene Oxide (rGO) and 3-aminophenylboronic acid (PBA). The boronic acid group recognizes cis-diols in LPS through the formation of boronate esters, while changes in charge distribution on the electrode surface affect the transfer of the redox probe $[Fe(CN)_6]^{3-/4-}$ and result in changes in electrochemical signals. The sensor shows LODs of 0.049 ng mL^{-1} (SPR), 0.032 ng mL^{-1} (CV), and a significant increase to 4.76 pg mL^{-1} (DPV). In addition to its high sensitivity, the fiber-optic configuration makes the system more compact than prism-based EC-SPR systems and enables real-time monitoring of LPS adsorption.

Electrochemical Biosensors

Electrochemical biosensors detect changes in the electrical properties at the electrode interface resulting from the interaction between the LPS and the identifying element. Signals can be obtained through voltammetry, amperometry, impedance, or other electrochemical techniques. The platform offers the advantages of small sample requirements, relatively simple instrumentation, low cost, fast response, and easy integration with disposable electrodes such as screen-printed carbon electrodes (SPCEs). These advantages make electrochemical biosensors very attractive for the development of portable devices and on-site food safety. Electrochemical biosensors also require small sample volumes and can achieve very low detection limits, making them ideal for diagnostic and field-monitoring applications. However, their application still faces challenges, particularly regarding stability and selectivity. Enzyme-based sensors, although commercially successful, are susceptible to environmental changes. The use of functional nanomaterials such as AuNPs, AgNPs, and FeNPs can increase sensitivity, but often decrease selectivity in complex biological samples. Electrochemical immunochemical biosensors offer high selectivity, but are constrained by high cost, low antibody stability, and limited reusability (Li *et al.*, 2024b).

The next approach utilizes molecular recognition peptide-based peptides to improve LPS recognition selectivity. Kosikowska-Adamus *et al.* (2024) developed a gold electrode modified with a conjugate of the antimicrobial peptide, DAL-PEG-DK5-PEG-OH, which was covalently immobilized on the electrode surface. The interaction between the peptide and the LPS led to changes in the characteristics of the electrode interface that could be monitored using CV and EIS. In CV measurements, the sensor responded to LPS *E. coli* O26:B6 in the range of $5 \times 10^{-13} – 5 \times 10^{-4}$ g mL^{-1}, while EIS measurements yielded a linear range of $5 \times 10^{-21}–5 \times 10^{-14}$ g mL^{-1} with an LOD of 4.93×10^{-21} g mL^{-1}. The selectivity of recognition was also confirmed through the specific interaction between peptides and LPS. Interestingly, the EIS system showed that the platform not only provides high sensitivity in buffer solutions but also has the potential to analyze more complex biological matrices.

Magnetic Biosensor

Magnetic biosensors are *biosensing platforms* that utilize magnetic materials or nanoparticles as supporting elements for signal recognition and/or transduction. In LPS detection, magnetic materials such as magnetic beads or Fe_3O_4 nanoparticles can be combined with identifying elements, such as aptamers or MIPs, to capture LPS selectively. Magnetic properties enable the rapid separation and enrichment of targets from solution, while improving the efficiency of target-identifying element interactions. Other advantages of the magnetic approach include a relatively large surface area, faster binding kinetics, low sample consumption, and ease of separation and washing with magnetic fields.

Zuo *et al*. (2014) report a magnetic bead-based aptasensor system powered by two LPS-binding aptamers. The system overcomes diffusion limitations on the planar sensor surface and enables the separation of nonspecific targets using a magnetic field. The sensor can detect LPS in less than 1 minute, uses only 2 µL of sample volume, and can be regenerated up to 7 times. The system also demonstrates the ability to operate in the presence of interferences such as BSA, RNA, glucose, and sucrose, indicating its potential for analysis in complex environments. The magnetic approach can also be used as a direct transducer, rather than just as a separation medium. Stuttgart *et al.* (2026) developed a biosensor-based Giant magnetoimpedance (GMI) using a ferromagnetic amorphous microwire. The working principle is that LPS is captured by the system aptamer–LPS–magnetic bead; the presence of magnetic beads then induces local changes in the magnetic field that modulate the impedance of the magnetic wire. The sensor achieved a LOD of 1.8 pg mL^{-1}, while the prototype device achieved a LOD of 13.1 pg mL^{-1} with a linearity of $R^2 = 0.9867$.

Piezoelectric Biosensor

Piezoelectric biosensors take advantage of changes in the resonant characteristics of piezoelectric crystals caused by changes in mass or interfacial properties at their surfaces. One of the most common platforms is the

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Quartz Crystal Microbalance (QCM). When LPS or LPS-related reaction products interact with the sensor surface, changes in the mass and viscoelasticity of the interface cause shifts in resonance frequencies that can be used as analytical signals. Key advantages of the platform include label-free, real-time operation, sensitivity to small mass changes, and compatibility with complex samples (Li *et al*., 2024b). In addition, Over *et al*. (2017) developed a QCM-based method for LPS detection by monitoring viscosity changes during LAL enzymatic reactions. The sensor shows a linear range of 0.005–10 EU/mL with an LOD of 0.005 EU/mL. A fibrinogen layer is used to amplify the signal and shorten the response time, while the sensor can be regenerated in less than 10 minutes.

Another piezoelectric approach was developed by Thompson *et al*. (2015) using an Electromagnetic Piezoelectric Acoustic Sensor (EMPAS) based on quartz discs. The sensor surface is functionalized with polymyxin B (PMB) as the LPS-identifying ligand. This system allows real-time, label-free LPS detection in human blood plasma. In plasma spiked with LPS at 1000 pg/mL, there was a distinctly different resonance frequency change than in plasma without LPS. The system showed potential for detecting LPS in complex biological matrices.

MOLECULARLY IMPRINTED POLYMER

Molecularly Imprinted Polymer (MIP) is an identifying material that is synthesized with the help of a target molecule, which is referred to as a template, to generate a specific binding site within a polymer matrix. MIP is made through polymerization of functional monomers and cross-linking agents (crosslinkers) in the presence of the template, so that a complementary binding cavity is formed to the template in terms of shape, size, and distribution of functional groups. These cavities allow MIP to selectively recognize and rebind to target molecules or their analogs, resembling the mechanism of action of natural biological receptors such as antibodies (Belbruno, 2019; Basak *et al*., 2022). In contrast to biological identifying elements, MIP has the advantages of high chemical and thermal stability, resistance to extreme environmental conditions, and relatively low production costs, making it very attractive for sensor and chemical analysis applications (Erdem *et al*., 2025).

MIP Principles and Mechanisms

Molecular imprinting is a synthesis technique to produce synthetic polymers with specific recognition sites for the target analyte. The basic principle is the polymerization of functional monomers in the presence of the target molecule (Template), so that after the template is eliminated, binding cavities complementary to the target in terms of shape, size, and functional groups will form. These printed cavities enable MIP to selectively recognize and rebind target molecules, resembling the mechanism of action of natural biological receptors but with higher chemical and thermal stability (Belbruno, 2019; Erdem *et al*., 2025).

MIP synthesis generally involves five main components, namely Template, functional monomers, Crosslinker, solvents (porogens), and initiators (Basak *et al*., 2022). Templates and the monomer first form a pre-polymerized complex through supramolecular interactions, which are then "locked" by polymerization and cross-linking. Monomer–template interactions can be covalent, semi-covalent, or non-covalent, with the non-covalent approach being the most widely used as it is flexible and easy to apply. Once the polymer is formed, the template is extracted, resulting in micro- or nano-dimensional cavities that act as selective recognition sites (Cui *et al*., 2020; Basak *et al*., 2022).

In LPS detection, MIP serves as a synthetic identifying element that replaces antibodies. LPS, or a dummy template that resembles its chemical structure, was used during synthesis to form a cavity capable of selectively recognizing LPS. The mechanism of LPS recognition by MIP is primarily governed by electrostatic interactions, hydrogen bonds, and hydrophobic interactions, particularly between the negatively charged groups on lipid A and the positively charged monomers. Rebinding of LPS into imprinting cavities will trigger changes in the physicochemical properties of the sensor surface, which are then transduced into a measured signal, making MIP very promising for the development of stable, selective, and suitable LPS biosensors for food safety applications and biological products (Cui *et al*., 2020; Erdem *et al*., 2025).

The use of MIP for LPS detection offers several advantages over antibody-based approaches. MIP can be designed to recognize specific parts of LPS. MIP is more stable against variations in pH, temperature, and ionic strength, which are often obstacles in natural biomolecule-based biosensors. MIP can be used repeatedly without significant performance loss, making it suitable for electrochemical sensor applications that are portable and *on-site* (Stoica *et al*., 2021; Neagu *et al*., 2024).

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In general, MIP for LPS detection is combined with a wide range of platform transducers, especially electrochemical sensors, in which LPS binding to the imprinting cavity triggers changes in current, potential, or impedance signals. This approach offers great opportunities for developing selective, sensitive, stable, and economical LPS biosensors as an alternative to conventional methods such as the LAL assay and ELISA (Mobed and Hasanzadeh, 2022; Erdem *et al*., 2025).

Components and Strategies of MIP Synthesis as a Lipopolysaccharide Sensor System

The performance of MIP for LPS detection is greatly influenced by the selection of the template, functional monomers, crosslinker, synthesis method, and supporting materials. This becomes more complex because LPS, as a template, is an amphiphilic biomacromolecule of large size and structure, consisting of lipid A domains, a core oligosaccharide, and an O-antigen. Therefore, the MIP design must not only ensure cavity-shape suitability but also provide chemical interactions that correspond to the target functional group (Tothill and Abdin, 2017).

Functional monomers play a role in shaping the initial interaction with the template and in determining the chemical character of the identification site. Ogawa *et al*. (2012) used acryloyl lysine and acryloyl Phenylalanine to form a recognition site based on a combination of electrostatic and hydrophobic interactions against lipid A. Use of lipid A as the template was chosen because this domain is a biologically active part and has a phosphate group that can interact with the charged group on the monomer. The study shows that the introduction of LPS depends not only on the suitability of the cavity shape, but also on the combination of electrostatic and hydrophobic interactions.

The selection of monomers can be done experimentally or through computational approaches. For example, Altints *et al*. (2016) screened 21 monomers and selected itaconic acid, methacrylic acid, and acrylamide based on the strength of their interactions with endotoxins. Itaconic acid performs best with a LOD of 0.44 ± 0.02 ng mL^{-1} and a dissociation constant of about 5.24×10^{-10} M. The differences in performance among monomers show that the strength and location of monomer–template interactions can determine the affinity and selectivity of MIP.

Another approach uses a combination of monomers to adjust the amphiphilic properties of LPS. Ling *et al*. (2024) design monomers with hydrophilic and hydrophobic characteristics to interact with the polysaccharide and lipid components of LPS. Specifically, sulfonyl dopamine is used as a functional monomer and as a source of fluorescence signals, while 4-vinylpyridine plays a role in the formation of the recognition site. The approach yields a fluorescence sensor with an LOD of 0.46 µg L^{-1} and a linear range of 1 – 100 µg L^{-1}.

Crosslinker, on the other hand, serves to maintain the three-dimensional configuration of the imprinting site after the template is removed. The degree of cross-linking needs to be controlled because an overly rigid structure can inhibit the diffusion of LPS towards the binding site, whereas cross-linking that is too low can result in less stable, more easily deformed cavities. Therefore, cross-linking optimization must balance cavity stability and target accessibility. In some polydopamine-based systems, polymer networks can form via self-polymerization, thereby reducing the need for conventional crosslinkers (Ling *et al*., 2024; Lee *et al*., 2025).

The synthesis method also determines particle size, morphology, layer thickness, porosity, and imprinting-site accessibility. The solid-phase photopolymerization method was reported to be able to produce nanoMIPs with a size of about hundreds of nanometers and allow the material to be integrated on the sensor surface and produce high affinity to LPS and good MIP surface regeneration ability (> 30 cycles) (Abdin *et al*., 2015; Altints *et al*., 2016). Meanwhile, the sol–gel method offers an advantage in forming porous, chemically stable structures. Neagu *et al*. (2024) developed MIP microparticles using quaternary ammonium salts as a supporting component and showed that VBTAC-based MIP (vinylbenzyl trimethylammonium chloride) has a more effective LPS binding cavity than a non-imprinted polymer (NIP). For platform electrochemistry, this approach was developed into a Printable MIP/ZnO, which enables the integration of identifying materials with SPCE and simplifies sensor fabrication (Neagu *et al*., 2024).

The supporting material helps connect the MIP recognition function to the signal transduction process. In electrochemical sensors, materials such as ZnO or carbon substrates can increase the surface area, improve electron transfer, and provide a surface for MIP immobilization. In optical or photonic sensors, the supporting material can serve as an element that transforms the LPS binding process into changes in the refractive index, fluorescence, or distance between photonic structures. Thus, the supporting material not only serves as a mechanical matrix but also determines the sensor's signal sensitivity and stability.

The selection of MIP components should be viewed as an integrated design strategy. The monomers determine the type of chemical interaction; the crosslinker maintains cavity fidelity; the synthesis method controls

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morphology and site accessibility; and the supporting material links recognition to signal transduction. Optimization of these four aspects is necessary to achieve a balance between selectivity, rebinding capacity, binding kinetics, sensitivity, stability, and sensor capabilities used in complex matrices. Various MIP design strategies developed for LPS detection show that changes in material composition, identifying element, and transducer configuration can have different effects on sensitivity, selectivity, and sensor detection limits. The influence of the design strategy on the performance of LPS sensors is summarized in Table 3.

Table 3. The effect of MIP design strategy on LPS sensor performance.

Templates	Monomers/ identifying components	Cross-linking/ strategy	Synthesis method	Platform	Impact on performance	Ref.
Lipid A	A-Lys + A-Phe and polyacrylamide	Hydrogel network	Polymerization	Fluorescence	Electrostatic and hydrophobic interactions enhance selective recognition	(Ogawa *et al.*, 2012)
E. coli LPS	Functional monomer-based nanoMIP	Cross-linked nanoMIP	Solid-phase photopolymerization	SPR	High affinity/selectivity; LOD 15.6 ng mL^{-1}	(Abdin *et al.*, 2015)
E. coli LPS	YES, YES, AA	Cross-linked nanoMIP	Solid-phase photopolymerization	SPR	IA produces the best LOD of 0.44 ng mL^{-1}	(Altintas *et al.*, 2016)
P. aeruginosa LPS	Functionalized monomers	Cross-linked nanoparticle	Inverse microemulsion	Recognition	Nanoparticle morphology improves accessible binding sites	(Long *et al.*, 2016)
P. aeruginosa LPS	Sol–gel MIP	Silica network	Sol–frost	SPCE	MIP provides LPS recognition on the electrode surface	(Stoica *et al.*, 2021)
LPS	VBTAC/QAS	Sol–frost	Sol–frost	Recognition	VBTAC-MIP shows cavity formation and binding better than NIP	(Neagu *et al.*, 2024)
LPS	Hydrophilic + hydrophobic monomers	PDA network	Self-polymerization	Fluorescence	LOD 0.46 µg L^{-1}; real milk recovery 92.15 – 99.14%	(Ling *et al.*, 2024)
P. aeruginosa LPS	MIP & ZnO	Sol–frost	Printable/inkjet	SPCE	LOD 0.058 µM; response <1 min	(Neagu *et al.*, 2024)
S. typhimurium LPS	PDA & boronic acid functionality	PDA self-polymerization	Surface imprinting	DPV/SPCE	LOD 10 CFU mL^{-1}; real food application	(Lee *et al.*, 2025)

Development of MIP as a Lipopolysaccharide Sensor System

The MIP approach has developed as a promising synthetic receptor alternative for LPS detection. MIP is designed via a polymerization process using a target molecule as a template (Abdin *et al.*, 2015; Su and Ding, 2015), resulting in a specific recognition site in terms of form and chemical interactions. Compared with biological receptors such as antibodies, MIP has the advantages of high thermal and chemical stability, resistance to pH

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extremes, ease of regeneration, and lower production costs, making it ideal for portable sensor applications and On-site monitoring (Ayerdurai *et al*., 2023).

However, the development of MIP for LPS has particular challenges due to the complex structure of LPS, which is large in size, amphiphilic, and has a heterogeneous distribution of functional groups. The LPS molecule is composed of three main parts, namely lipid A, oligosaccharide nucleus, and O-antigen polysaccharide chain. The lipid A part has the highest structural conservation and is responsible for endotoxin activity, so it is often used as a primary target in MIP receptor design. Sulc *et al*. (2017) developed a strategy of dummy template imprinting using phospholipids as lipid A analogs to produce polymers that are selective against endotoxins. This approach is based on the similarity of the phosphate group and lipid chain structures between phospholipids and the A lipid portion of LPS, thereby allowing the formation of recognition sites through electrostatic, hydrogen-bond, and hydrophobic interactions.

Gavrila *et al.* (2020) developed an MIP film via the sol–gel method, using an organosilane monomer and LPS from *Pseudomonas aeruginosa* as templates to produce a biomimetic surface capable of capturing Gram-negative bacteria by recognizing LPS components on their cell membranes. The material shows that using LPS as a template not only enables the detection of endotoxin molecules but also supports the development of selective bacterial capture strategies.

Further approaches are developed by integrating MIP with various supporting materials and transducers. Çimen *et al.* (2021) developed an MIP nanofilm-based SPR sensor using poly(hydroxyethyl methacrylate)-N-methacryyl-L-histidine as an endotoxin recognition matrix. Integration of the MIP layer with the SPR transducer enables real-time detection of endotoxins via changes in the refractive index induced by LPS interactions with the imprinting cavity. The sensor shows detection capability over the range of 0.5 – 100 ng mL^{-1}, with an LOD of 0.023 ng mL^{-1}.

Another innovation is the development of ink-based sensors (ink-based MIP), in which silica gel-based MIP microparticles are formulated with ZnO nanoparticles and printed directly onto SPCE (Neagu *et al*., 2024). This sensor exhibits superior analytical performance with a detection limit of 0.058 µM, a response time of less than 1 minute, and high selectivity for LPS from *P. aeruginosa* compared to LPS from *Salmonella enterica* and *E. coli*. This approach is particularly relevant for the development of disposable sensors, which can be widely applied in food safety monitoring systems (Neagu *et al*., 2024).

In addition to optical and electrochemical transducer-based sensors, recent developments have also led to multifunctional nanoparticle-based MIPs. Wu *et al.* (2025) report an LPS-imprinted magneto-TiO_2 nanoparticle that employs a polydopamine layer as the imprinting matrix. The system combines specific LPS recognition with photocatalytic activity and magnetic separation, suggesting that the MIP not only acts as a recognition element but also serves as a multifunctional platform for endotoxin removal and control of pathogenic bacteria.

Recent developments suggest that MIP design is shifting from single-molecule-based recognition to biomimetic systems that mimic bacterial surface characteristics. Özsoylu *et al.* (2026) develop *biomimetic* Combination-based MIP surface imprinting and molecular imprinting using LPS as a representation of surface components of *Escherichia coli*. This strategy results in dual recognition through a combination of bacterial shape suitability and chemical interaction with LPS, thereby improving the ability to capture bacteria compared to conventional imprinting systems.

Although studies have shown significant advances in the design and performance of MIP-based LPS sensors, most testing is still conducted in model media such as buffer or aqueous solutions. Direct application to real food samples remains limited and requires special attention, particularly regarding matrix effects, surface fouling, and validation of selectivity against matrix interference in foodstuffs (Lee *et al*., 2025). Therefore, the integration of selective MIP engineering, comprehensive material characterization, and sensor testing on real food matrices is an important research direction going forward to ensure the practical relevance of LPS sensors in food safety systems (Lee *et al*., 2025). A comparison of MIP-based LPS methods and platforms/biosensors is presented in Table 4.

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Table 4. Comparison of MIP-based LPS sensor methods and platforms.

Types of Bacterial LPS	Platform/Biosensor	MIP Synthesis Method	Performance	Ref.
E. coli O111:B4	Optical SPR	solid-phase photopolymerization	LOD: 15.6 ng/mL	(Abdin *et al.*, 2015)
E. coli	Optical SPR	UV polymerization	Linear range: 0.5–100 ng/mL; LOD: 0.023 ng/mL; LOQ: 0.078 ng/mL	(Çimen *et al.*, 2021)
E. coli	Bacterial capture	photolithography-based surface imprinting	Imprinting factor: 6.5	(Özsoylu *et al.*, 2026)
Pseudomonas aeruginosa	SPCE–MIP electrochemical sensor	sol–gel imprinting	LOD: 16.7 µg/mL	(Stoica *et al.*, 2021)
Pseudomonas aeruginosa	MIP–ZnO ink-based printing SPCE	Soil–gel synthesis	LOD: 0.058 µM	(Neagu *et al.*, 2024)
Pseudomonas aeruginosa	Magneto-TiO_2	Surface imprinting	Qmax = 13.6 mg/g	(Wu *et al.*, 2025)
Salmonella typhimurium	Bacterial capture	sol–gel imprinting	LPS Reduction Efficiency: 90%	(Gavrilă *et al.*, 2022)
Salmonella sp.	SPCE–MIP electrochemical sensor	self-polymerization dopamine	LOD: 10 CFU mL^{-1}	(Lee *et al.*, 2025)

Application of MIP on Real Food Matrix

MIP-based sensors have demonstrated good LPS recognition capabilities in standard solutions and model media, but their application to real food matrices remains relatively limited. This condition is important to note because food components such as proteins, fats, polysaccharides, salts, and other organic compounds can affect the LPS binding process, diffusion to the imprinting site, electron transfer, and sensor signal stability. Therefore, testing on real matrices is needed to assess whether the sensor performance obtained in a standard solution is maintained under actual application conditions.

One application of MIP-LPS in food is the development of polydopamine-based electrochemical sensors (PDAs) that use LPS as a template to detect *Salmonella typhimurium*. The sensor shows a detection limit of 10 CFU mL^{-1} and a linear range of 10^2 – 10^8 CFU mL^{-1}, with determination coefficients of 0.80, 0.90, and 0.87, respectively, for the tested matrix (Lee *et al.*, 2025). In addition, the validation results show repeatability has an RSD of 3.31%, and reproducibility between batches is 2.14%. These results show that integrating MIP with SPCE has the potential to yield a Salmonella detection system that is fast and suitable for on-site applications.

Another approach is the development of a photonic crystal sensor using glycated albumin combined with LPS imprinting. The PC-G-alb-LPSimp sensor can detect E. coli LPS with an LOD of 0.76 ng mL^{-1} and a response time of approximately 6 minutes. Testing on real samples (milk, juice, river water, serum) showed recovery in the range of 90 – 100% (Murtaza *et al.*, 2020). Ling *et al.* (2024) developed a polydopamine-based MIP fluorescence membrane with a combination of hydrophilic and hydrophobic monomers to recognize the polysaccharide and lipid portions of the LPS. The sensor showed an LOD of 0.46 µg L^{-1} and a linear range of 1 – 100 µg L^{-1}. In milk samples, recovery reached 92.15 ± 3.63%, 99.14 ± 1.68%, and 94.13 ± 2.71% at spike concentrations of 40, 60, and 80 µg L^{-1}. These values indicate that MIP designs that account for the amphiphilic character of LPS can maintain recognition capabilities in complex matrices.

Although these results show good prospects, the number of studies that test MIP–LPS directly on real foods remains much smaller than the number that use pure LPS solutions or model media. Thus, claims regarding sensor sensitivity and selectivity need to be distinguished between performance in standard solutions and performance in real media. Further research needs to expand the types of food tested, incorporate variation in matrix composition, conduct systematic recovery and interference studies, and compare sensor results with reference methods such as LAL or microbiological methods. This approach is needed to ensure that the imprinting site remains accessible and produces a consistent response when the sensor is used under real conditions. Table 5 shows the application of MIP-LPS to various real food matrices.

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Table 5. Application of MIP-LPS on real food matrices.

Platform	Target	Real Samples	LOD	*Recovery*	Interference / Matrix	Validation	Ref.
Photonic crystal	*E. coli* LPS	Milk	0.76 ng mL^{-1}	94.4 – 99.8%	No significant matrix influence	Recovery, repeatability	(Murtaza *et al.*, 2020)
Photonic crystal	*E. coli* LPS	Orange juice	0.76 ng mL^{-1}	94.9 – 100.0%	No significant matrix influence	Recovery	(Murtaza *et al.*, 2020)
Fluorescence MIP membrane	LPS	Milk	0.46 µg L^{-1}	92.15 – 99.14%	Food matrix	Recovery, RSD	(Ling *et al.*, 2024)
MIP-LPS SPCE–DPV	*S. typhimurium*	Milk	10 CFU mL^{-1}	—	Baseline shift due to matrix components	R^2 = 0.90; repeatability RSD 3.31%; reproducibility RSD 2.14%	(Lee *et al.*, 2025)
MIP-LPS SPCE–DPV	*S. typhimurium*	Pork	10 CFU mL^{-1}	—	Baseline shift due to matrix	R^2 = 0.87; Cohen's kappa	(Lee *et al.*, 2025)
MIP-LPS SPCE–DPV	*S. typhimurium*	Tap water	10 CFU mL^{-1}	—	Baseline shift	R^2 = 0.80	(Lee *et al.*, 2025)

Characterization and Performance of MIP-Based Lipopolysaccharide Sensors

Material characterization is a crucial stage in the development of MIP-based LPS sensors because it determines the success of selective site imprinting and directly impacts sensor performance. Various characterization techniques include FTIR, SEM, BET, DLS, and TGA, as well as sensor performance tests with various principles according to the transducer used to confirm the chemical structure, morphology, surface properties, stability, and mechanism of transduction of MIP signals to LPS (Abdin *et al.*, 2015; Long *et al.*, 2016; Stoica *et al.*, 2021; Neagu *et al.*, 2024; Lee *et al.*, 2025).

Infrared spectroscopy (FTIR) is widely used to identify the functional groups in the MIP and to verify the success of the imprinting process. In MIP with LPS templates, changes in absorption band intensity associated with the –OH, –NH, –Si–O–Si, and –C=O groups are often associated with hydrogen and electrostatic interactions between functional monomers and LPS during polymerization (Sulc *et al.*, 2017; Stoica *et al.*, 2021; Neagu *et al.*, 2024; Wu *et al.*, 2025). In silica-based MIP, FTIR is used to identify the formation of Si–O–Si bonds from the sol–gel condensation process as well as the presence of organic groups that act as LPS recognition sites (Gavrila *et al.*, 2020). After removal of the template, the reduction or loss of the typical LPS band confirms the formation of specific recognition cavities, which underlie sensor selectivity. The difference in absorption bands between FTIR MIP and NIP spectra is directly correlated with increased LPS rebinding capacity (Neagu *et al.*, 2024).

The surface morphology of MIP is characterized using scanning electron microscopy (SEM) or transmission electron microscopy (TEM) and plays an important role in determining the accessibility of an imprinting site. The rough, porous surface enhances the diffusion of LPS into the recognition cavity, thereby accelerating the sensor response kinetics (Gavrilă *et al.*, 2022; Neagu *et al.*, 2024; Wu *et al.*, 2025; Özsoylu *et al.*, 2026). In MIP in the form of nanoparticles or microparticles, dynamic light scattering (DLS) is used to evaluate the size distribution and homogeneity of particles. Long *et al.* (2016) reported that MIP nanoparticles of uniform size exhibited a higher LPS-binding capacity than NIP, thereby improving the sensitivity of the detection system.

The Brunauer–Emmett–Teller (BET) analysis provides quantitative information on the specific surface area and pore-size distribution of the MIP. MIP with larger surface area and pore volume generally exhibit a higher LPS-binding capacity, due to an increase in the number of accessible imprinting sites (Long *et al.*, 2016; Neagu *et al.*, 2024). In SPCE-based electrochemical sensors, these porosity properties also affect the electron-transfer pathway, thus contributing to improved analytical signals. In addition, thermogravimetric analysis (TGA) is used

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to evaluate the thermal stability and composition of MIPs. Thermally stable MIP is important to ensure consistent sensor performance during storage, regeneration, and repeated use (Gavrila *et al.*, 2020; Neagu *et al.*, 2024).

In addition to structural characterization, sensor performance is evaluated based on analytical parameters such as sensitivity, linear range, detection limit (LOD), selectivity, response time, and regeneration capability. In nanoMIP-based SPR sensors, Abdin *et al.* (2015) report LPS detection of E. coli O111:B4 with a linear range of 15.6 – 500 ng/mL and an LOD of 15.6 ng/mL. Meanwhile, Çimen *et al.* (2021) achieved increased sensitivity by using an MIP nanofilm on SPR surfaces, with an LOD of 0.023 ng/mL.

On electrochemical platforms, signal changes generally arise from changes in electron transfer due to interactions between LPS and imprinting cavities on the electrode surface. Differences in current response between MIP and NIP after rebinding LPS reflect the contribution of imprinting sites to target recognition mechanisms (Stoica *et al.*, 2021; Neagu *et al.*, 2024; Lee *et al.*, 2025). In MIP/ZnO-based SPCE sensors, integrating MIP with conductive materials such as ZnO, conductive carbon, or metal nanoparticles can increase the active surface area and accelerate electron transfer. A decrease or increase in DPV current after LPS binding is associated with changes in electron-transfer resistance at the electrode surface, which is quantitatively used to determine the sensor's detection limit (LOD) and linear range (Neagu *et al.*, 2024).

Overall, the correlation between material characterization and sensor performance confirms that optimal MIP design depends not only on chemical composition, but also on controlled microstructure and nanostructure engineering. An integrated characterization approach is crucial to the development of reliable and applicable MIP-based LPS sensors for food safety systems. The characterization and performance of MIP-based LPS sensors are presented in Table 6.

Table 6. Comparison of characterization and performance of MIP-based LPS sensors.

Platform Sensor	Target	LOD	Linear Range	Characterization/ Performance Parameters	Ref.
SPR–nanoMIP	LPS *E. coli* O111:B4	15.6 ng mL^{-1}	15.6–500 ng mL^{-1}	DLS, FTIR, affinity analysis	(Abdin *et al.*, 2015)
MIP nanoparticles (optical/recognition-based)	LPS *P. aeruginosa*	–	–	SEM/TEM, DLS, rebinding test	(Long *et al.*, 2016)
Bacterial capture	*LPS S. typhimurium*	LPS Reduction Efficiency: 90%	-	FTIR, SEM, AFM, Cryo-TEM, XRD, TGA	(Gavrila *et al.*, 2020)
SPR-MIP	LPS *E. coli*	0.023 ng mL^{-1}	0.5 – 100 ng mL^{-1}	Contact angle, AFM, ellipsometry, SPR kinetic analysis	(Çimen *et al.*, 2021)
SPCE–MIP (electrochemistry)	LPS *P. aeruginosa*	~µg mL^{-1} (qualitative)	–	SEM, CV	(Stoica *et al.*, 2021)
MIP (material studies)	LPS *P. aeruginosa*	–	–	FTIR, SEM, BET, TGA	(Neagu *et al.*, 2023)
Printed SPCE (MIP/ZnO/CP)	LPS *P. aeruginosa*	0.058 µM	1 – 100 µM	FTIR, SEM, DLS, BET, TGA, CV, DPV	(Neagu *et al.*, 2024)
MIP sensors for food	*Salmonella* spp. (via LPS)	10 CFU mL^{-1}	10^2 – 10^8 CFU mL^{-1}	DPV, selectivity test	(Lee *et al.*, 2025)
Magneto-TiO_2	LPS *P. aeruginosa*	Qmax = 13.6 mg/g	Capturing efficiency : >70%	SEM/TEM, XPS, FTIR, zeta potential	(Wu *et al.*, 2025)
Bacterial capture	LPS *E. coli*	*Imprinting factor:* 6.5		AFM, SEM, XPS, contact angle, zeta potential	(Özsoylu *et al.*, 2026)

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Relationship between the Structure, Properties and Performance of MIP-based Lipopolysaccharide Sensors

The development of MIP-based LPS sensors requires a comprehensive understanding of the relationship between material structure, physicochemical properties, and sensor performance. Understanding the structure–property–performance (SPP) relationship is key to designing MIPs that are not only molecularly selective, but also capable of producing sensitive, stable, and reproducible sensor signals, especially for food safety applications. The structure–trait–performance relationship in MIP–LPS is not always linear. Increasing surface area and porosity can increase the number of available binding sites and shorten the LPS diffusion path, but structures that are too porous or too flexible can degrade the stability of the imprinting cavity. In contrast, overly dense polymer networks can maintain the cavity shape well but limit access to large LPS. Therefore, MIP design needs to optimize the balance between cavity accuracy, site accessibility, interaction strength, and mass transport.

The characteristics of LPS as amphiphilic biomacromolecules also make monomer selection an important factor. Weak interactions can result in low rebinding capacity, whereas strong interactions can inhibit template release and sensor regeneration. A combination of electrostatic and hydrophobic interactions is required for LPS recognition (Ogawa *et al.*, 2012). The structure–trait–performance relationship becomes increasingly complex because the imprinting must function in the presence of matrix interference. Lee *et al.* (2025) indicate that matrix components can cause deviations from baseline by altering sensor conductivity. At the molecular level, the structure of MIP is determined by the types of functional monomers and cross-linking agents, as well as the synthesis method. LPS targets are rich in phosphate, hydroxyl, and lipid groups; charged or polar monomers (e.g., amines, silanols, or quaternary cations) play an important role in forming non-covalent interactions during the imprinting process (Raetz and Whitfield, 2002; Long *et al.*, 2016). A study by Neagu *et al.* (2023) suggests that monomer selection and synthesis conditions directly affect imprinting cavity quality, as reflected in increased imprinting factor and capacity for rebinding LPS.

The imprinting structure formed will determine the physicochemical properties of the MIP, especially the specific surface area, pore size distribution, and thermal stability. The MIP with high surface area and porosity provides more active sites accessible to the LPS molecules, thereby improving the binding efficiency and sensor response speed. In addition, good thermal stability ensures the integrity of the MIP structure during regeneration or repeated use (Stoica *et al.*, 2021; Neagu *et al.*, 2023, 2024; Özsoylu *et al.*, 2026).

At the micro- and nano-scales, the surface morphology and particle size of MIP have a direct effect on the kinetics of MIP–LPS interactions. MIP in the form of nanoparticles or porous layers with a rough surface provides a shorter diffusion distance and increases the rate of rebinding LPS. In addition, MIP nanoparticles with a uniform size distribution exhibit higher binding affinity than NIP, indicating that particle-size control is an important parameter for optimizing sensor performance (Long *et al.*, 2016; Neagu *et al.*, 2023).

At the sensor level, the integration of MIP with the transducer determines how molecular interactions are translated into analytical signals. In optical sensors, changes in refractive index, fluorescence intensity, or resonance are used as indicators of LPS bonds. In electrochemical sensors, changes in electron-transfer resistance or surface capacitance serve as quantification parameters. Therefore, optimization focuses not only on MIP synthesis, but also on the selection of supporting materials and transduction platforms.

In SPCE–MIP-based electrochemical sensors, the presence of an imprinting that effectively causes a significant change in the electron transfer resistance after LPS binding (Stoica *et al.*, 2021; Neagu *et al.*, 2023; Lee *et al.*, 2025). Neagu *et al.* (2024) showed that combining a porous MIP with ZnO nanoparticles increased electron-transfer pathways and resulted in a low LOD (0.058 μM) and a very fast response time (<1 minute). In contrast, MIPs with poorly controlled structures or low porosity tend to exhibit weak sensor response and limited selectivity.

In the context of food pathogen detection, MIP with an optimized structure is not only able to detect LPS or target bacteria with high sensitivity, but also maintain good performance on real food matrices despite interference in MIP structure optimization at the synthesis stage, which is a determining factor for the successful application of MIP-based LPS sensors in food safety systems (Murtaza *et al.*, 2020; Ling *et al.*, 2024; Lee *et al.*, 2025). The structure–trait–performance relationship in MIP–LPS confirms that sensor performance is inseparable from its material engineering. A design approach that integrates monomer selection, control of porosity and morphology, and appropriate transducers is an essential strategy for producing sensitive, selective, and applicable MIP-based LPS sensors.

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CONCLUSION

This review shows that LPS is an important target molecule for monitoring Gram-negative bacterial contamination due to its high stability and biological activity. MIP offers a potential synthetic receptor alternative due to its chemical and thermal stability, relatively low production costs, and controllable molecular regeneration and recognition capabilities. The performance of MIP–LPS is strongly influenced by the selection of templates, functional monomers, cross-linking strategies, synthesis methods, morphology, porosity, and type of supporting material. These factors together determine the accessibility of the imprinting site, rebinding capacity, selectivity, binding kinetics, and signal transduction efficiency. A variety of platforms have been developed, including optical, fluorescence, photonic, and electrochemical platforms. The SPCE-based electrochemical biosensor platform shows strong prospects for portable applications, with a simple configuration, low sample requirements, and compatibility with mass fabrication. MIP-based SPCE performance testing for LPS detection in standard solutions or model media, as well as in real food matrices (milk, orange juice, water, and meat), yields promising recovery and validation values. The effects of the matrix, fouling, stability, reproducibility, and validation on reference methods still need to be studied more systematically. Thus, the next direction of research focuses not only on improving sensitivity and lowering LOD, but also on sensor validation in real food matrices, more comprehensive interference testing, standardization of sample preparation, evaluation of stability and regeneration, and comparison with reference methods such as LAL and microbiological methods. This approach is needed so that MIP–LPS can evolve from a proof-of-concept system to a biosensing platform that can be applied on-site in food safety systems.

CONFLICT OF INTEREST

There are no conflicts of interest in this article.

AUTHOR CONTRIBUTION

ZD: Conceptualization, Methodology, Software, Data Analysis, Writing – Original Draft; FK: Conceptualization, Writing – Original Draft, Supervision; AK: Writing – Review and Editing, Supervision.

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DECLARATION OF GENERATIVE AI

During the preparation of this work, the author used Generative AI, ChatGPT, and LM Notebook to tidy up, simplify, and filter the manuscript in terms of both writing and essence, as well as to generate ideas for creating image summaries and graphical abstracts. After using these tools/services, the author reviews and edits the content as needed and takes full responsibility for the content of the published articles.

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