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Biosensors for rapid detection of *Salmonella* in food: A review

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Abstract

Salmonella is one of the main causes of foodborne infectious diseases, posing a serious threat to public health. It can enter the food supply chain at various stages of production, processing, distribution, and marketing. High prevalence of *Salmonella* necessitates efficient and effective approaches for its identification, detection, and monitoring at an early stage. Because conventional methods based on plate counting and real-time polymerase chain reaction are time-consuming and laborious, novel rapid detection methods are urgently needed for in-field and on-line applications. Biosensors provide many advantages over conventional laboratory assays in terms of sensitivity, specificity, and accuracy, and show superiority in rapid response and potential portability. They are now recognized as promising alternative tools and one of the most on-site applicable and end user–accessible methods for rapid detection. In recent years, we have witnessed a flourishing of studies in the development of robust and elaborate biosensors for detection of *Salmonella* in food. This review aims to provide a comprehensive overview on *Salmonella* biosensors by highlighting different signal-transducing mechanisms (optical, electrochemical, piezoelectric, etc.) and critically analyzing its recent trends, particularly in combination with nanomaterials, microfluidics, portable instruments, and smartphones. Furthermore, current challenges are emphasized and future perspectives are discussed.

KEYWORDS
biosensor, electrochemical, food, optical, piezoelectric, *Salmonella*

Abbreviations: 3D, three-dimensional; AgNPs, silver nanoparticles; AI, artificial intelligence; ALP, alkaline phosphatase; AMPs, antimicrobial peptides; AuNPs, gold nanoparticles; AuNRs, gold nanorods; CANARY, Cellular Analysis and Notification of Antigen Risks and Yields; CDC, Centers for Disease Control and Prevention; cDNA, complementary DNA; DPV, differential pulse voltammetry; ELISA, enzyme-linked immunosorbent assay; FAM, carboxyfluorescein; Fc, fragment crystallizable; FRET, Förster resonance energy transfer; GO, graphene oxide; HRP, horseradish peroxidase; Ig, immunoglobulin; IMBs, immunomagnetic beads; IMS, immunomagnetic separation; ISO, International Organization for Standardization; LAMP, loop-mediated isothermal amplification; LOD, limit of detection; MNPs, magnetic nanoparticles; MOF, metal–organic framework; MRS, magnetic relaxation switching; NAEBs, nanoaggregate-embedded beads; PCR, polymerase chain reaction; QCM, quartz crystal microbalance; QCM-D, quartz crystal microbalance with dissipation monitoring; QDs, quantum dots; QMRA, quantitative microbial risk assessment; RCA, rolling circle amplification; SELEX, Systematic Evolution of Ligands by Exponential Enrichment; SERS, surface-enhanced Raman scattering; SPR, surface plasmon resonance; ssDNA, single-stranded DNA; TMB, 3,3′,5,5′-tetramethylbenzidine; TMDs, transition metal dichalcogenides; UCNPs, upconversion nanoparticles; VBNC, viable but nonculturable; WHO, World Health Organization.

1 | INTRODUCTION

Foodborne diseases caused by pathogenic bacteria have become a noticeable threat to human health and global economy (Campuzano, Yáez-Sedeño, & Pingarrón, 2017; Chen, Picard, Wang, & Nugen, 2017; Ravindranath, Mauer, Deb-Roy, & Irudayaraj, 2009; Reta, Saint, Michelmore, Prieto-Simon, & Voelcker, 2018). Among foodborne pathogens, *Salmonella* is one of the most common pathogens associated with foodborne diseases and eventual deaths (Centers for Disease Control and Prevention [CDC], 2019). *Salmonella* is a species of rod-shaped Gram-negative bacteria belonging to the family of Enterobacteriaceae (Ansari, Yazdian-Robati, Shahdordizadeh, Wang, & Ghazvini, 2017; Silva, Magalhães, Freire, & Delerue-Matos, 2018). It contains two main species, *Salmonella enterica* and *Salmonella bongori* with more than 2,500 serotypes, and all of these serotypes can cause disease in humans (World Health Organization [WHO], 2018) People may get infected with *Salmonella* through the consumption of contaminated food with some symptoms such as diarrhea, fever, stomach cramps, nausea, vomiting, and headache (Jasim et al., 2019). WHO claims that *Salmonella* is one of the four major global causes of diarrheal diseases and one of the microorganisms in which some resistant serotypes have emerged (WHO, 2018). In the United States, *Salmonella* is also the number one of top four bacterial pathogens that cause foodborne illnesses, apart from *Clostridium perfringens*, *Campylobacter*, and *Staphylococcus aureus* (CDC, 2020a). According to CDC, *Salmonella* is estimated to cause 1.35 million infections with 26,500 hospitalizations and 420 deaths in the United States every year (CDC, 2020b). In an outbreak between March 2013 and July 2014, over 600 individuals were infected with *Salmonella* Heidelberg, causing a recall of over 23,000 units of rotisserie chicken products (CDC, 2014).

Considering its high prevalence, extremely low infection limits (1 CFU), and potential hazards, the limits of *Salmonella* in food regulated by laws have been tightened over the years (Silva et al., 2018). For example, Commission Regulation (EC) No. 2073/2005 (amended by No. 1441/2007) requires the absence of *Salmonella* in a defined amount of a given food product (10 or 25 g) placed on the market during the shelf life.

Current routine methods for *Salmonella* detection include culture methods, nucleic acid-based methods, and enzyme-linked immunosorbent assay (ELISA) (details are given in the Supporting Information). However, some of them require highly trained personnel and sophisticated instruments, and some are time-consuming and laborious with false positive or negative results (Ansari et al., 2017). Therefore, there is a continuous need for the development of sensitive, specific, and reliable methods for rapid detection of *Salmonella* in food.

Biosensors offer many advantages over laboratory-based assays, including high sensitivity, specificity, and accuracy, and show superiority in rapid response, low cost, potential portability, and possible in situ applications (Rotariu, Lagarde, Jaffrezic-Renault, & Bala, 2016). Therefore, they are recognized as promising alternative tools for rapid detection of *Salmonella* in food. In recent years, we have witnessed a flourishing of research studies in this field with numerous publications. Several reviews regarding this subject also have been published with specific focuses on nanomaterials (Pashazadeh et al., 2017), electrochemical signal readout (Cinti, Volpe, Piermarini, Delibato, & Palleschi, 2017; Silva et al., 2018), and aptamer recognition (Ansari et al., 2017). However, to the best of our knowledge, there is no systematical review on biosensors for *Salmonella* detection in food. Therefore, this review aims to give a comprehensive overview on *Salmonella* biosensors (Figure 1), with in-depth discussion on different bioreceptors and various transducers. The recent trends, current challenges, and future perspectives are also reviewed and outlined.

2 | BIORECEPTORS USED IN *Salmonella* BIOSENSORS

Biosensor is "a self-contained integrated device which is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element which is in direct spatial contact with a transducer," as defined by the International Union of Pure and Applied Chemistry (IUPAC) (Kirsch, Siltanen, Zhou, Revzin, & Simonian, 2013). They have been widely flourished for *Salmonella* detection in recent several years. Bioreceptors are one of the most crucial components of a *Salmonella* biosensor to make specific and sensitive detection possible. In principle, any biomolecule/assembly that can recognize the target is able to be used as a bioreceptor (Bazin, Tria, Hayat, & Marty, 2017). Among all types of bioreceptors, antibodies, aptamers, bacteriophages, antimicrobial peptides (AMPs), and nucleic acid probes are most common for *Salmonella* recognition. A detailed comparison of these five bioreceptors is listed in Table 1.

2.1 | Antibodies

Antibodies are large proteins produced by the immune system that can bind to their targets with both extremely high affinity and specificity (Crivianu-Gaita &

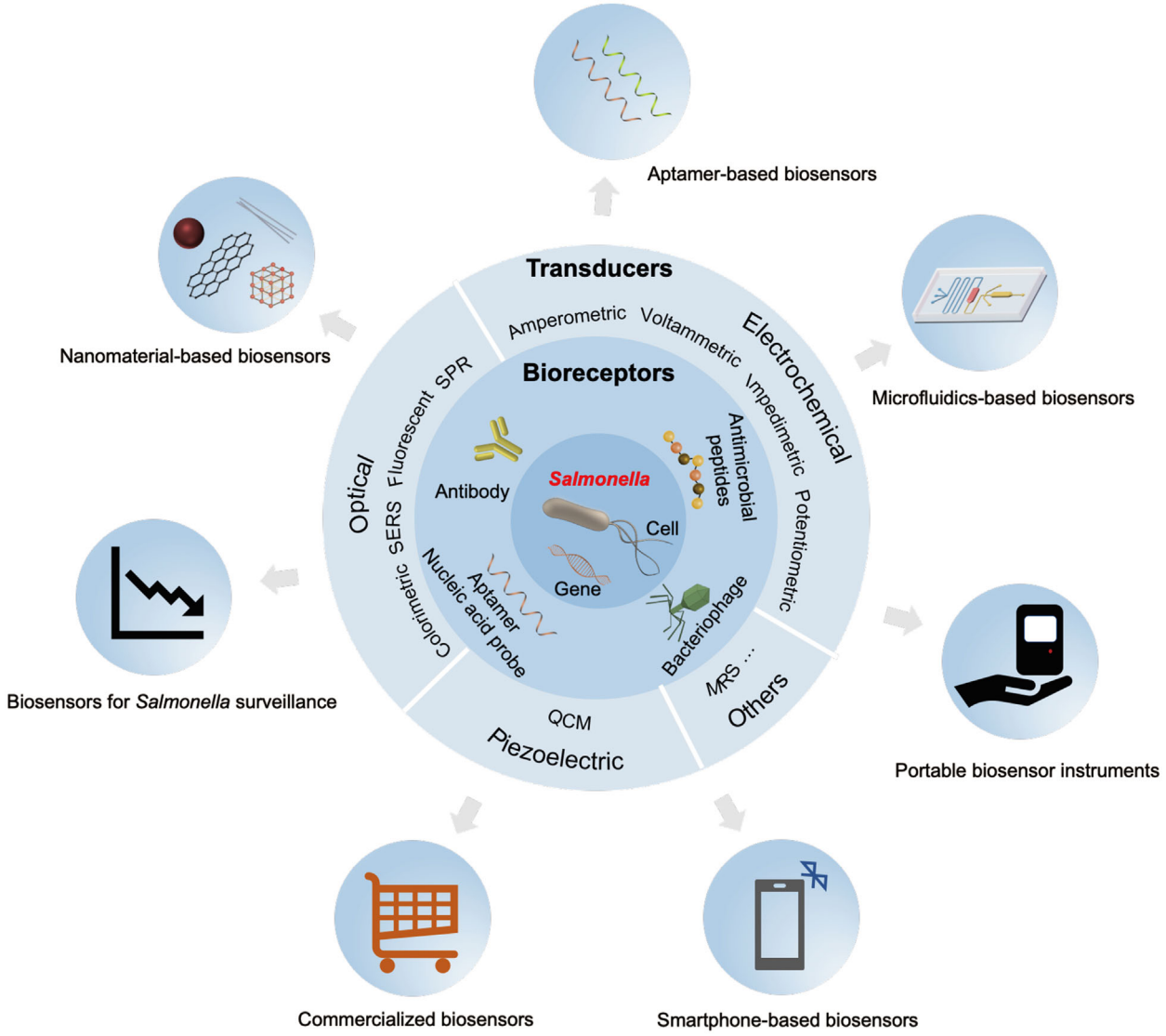

FIGURE 1 Schematic overview of biosensors for *Salmonella* detection and its recent trends

TABLE 1 Comparison of different bioreceptors for *Salmonella* recognition

Bioreceptor	Advantages	Limitations
Antibody	High affinity and specificity	Poor stability; high cost; laborious production
Aptamer	High stability, affinity, and specificity; ease of synthesis and modification; low cost	Sensitive to nuclease attack
Bacteriophage	Potential for discrimination of live and dead bacterial cells; low cost	Low capture efficiency when drying; potential lysis of bacterial cells during the detection
AMPs	High affinity and stability; simple synthesis; low cost	Poor specificity
Nucleic acid probe	High stability; ease of synthesis and modification	Mainly restricted to genosensors

Abbreviation: AMPs, antimicrobial peptides.

Thompson, 2015). They can be classified into five main classes: immunoglobulin (Ig) A, IgD, IgE, IgG, and IgM based on their heavy chains with IgG as the predominant class of antibodies used in the field of biosensing (Crivianu-Gaita & Thompson, 2016). A typical IgG molecule is composed of two heavy chains and two light chains that form a characteristic Y-shaped structure (Conroy, Hearty, Leonard, & O'Kennedy, 2009). It also contains

two regions: the fragment crystallizable (Fc) region and the fragment antigen-binding region for immune response activation and antigen recognition, respectively (Furst & Francis, 2019).

As one of the "gold standard" recognition elements, antibodies are prominently used in *Salmonella* biosensors due to their unique properties, especially high affinities for their targets. However, the production of high-quality antibodies always requires isolation from immunized mammals or mammalian cells, which is expensive, time-consuming, and laborious (Bruce & McNaughton, 2017).

To overcome these limitations, nanobody, a small protein (~15 kDa) is also developed for *Salmonella* recognition. It consists of a single heavy-chain variable domain and can be mass produced based on standard microbial expression systems (Jayan, Pu, & Sun, 2020). He et al. (2020) isolated a nanobody after biopanning of a constructed nanobody library and demonstrated its feasibility for *Salmonella* Enteritidis detection using a conventional ELISA test, achieving a limit of detection (LOD) of 1.4×10^5 CFU/mL. However, the development of nanobody for *Salmonella* biosensing is immature, and to the best of our knowledge, no relevant biosensor has been reported, as it is always challenging to prepare immune libraries and select desirable nanobodies.

2.2 | Aptamers

Aptamers are single-stranded DNA (ssDNA) or RNA obtained by an in vitro selection process called Systematic Evolution of Ligands by Exponential Enrichment (SELEX), first reported by Gold and Szostak in the early 1990s (Park, 2018; Robati et al., 2016). Due to the specific three-dimensional (3D) structures, aptamers can bind to a variety of targets from small molecules to whole cells with high affinity and specificity (Song, Wang, Li, Zhao, & Fan, 2008). They have gradually become powerful tools for target recognition with incomparable inherent advantages such as physical and chemical stability, ease of synthesis and modification, nontoxicity, structure memory, and long half-life (Shahdordizadeh et al., 2017). Aptamers have been used as alternatives to conventional antibodies for the fabrication of various types of biosensors for *Salmonella* detection (Bayramoglu, Ozalp, Dincbal, & Arica, 2018; Duan et al., 2018; Li et al., 2018; Srinivasan, Ranganathan, DeRosa, & Murari, 2018). More importantly, as single oligonucleotides, they can hybridize with their complementary DNA (cDNA) and may undergo significant conformational changes in the presence of the targets, offering more flexibility in the design of novel biosensors. Due to the outstanding proprieties and great potential, aptamer-based biosensors, namely, aptasensors, for *Salmonella* detection are emphasized particularly in Section 4.2.

2.3 | Bacteriophages

Bacteriophages are bacteria virus that can infect their host bacteria and utilize the "machinery" of the host cells to conduct replication cycles (Bhardwaj, Bhardwaj, Mehta, Kim, & Deep, 2017; Chen, Alcaine, Jiang, Rotello, & Nugen, 2015; Yue et al., 2017). As novel bioreceptors, they offer several advantages including high specificity to host bacteria, tolerance to harsh environmental conditions, and capability to reproduce large quantities of progeny phages (Farooq, Yang, Ullah, & Wang, 2018). Because bacteriophages can only replicate in a viable host, phage-based biosensors have the potential to distinguish between live and dead bacterial cells (Chen, Alcaine, et al., 2015), which make them unique over other bioreceptor-based sensing methods for *Salmonella* detection. This interesting property was demonstrated by Fernandes et al. (2014) who used a broad spectrum virulent phage (PVP-SE1) as a bioreceptor to distinguish viable and viable but non-culturable (VBNC) *Salmonella* cells from the dead ones. Furthermore, various types of bacteriophages have been reported for *Salmonella* biosensing, including M13, E2, PRD1, and P22 (Chai et al., 2013; Lakshmanan et al., 2007; Laube, Cortés, Llagostera, Alegret, & Pividori, 2014; Li et al., 2010; Mack et al., 2017; Niyomdecha et al., 2018; Olsson, Wargenau, & Tufenkji, 2016; Park, Park, Wikle, & Chin, 2013). Some bacteriophage-based platforms are also being commercialized for *Salmonella* detection. One example is Sample6 DETECT System (Sample6 Technologies, Inc., Boston, MA, USA). It utilizes engineered bacteriophages to specifically interact with the target bacteria including *Salmonella*, and cause the bacteria express luminescent enzymes. This platform enables highly sensitive detection of foodborne pathogens with results comparable to polymerase chain reaction (PCR) and immunoassays.

The big challenge of bacteriophages as bioreceptors is that bacteriophages may lose their capture activity when they are dry (Singh et al., 2010). Moreover, lysis of the host bacterial cells during the detection can result in a decrease in measured signals (Jayan et al., 2020; Templier, Roux, Roupioz, & Livache, 2016). Nevertheless, phage-based biosensors hold the promise to address one of the key challenges facing the researchers in this field that live *Salmonella* is always hard to be discriminated rapidly and accurately. More innovative and feasible demonstration of this type of biosensors would be highly expected in the near future.

2.4 | Antimicrobial peptides

AMPs are short peptide fragments (12 to 50 amino acid residues), existing in multiple niches in nature (Qiao, Lei, Fu, & Li, 2017b). They are important components of innate immune system that provide the first line of defense against invading pathogens (Patel & Akhtar, 2017). AMPs can attach to the membrane of bacteria mainly via electrostatic and hydrophobic interactions (Qiao, Lei, Fu, & Li, 2017a). The ease of synthesis and modification, low cost, and intrinsic stability in harsh conditions render AMPs promising candidates as bioreceptors for *Salmonella* detection. A multi-AMP array was developed for *Escherichia coli* O157:H7 and *Salmonella* Typhimurium detection based on both direct and sandwich formats (Kulagina, Shaffer, Anderson, Ligler, & Taitt, 2006). Five types of AMPs—Polymyxin B, Polymyxin E, Magainin I, Cecropin A, and Parasin—were tested with LODs ranging from 10^5 to 5×10^6 cells/mL for *S*. Typhimurium. Mannoor, Zhang, Link, and McAlpine (2010) immobilized semiselective magainin I AMPs on microcapacitive electrode arrays and demonstrated its recognition capabilities toward both *E. coli* and *Salmonella*.

The high affinity of AMPs toward their target bacteria makes AMPs-based biosensors function well even with low cell concentrations. The main deficiency of AMPs as bioreceptors for *Salmonella* recognition is their semiselectivity that they always fail to differentiate *Salmonella* from other pathogenic bacteria. Moreover, the mechanisms of AMPs' action are still unclear, which hinders their wide application (Qiao, Fu, Lei, & Li, 2020).

2.5 | Nucleic acid probes

Genosensors based on the detection of the specific nucleic acids in bacterial cells are also extensively studied for *Salmonella* detection. They rely on the natural specificity and affinity of ssDNA/RNA to its commentary strand (Paniel, Baudart, Hayat, & Barthelmebs, 2013). In these biosensors, nucleic acid probes play an essential role for target recognition. In most cases, DNA extracted from *Salmonella* cells is denatured and exposed to the DNA probes. Then hybridization occurs at the sensor surface and induces a measurable signal (Vanegas, Gomes, Cavallaro, Giraldo-Escobar, & McLamore, 2017). Das et al. (2014) modified ssDNA probes on the surface of the screen-printed electrode to target the Vi genes from *Salmonella* Typhi with a LOD of 50 pM. In order for higher sensitivities, various DNA amplification strategies such as rolling circle amplification (RCA) (Zhu et al., 2014) and PCR (Luo et al., 2014; Ye et al., 2019) are commonly integrated into genosensors.

Nucleic acid probes are ease of synthesis and modification, thermally stable, and flexible. However, they are always restricted to genosensors. The main challenges of genosensors may include laborious extraction and fragmentation of the genomic DNA, as well as the requirement of signal amplifications.

3 | BIOSENSORS WITH DIFFERENT TRANSDUCES FOR DETECTION OF *Salmonella* IN FOOD

In recent years, biosensors for *Salmonella* detection with the aforementioned bioreceptors and different signal transducing mechanisms have attracted ever-increasing interest. Among them, some have been validated in food matrices and some are potential for food samples. In this section, various biosensors for *Salmonella* detection classified by transducers are discussed with a specific focus on electrochemical, optical, and piezoelectric biosensors.

3.1 | Electrochemical biosensors

Electrochemical biosensors are one of the most common biosensors for *Salmonella* detection due to their privileged merits of high sensitivity, low cost, and miniaturization potential (Silva et al., 2018). Based on different transducers, they can be classified into amperometric, voltammetric, impedimetric, and potentiometric biosensors (Figure 2). Table 2 (2015 to 2020) and Table S1 (before 2015) summarize the electrochemical biosensors for *Salmonella* detection.

3.1.1 | Amperometric biosensors

Amperometric biosensors measure the current changes on the application of a constant potential during a fixed period of time (Riu & Giussani, 2020). Over the past several decades, they have played an important role in rapid biosensing of *Salmonella* in food.

Previously, our group measured phenol concentrations using a tyrosinase carbon paste electrode to indirectly detect *S*. Typhimurium with a LOD of 5×10^3 CFU/mL in chicken carcass wash water within 2.5 hr (Che, Li, Slavik, & Paul, 2000). *Salmonella* Typhimurium cells were sandwiched between immunomagnetic beads (IMBs) and alkaline phosphatase (ALP)-labeled antibodies. ALP catalyzed the conversion of phenylphosphate substrate to phenol that was further quantified using the tyrosinase carbon paste electrode. Later, we modified the approach with a bienzyme (tyrosinase and horseradish peroxidase [HRP]) electrode, achieving an

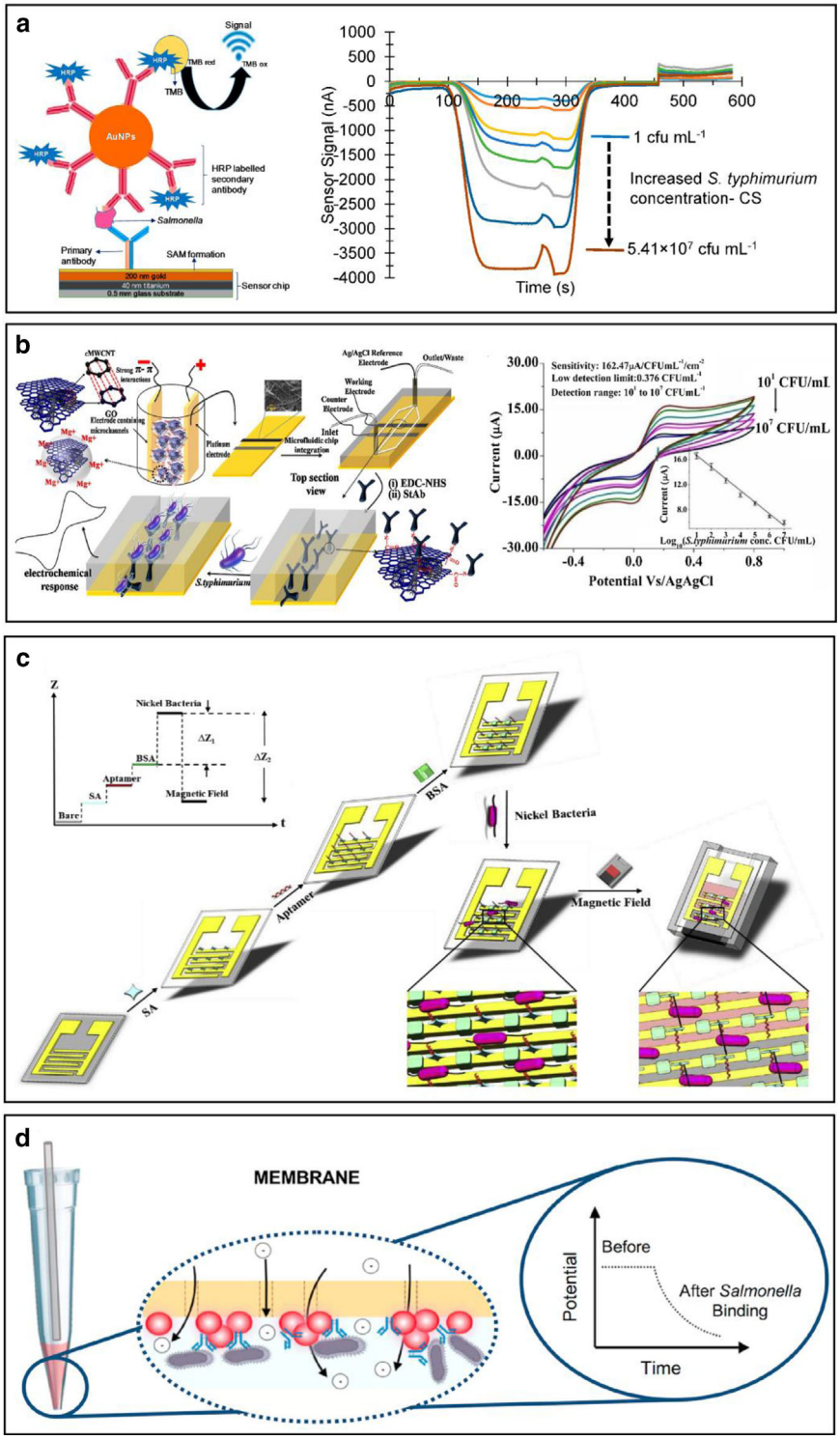

FIGURE 2 Examples of electrochemical biosensors for *Salmonella* detection. (a) An amperometric biosensor based on horseradish peroxidase with gold nanoparticles for signal amplification (Savas et al., 2018). (b) A voltammetric biosensor combined with a microfluidic device (Singh et al., 2018). (c) An aptamer-based impedimetric biosensor using nickel nanowire bridge (Wang, Huo, Qi, et al., 2020). (d) A label-free potentiometric biosensor (Silva, Magalhaes, et al., 2019). Figures 2b, 2c, and 2d are reprinted with permission from Elsevier B.V.

improved LOD of 4.2×10^2 CFU/mL (Yang, Ruan, & Li, 2001). Different from those indirect detection principles, subsequent researches focused on a direct sandwich ELISA format for *Salmonella* detection. Salam and Tothill (2009) immobilized antibodies on the surface of a screen-printed gold working electrode to specifically capture *S.* Typhimurium. A sandwich structure was formed after the introduction of HRP-labeled antibodies. Taking 3,3′,5,5′-tetramethylbenzidine (TMB)/H_2O_2 as the enzyme mediator/substrate system, this approach allowed sensitive detection of *S.* Typhimurium at approximately 21 CFU/mL.

To further improve the detection sensitivity, Liébana et al. (2009) incorporated PCR into an amperometric biosensor with an extremely low LOD of 1 CFU/mL in broth and diluted milk without any pretreatment.

TABLE 2 Summary of the electrochemical biosensors reported for *Salmonella* detection (2015 to 2020)

Serotype	Label	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
Amperometric:							
S. Typhimurium	HRP	Antibody	Milk	10 to 5×10^4 CFU/mL	5 CFU/mL	~10 min	Lu, Pang, et al. (2017)
S. Typhimurium	HRP	Antibody	Skimmed/whole milk	–	10 CFU/mL	125 min	Alexandre et al. (2018)
S. Typhimurium	HRP	Antibody	Whole milk	–	538 and 291 CFU/mL for MMPs and MNPs in whole milk	1 hr	Brandão et al. (2015)
S. Typhimurium	HRP	Antibody	–	–	10 CFU/mL	125 min	Melo et al. (2018)
S. Typhimurium	AuNPs–HRP	Antibody/DNA probe	–	1 to 5.41×10^7 CFU/mL for the immunosensor and 2 to 20 nM for the genosensor	1 CFU/mL for the immunosensor and 0.94 nM for the genosensor	12 min for the immunosensor	Savas et al. (2018)
Voltammetric:							
S. Typhimurium	–	Aptamer	Chicken meat	10 to 10^8 CFU/mL	10 CFU/mL	10 min	Muniandy et al. (2017)
S. Typhimurium	–	Antibody	–	10 to 10^7 CFU/mL	0.376 CFU/mL	–	Singh et al. (2018)
Salmonella spp.	–	DNA probe	–	10 to 400 pM	2.1 pM	–	Tabrizi and Shamsipur (2015)
S. Typhimurium	–	Aptamer	Chicken meat	10 to 10^8 CFU/mL	10 CFU/mL	≤1 hr	Muniandy et al. (2019)
S. Typhimurium	–	Aptamer	Chicken meat	10 to 10^8 CFU/mL	10 CFU/mL	10 min	Appaturi et al. (2020)
S. Typhimurium	Methylene blue	Aptamer	Raw chicken	10 to 10^6 CFU/mL	10 CFU/mL	–	Dinshaw et al. (2017)
Salmonella spp.	AuNPs–ALP	Aptamer	Milk	20 to 2×10^6 CFU/mL	20 and 200 CFU/mL in pure culture and milk	4 hr	Li et al. (2016)
S. Pullorum and *S.* Gallinarum	HRP	Antibody	Chicken	10^2 to 10^6 CFU/mL	32 CFU/mL	–	Fei, Dou, and Zhao (2015a)
S. Typhimurium	ALP	DNA probe	–	10 to 10^7 CFU/mL	1,000 copies of genomic DNA	–	Yan et al. (2016)
S. Pullorum and *S.* Gallinarum	HRP	Antibody	Eggs and chicken meat	10^4 to 10^9 CFU/mL	3×10^3 CFU/mL	24 hr	Fei, Dou, and Zhao (2015b)
S. Typhimurium	HRP	Antibody	Tap water and milk	10 to 10^5 CFU/mL	5 CFU/mL	4 hr	Xiang et al. (2015)
S. enterica	ALP	DNA probe	–	5 to 250 nM	2.4 nM	–	Barreda-García, Miranda-Castro, de-los-Santos-Álvarez, and Lobo-Castañón (2018)

(Continues)

TABLE 2 (Continued)

Serotype	Label	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium	ALP	Aptamer	Bottled mineral water and milk	20 to 2×10^8 CFU/mL	16 and 18 CFU/mL in pure culture and milk	–	Ge et al. (2018)
S. Typhimurium	AuNPs loaded with thionine	Aptamer	Milk	25 to 500 CFU/mL	13 CFU/mL	–	Zong et al. (2016)
S. Typhimurium	MWCNTs–methylene blue-modified magnetic particles	Antibody	Milk	10 to 10^6 CFU/mL	7.9 and 17.3 CFU/mL in pure culture and milk	40 min	Ngoensawat, Rijiravanich, Surareungchai, and Somasundrum (2018)
S. Typhimurium	Ferrocene	DNA probe	Spring water	1 to 5×10^3 fM	0.67 fM	~3 hr	Guo, Wang, et al. (2017)
S. Typhimurium	Methylene blue	Aptamer	Milk	72 to 7.2×10^6 CFU/mL	28 CFU/mL	–	Pei et al. (2017)
S. Pullorum	rGO/AuNPs	Antibody	Chicken livers	10^2 to 10^6 CFU/mL	89 CFU/mL	–	Fei et al. (2016)
Salmonella spp.	CdS	DNA probe	–	10 to 60 aM	34 aM	<2 hr	Vijian, Chinni, Yin, Lertanantawong, and Surareungchai (2016)
S. Typhimurium	AuNPs	Antibody	Milk	10 to 100 cells/mL	7.7 cells/mL	1.2 hr	de Oliveira et al. (2018)
S. Typhimurium	AuNPs–HRP	Aptamer	Milk	20 to 2×10^8 CFU/mL	5 CFU/mL	–	Dai et al. (2019)
S. Typhimurium	AuNPs–HRP	DNA probe	–	9.6 to 9.6×10^4 CFU/mL	8.07 CFU/mL	≤2 hr	Ye et al. (2019)
S. Typhimurium	AuNPs–urease	Antibody	Milk	10 to 10^6 CFU/mL	10 CFU/mL	1 hr	Hou, Tang, Qi, Guo, and Lin (2020)
S. Typhimurium	QDs	Antibody	Milk	–	–	2.5 hr	Murasova et al. (2020)
S. Typhimurium	AgNCs	DNA probe	–	1 to 10^5 fM	0.162 fM	–	Ye et al. (2018)
Impedimetric:							
Salmonella spp.	–	DNA probe	–	1 to 400 pM	0.15 pM	–	Tabrizi and Shamsipur (2015)
S. Typhimurium	–	Aptamer	Apple juice	10^2 to 10^8 CFU/mL	3 CFU/mL	45 min	Sheikhzadeh et al. (2016)
S. Typhimurium	–	Aptamer	Chicken	75 to 7.5×10^5 CFU/mL	25 CFU/mL	≤60 min	Jia et al. (2016)
S. Typhimurium	–	Aptamer	Apple juice	10 to 10^8 CFU/mL	6 CFU/mL	–	Bagheryan et al. (2016)
S. Typhimurium	–	Antibody	Water, lichi, and orange juices	–	10, 10.4, and 10.7 CFU/mL in spiked water, lichi, and orange juices	–	Mutreja et al. (2016)

(Continues)

TABLE 2 (Continued)

Serotype	Label	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium	–	Antibody	Milk	10^3 to 10^8 CFU/mL	10^3 CFU/mL	20 min	Farka et al. (2016)
S. Typhimurium	–	Antibody	–	10 to 10^7 CFU/mL	1.56 CFU/mL	–	Singh et al. (2018)
S. Typhimurium	–	Mannose	–	50 to 10^3 CFU/mL	50 CFU /mL	–	Cui et al. (2018)
S. Typhimurium	–	Antimicrobial peptides	–	10 to 10^4 CFU/mL	10 CFU/mL	–	de Miranda et al. (2017)
S. Typhimurium	–	Aptamer	Egg	6.5×10^2 to 6.5×10^8 CFU/mL	1 CFU/mL	40 min	Ranjbar, Shahrokhian, and Nurmohammadi (2018)
S. Enteritidis and *S.* Typhimurium	–	Aptamer	Raw chicken meat	55 to 5.5×10^6 CFU/mL; 67 to 6.7×10^5 CFU/mL	55 CFU/mL67 CFU/mL	10 min	Hasan et al. (2018)
Salmonella spp.	–	DNA probe	–	0.01 to 0.4 nM	0.084 nM	–	Nguyet et al. (2019)
Salmonella serogroups B and D	–	Antibody	Turkey	300 to 1,000 cells/mL	300 cells/mL	1 hr	Liu et al. (2019)
Salmonella serogroups B and D	–	Antibody	Turkey and chicken	–	7 cells/mL	40 min	Jasim et al. (2019)
S. Typhimurium	–	Bacteriophage	–	10 to 10^8 CFU/mL	12 CFU/mL	40 min	Quiton, Carreon, Cruz-Papa, and Bergantin (2018)
S. Typhimurium	–	Antibody	–	10^2 to 10^7 CFU/mL	50 CFU/mL	–	Zhu et al. (2020)
S. Typhi	AuNPs	Antibody	–	–	100 CFU/mL	–	Pal et al. (2016)
S. Typhimurium	GOx	Antibody	Chicken rinse water	10^2 to 10^6 CFU/mL	1.04×10^3 CFU/mL in chicken rinse water	<2 hr	Xu et al. (2016)
S. Typhimurium	AuNPs–urease	Antibody	Chicken (breast, carcass, intestine, leg, meat, and wing) and duck (breast, leg, liver, and wing)	10^2 to 10^5 CFU/mL	10^2 CFU/mL	2 hr	Wang, Xue, et al. (2020)
S. Typhimurium	NINWs	Aptamer and antibody	Chicken	10^2 to 10^6 CFU/mL	80 CFU/mL	2 hr	Wang, Huo, Qi, et al. (2020)
Potentiometric:							
S. Typhimurium	CdS	Antibody	Milk	–	20 cells/mL	75 min	Silva et al. (2015)
S. Typhimurium	–	Antibody	Apple juice	12 to 1.2×10^4 cells/mL	5 cells/mL	<1 hr	Silva, Almeida, et al. (2019)
S. Typhimurium	–	Antibody	Apple juice	13 to 1.3×10^6 cells/mL	6 cells/mL	<1 hr	Silva, Magalhães, et al. (2019)

Abbreviations: AgNCs, silver nanoclusters; ALP, alkaline phosphatase; AuNPs, gold nanoparticles; GOx, glucose oxidase; HRP, horseradish peroxidase; MMPs, micro-sized magnetic particles; MNPs, magnetic nanoparticles; MWCNTs, multi-walled carbon nanotubes; NINWs, nickel nanowires; QDs, quantum dots; rGO, reduced graphene oxide.

IMBs were used for the capture and preconcentration of *Salmonella* from milk samples. The captured bacteria were lysed to release genomic DNA which was further amplified by PCR with two labeled primers (biotin and digoxigenin). Then the double-tagged amplicon was captured by the streptavidin-modified magnetic beads, labeled with HRP, and electrochemically detected. This research also demonstrated that immunomagnetic separation (IMS) could effectively replace the conventional selective culture to significantly reduce the assay time from 3–5 days to 3.5 hr.

Later, Melo et al. (2018) focused on the optimization of various steps toward the assembly of the biosensor, including the pretreatment of the gold electrode, immobilization of antibodies, and concentrations of enzymatic substrate and mediator with a LOD of 10 CFU/mL.

As reported, the amperometric strategy is very sensitive for *Salmonella* detection. However, most of amperometric biosensors rely on tedious labeling to increase the electrochemical reaction at the electrode surface, which limits their in-field applications.

3.1.2 | Voltammetric biosensors

Voltammetric biosensors monitor the changes in current under varying potentials (Xu, Wang, & Li, 2017).

Label-free voltammetric detection of *Salmonella* can be accomplished by monitoring the attachment of the bacterial cells to electrode surface, as well as the hybridization of the target DNA with previously immobilized DNA probes, based on different detection techniques such as cyclic voltammetry and differential pulse voltammetry (DPV) (Appaturi et al., 2020; García et al., 2012; Singh et al., 2018; Tabrizi & Shamsipur, 2015). For example, Singh et al. (2018) deposited graphene oxide (GO)-wrapped carboxylated multiwalled carbon nanotubes composites with superior electron transfer behavior onto a patterned indium tin oxide electrode for improved antibody loading and detection sensitivity. *Salmonella* Typhimurium was captured by the immobilized antibodies and then detected using cyclic voltammetry with a low LOD of 0.376 CFU/mL. An electrochemical genosensor based on DNA probe-modified nanoporous glassy carbon electrode was developed for the detection of *Salmonella* DNA (Tabrizi & Shamsipur, 2015). The porous glassy carbon electrode provided a suitable platform for the immobilization of DNA probes. Consequently, as low as 2.1 pM of target DNA could be detected using a DPV method.

Incorporating electrochemical labels, such as enzymes (e.g., HRP and ALP), metallic nanoparticles, and so on, into a voltammetric biosensor also contributes to high detection sensitivities. Gold nanoparticles (AuNPs)–HRP conjugates were used for signal amplification for *S*. Typhimurium detection (Dai et al., 2019). Target bacteria and the cDNA modified on the electrode competitively bound to aptamers on AuNPs-HRP. By employing metal–organic framework (MOF)–graphene composites with excellent electrochemical performance as substrate and the catalytic action of HRP on the H_2O_2–hydroquinone system, this method achieved a satisfactory LOD of 5 CFU/mL. Zhu et al. (2014) incorporated RCA into an electrochemical biosensor with a LOD of 6.76 aM for target DNA. The *inv*A gene hybridized with the capture DNA on electrode surface and formed a sandwich structure with the circularization mixture. RCA was initiated in the presence of dNTPs and phi29 DNA polymerase to produce long ssDNA, which was an ideal carrier to load a considerable number of AuNPs–DNA probes. Enzymatic electrochemical signals were triggered after attaching ALP to AuNPs surface. The results demonstrated that as low as 6 CFU/mL of *Salmonella* could be detected in real milk samples.

Label-based voltammetric detection of *Salmonella* also can be accomplished based on the oxidation and reduction of metallic elements under the applied potentials (de Oliveira, Martucci, & Faria, 2018; Fei, Dou, & Zhao, 2016). Afonso et al. (2013) developed a disposable biosensor using AuNPs as electrochemical labels. *Salmonella* was sandwiched between IMBs and AuNPs, and subsequently detected using DPV based on the electrooxidation of AuNPs to $AuCl_4^-$ and reversed electroreduction to Au(0) on electrode surface. Taking advantage of IMBs for preconcentration and AuNPs as labels, this method showed a LOD of 143 cells/mL and performed well in shimmed milk samples. Later, Freitas, Viswanathan, Nouws, Oliveira, and Delerue-Matos (2014) proposed a similar approach based on Fe@Au core/shell nanoparticles and CdS nanocrystals by employing square-wave anodic stripping voltammetry detection. The Fe@Au core/shell nanoparticles were detached before detection. The results demonstrated that as low as 13 cells/mL of *S*. Typhimurium could be detected in less than 1 hr.

Zong et al. (2016) amplified the DPV signals based on entropy-driven molecular switch for *S*. Typhimurium detection with a LOD of 13 CFU/mL. *Salmonella* bound to its aptamer and released cDNA. Then the cDNA opened the capture hairpin DNA immobilized on the electrode surface. With the addition of the link DNA that had more complementary bases with the capture DNA, the cDNA was displaced and recycled. Thus, the capture hairpin DNA was continuously opened. DPV signals were obtained after labeling with electrochemical reagent–modified AuNPs. This biosensor was further validated in milk with recoveries between 96.1% and 103.0%.

Voltammetric biosensors seem to be one of the most attractive electrochemical biosensors for *Salmonella* detection with high sensitivity and simplicity. As it is known, the detection performance of label-free voltammetric biosensors depends largely on the electrochemical properties of the electrode substrates and the immobilization of the bioreceptors. And the label-based ones are mainly restricted by the saturation kinetics and stability of the adopted labels. In this respect, voltammetric biosensors will no-doubt benefit from the rapid development of nanomaterials and biotechnology in the near future to fulfill extremely sensitive and reliable detection and monitoring of *Salmonella* in food.

3.1.3 | Impedimetric biosensors

Impedimetric biosensors, measuring the changes of an electrical field, are recognized as promising techniques for the detection of *Salmonella* (Silva et al., 2018; Xu, Wang, et al., 2017). They have played a vital role in *Salmonella* detection along with less assay time, higher sensitivity, and miniaturization potential (Lindholm-Sethson et al., 2010; Pashazadeh et al., 2017).

It is reported that natural cell membranes (thickness 5 to 10 nm) exhibit a capacitance of 0.5 to 1.3 $\mu F/cm^2$ and a membrane resistance of 10^2 to 10^5 $\Omega \cdot cm^2$, making it possible to increase the interface impedance on electrode surface in the presence of captured bacteria (Wang, Ye, & Ying, 2012). Therefore, the attachment of bacteria to electrode surface can be directly monitored. Nandakumar et al. (2008) developed a label-free impedimetric biosensor based on "Bayesian decision theory" that could detect 500 CFU/mL of *S*. Typhimurium, in a detection time of 6 min. However, it is far from satisfactory due to the extremely low infection limits of *Salmonella*. In fact, great efforts have been made on electrode modification to obtain higher sensitivities. Bagheryan, Raoof, Golabi, Turner, and Beni (2016) proposed a label-free approach for sensitive detection of *S*. Typhimurium in food samples by immobilizing aptamers onto the surface of screen-printed carbon electrodes, in which a diazonium-supporting layer was grafted for the formation of an aptamer layer with high density. They obtained a satisfactory LOD of 6 CFU/mL and also demonstrated its feasibility for *S*. Typhimurium detection in apple juice. Sheikhzadeh, Chamsaz, Turner, Jager, and Beni (2016) reported on the use of polypyrrole-based polymers to design a label-free impedimetric biosensor for *S*. Typhimurium detection, reaching a lower LOD of 3 CFU/mL. This biosensor was fabricated based on the use of poly [pyrrole-co-3-carboxyl-pyrrole] copolymer for aptamer immobilization. The intrinsic electrical properties of the polymeric surface eliminated the extra addition of redox probes. Later, Singh, Ali, Kumar, Ahmad, and Sumana (2018) deposited functionalized MoS_2 nanosheets on the patterned hydrolyzed indium tin oxide microelectrode surface, reaching an extremely low theoretical LOD of 1.56 CFU/mL for *S*. Typhimurium.

Compared with label-free impedimetric biosensors, the label-based ones are less attractive mainly due to their tedious labeling process. Despite this limitation, novel labeling approaches were investigated in order to achieve outstanding performance. For example, AuNPs were used to fabricate a novel impedance immunosensor to detect *S*. Typhi (Pal, Sharma, & Gupta, 2016). The bacteria were tagged with AuNPs via antigen–antibody interaction, and a micron-gap interdigitated electrode that can generate high electric field gradients near the edge of the electrode was used to monitor the small changes around the microenvironment of bacterial cells. By measuring the changes in impedance, the LOD of this biosensor was 100 CFU/mL. Our group developed a label-dependent impedimetric immunosensor based on glucose oxidase for rapid detection of *E. coli* O157:H7 and *S*. Typhimurium in food (Xu, Wang, & Li, 2016). Streptavidin-coated magnetic beads were functionalized with biotinylated antibodies for the separation of the target cells. The captured bacteria were further labeled with glucose oxidase to trigger an enzymatic reaction that produced gluconic acid and decreased the impedance of the solution. The LOD for *S*. Typhimurium in chicken rinse water was 1.04×10^3 CFU/mL. Recently, Wang, Huo, Qi, et al. (2020) labeled *S*. Typhimurium with nickel nanowires as conductive bridges to achieve a LOD of 80 CFU/mL in 2 hr of assay time and demonstrated its application in spiked chicken samples.

As mentioned above, enormous efforts have been made on impedimetric biosensors for *Salmonella* detection, particularly for the label-free ones with shorter detection time and simpler manipulations. However, impedimetric biosensors are heavily relying on the advance in the fabrication of electrodes especially in micro or nano range. In this regard, with the emerging of new interdigitated electrodes, electrode arrays, cost-effective screen-printed electrodes, and so on, the impedimetric biosensors are expected to play a greater role in realizing super sensitivity, high-throughput detection, and point-of-care testing in bacterial pathogen analysis and monitoring. Moreover, impedance method is known for its signal instability due to the electrode to electrode and probe variations. Normalization of the impedance signals can be helpful to minimize this inconsistency in laboratory research (Gökçe et al., 2020). For commercialized impedimetric biosensors, the potential solutions include the better control of electrode manufacturing in mass production as well

as self-calibration against electrode variations during tests to ensure reproducible results.

3.1.4 | Potentiometric biosensors

Potentiometric biosensors usually use a high impedance voltmeter to measure the difference in electrical potential/electromotive force between working and reference electrodes under a zero or negligible current flow (Velusamy, Arshak, Korostynska, Oliwa, & Adley, 2010).

Silva, Magalhães, Oliva-Teles, and Delerue-Matos (2015) reported a potentiometric method based on a cadmium-selective polymeric membrane microelectrode for *S.* Typhimurium detection using CdS nanoparticles as labels. The bacterial cells were specifically captured by the functionalized magnetic nanoparticles (MNPs) and then bound to antibodies labeled with CdS nanoparticles. The concentration of *S.* Typhimurium was determined by the amount of cadmium ions released upon the dissolution of the nanoparticles. This biosensor obtained a LOD of 20 cells/mL and the assay time was 75 min.

However, resorting to nanomaterials for signal generation/amplification increases the analysis time and the complexity of the assay. Label-free potentiometric detection was accomplished by measuring the charge changes in the presence of *S.* Typhi that could respond to 0.2 CFU/mL of target bacteria in less than 60 s (Zelada-Guillén, Blondeau, Rius, & Riu, 2013; Zelada-Guillén, Riu, Düzgün, & Rius, 2009). Recently, potentiometric sensors based on the blocking surface principle that claimed to achieve amplification capabilities close to the label-based approaches were proposed for *Salmonella* detection (Silva, Almeida, et al., 2019; Silva, Magalhães, et al., 2019). The binding of *Salmonella* cells disrupted the internal marker ion flux through the sensing membrane that was able to induce a potentiometric response. Using an ion-selective electrode with a polymer inclusion membrane or a paper-based strip electrode as transducers, these methods allowed sensitive detection of *Salmonella* with LODs at several cells/mL in less than 1 hr. Furthermore, they were also able to demonstrate this application in apple juice.

Though potentiometric biosensors are capable of label-free detection with extremely high sensitivity, they are less studied for *Salmonella* detection, probably due to the tedious optimization of experimental conditions and stabilization of the reference electrode (Silva et al., 2018).

3.2 | Optical biosensors

Optical biosensors are those devices that comprise a transducer capable of converting the interactions of bioreceptors with their targets into measurable optical signals (Jiang, Lan, Yao, Zhao, & Ping, 2018). They have attracted ever-increasing attention due to their simplicity, sensitivity, stability, and rapidity (Khansili, Rattu, & Krishna, 2018). Optical biosensors for *Salmonella* detection are mainly classified into four types: colorimetric, surface-enhanced Raman scattering (SERS), fluorescent, and surface plasmon resonance (SPR) biosensors, based on different optical signal-transducing mechanisms (Figure 3). Optical biosensors for *Salmonella* detection are summarized in Table 3 (2015 to 2020) and Table S2 (before 2015).

3.2.1 | Colorimetric biosensors

Colorimetric biosensors along with naked-eye signal output are attractive for the detection of *Salmonella* due to their advantages of quick response, simple operation, and no need for complicated apparatus (Ding, Wang, Li, & Chen, 2016). They have been extensively studied on the basis of (a) the inherent optical characteristics of nanoparticles and (b) color change originated from enzymatic or chemical reactions (Chen & Xie, 2015).

Colorimetric biosensors based on AuNPs aggregation

AuNPs possess unique optical properties with color shifts corresponding to their dispersion and aggregation status that well-dispersed AuNPs solution displays a red color and the aggregated one appears in purple or blue (Bui, Ahmed, & Abbas, 2015). Based on DNA hybridization, AuNPs-based methods are commonly used for the detection of *Salmonella* genomic DNA (Majdinasab, Aminlari, Sheikhi, Niakousari, & Shekarforoosh, 2013; Prasad, Shankaracharya, & Vidyarthi, 2011; Thavanathan, Huang, & Thong, 2015). For example, Thavanathan et al. (2015) modified DNA probes on AuNPs and GO to target the *inv*A gene of *S. enterica*. The hybridization of DNA probes with the target genes induced the aggregation of AuNPs on GO surface, along with a color change from pink to purple. This biosensor achieved a LOD of 1 nM for the DNA target. This reflects the sensitivity of genosensors. However, extraction of DNA genomes from bacterial cells is always time-consuming and laborious.

To overcome this limitation, direct detection of the whole cell of *Salmonella* is performed. Wang, Singh et al. (2010) proposed a simple colorimetric method for label-free detection of *S.* Typhimurium cells using antibody-conjugated oval-shaped AuNPs for signal output, achieving a LOD of 10^4 bacteria/mL. As *Salmonella* is much larger in size than the antibody-conjugated oval-shaped AuNPs, several AuNPs conjugated to one bacterial cell that made AuNPs aggregate. Moreover, destruction of the targeted bacteria was achieved by employing the

TABLE 3 Summary of the optical biosensors reported for *Salmonella* detection (2015 to 2020)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
Colorimetric:							
S. Typhimurium	AuNPs aggregation	Aptamer	Milk	10^2 to 10^7 CFU/mL	56 CFU/mL	–	Ma et al. (2017)
S. enterica	AuNPs aggregation	DNA probe	–	–	~10^5 CFU/mL	<1 hr	Thavanathan et al. (2015)
S. Typhimurium	AuNPs aggregation	Aptamer	–	–	10^2 CFU/mL	≤30 min	Lavu, Mondal, Ramlal, Murali, and Batra (2016)
S. Typhimurium	AuNPs aggregation	Antibody	Milk	–	10^2 CFU/mL in milk	30 min	You, Lim, Hahn, Choi, and Gunasekaran (2018)
S. Typhimurium	AuNPs aggregation	Antibody	Tomato	–	10 CFU/g in tomato	≤45 min	Hahn et al. (2017)
S. Typhimurium	AuNPs aggregation	Aptamer	Milk	10^2 to 10^9 CFU/mL	16 CFU/mL	–	Yi et al. (2019)
S. Typhimurium	AuNPs aggregation	Aptamer	Milk and shrimp	10 to 10^6 CFU/mL	10 CFU/mL	–	Xu, Bi, et al. (2018)
S. Typhimurium	AuNPs aggregation	DNA probe	Milk	30 to 8,600 CFU/mL	23 CFU/mL	–	Ma, Song, Xia, Jiang, and Wang (2017)
Salmonella spp.	AuNPs aggregation	Aptamer	Ham and chicken sausages	10^5 to 10^8 CFU/mL[a]	10^5 CFU/mL[a]	–	Ledlod, Areekit, Santiwatanakul, and Chansiri (2020)
S. Typhimurium	G-quadruplex catalysis	Aptamer	–	100 to 10^6 CFU/mL	100 CFU/mL	–	Lee, Jung, Lee, and Ha (2017)
S. Typhimurium	Catalase catalysis and AuNPs aggregation	Aptamer	Raw chicken	10 to 10^6 CFU/mL	10 CFU /mL	–	Zhu et al. (2016)
S. Typhimurium	MNPs catalysis	Aptamer	–	–	–	10 min	Park et al. (2015)
S. Typhimurium	Competitive binding of urease and bacteria toward AgNPs	Antibody	Apple juice	–	–	–	Singh et al. (2019)
S. Typhimurium	Sandwich (MNPs and AuNPs)	Aptamer	Milk	25 to 10^5 CFU/mL	10 CFU/mL	–	Duan, Xu, Wu, and Wang (2016)
S. Pullorum and *S.* Gallinarum	Sandwich (MNPs and HRP–SiNPs)	Antibody	Chicken livers	8.4×10^3 to 8.4×10^7 CFU/mL	1.7×10^3 CFU/mL	<1.5 hr	Zhu, Zhao, Wang, and Dou (2017)
S. Typhimurium	Sandwich (microplate and $ZnFe_2O_4$/rGO)	Aptamer	Milk	11 to 1.1×10^5 CFU/mL	11 CFU/mL	–	Wu et al. (2017)
S. Enteritidis	Sandwich (glass capillary and poly-HRP)	Aptamer	Milk	–	10^3 CFU/mL	–	Bayraç et al. (2017)
S. Typhimurium	Sandwich (microplate and PBNPs)	Antibody	Powdered milk	–	2×10^3 and 6×10^3 CFU/mL in pure culture and powdered milk	–	Farka et al. (2018)

(Continues)

TABLE 3 (Continued)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium and *S.* Enteritidis	Sandwich (cotton swab and colored nanobeads)	Antibody	Chicken meat	10 to 10^8 CFU/mL	10 CFU/mL in chicken meat (visual)	–	Alamer, Eissa, Chinnappan, and Zourob (2018)
S. enterica	Sandwich (MBs and AuNPs–HRP)	Antibody	Milk	10^3 to 10^7 CFU/mL	10^2 CFU/mL	1 hr	Chen and Xie (2015)
S. Typhimurium	Sandwich (MBs and β-galactosidase)	Antibody	Whole milk	–	10^2 and 10^3 CFU/mL in pure culture and whole milk	≤90 min	Srisa-Art et al. (2018)
S. Typhimurium	Sandwich (MNPs and BSA–CUR conjugates)	Antibody	Chicken	10^2 to 10^6 CFU/mL	50 CFU/mL	–	Huang et al. (2018)
S. Typhimurium	Sandwich (magnetic particle chains and Pt@ZIF-8)	Antibody	Chicken carcass	10 to 10^4 CFU/mL	11 CFU/mL	2.5 hr	Wang, Huo, Zheng, et al. (2020)
S. Typhimurium	Sandwich (MNPs and GNCs)	Antibody	Chicken	10 to 10^5 CFU/mL	16 CFU/mL	–	Guo et al. (2019)
S. Typhimurium	Sandwich (MNPs and FNCs)	Antibody	Chicken	3×10^2 to 3×10^6 CFU/mL	14 CFU/mL	–	Zhang et al. (2019)
S. Enteritidis	Sandwich (MBs and HRP enzyme–inorganic nanoflower)	Antibody	Tap water, milk, and cheese	1 to 10^6 CFU/mL	1 CFU/mL	–	Zeinhom et al. (2018)
S. Typhimurium	Sandwich (MNPs and Au@PtNCs)	Antibody	Chicken meat	18 to 1.8×10^7 CFU/mL	17 CFU/mL	1 hr	Zheng et al. (2020)
S. Enteritidis	Sandwich (MBs and Fe-MOF)	Antibody	Milk	0 to 10^7 CFU/mL	34 CFU/mL	–	Cheng et al. (2019)
S. Typhimurium	Sandwich (MNPs and ZnO capped mesoporous SiNPs loaded with curcumin)	Antibody	Chicken	10^2 to 10^7 CFU/mL	63 CFU/mL	1.5 hr	Huang et al. (2020)
S. Typhimurium	Sandwich (MNPs and catalase)	Antibody	Chicken	10 to 10^5 CFU/mL	35 CFU/mL	3 hr	Guo et al. (2020)
SERS:							
Salmonella spp.	Label free	Antibody	–	–	–	–	Chen, Park, and Eady (2017)
S. Typhimurium	Label free	Aptamer	–	–	10^8 CFU/mL	–	Chen et al. (2017)
S. Typhimurium	Label based (ROX)	Aptamer	Milk	15 to 1.5×10^6 CFU/mL	15 CFU/mL	–	Duan et al. (2016)

(Continues)

TABLE 3 (Continued)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium	Label based (PTAP)	Aptamer	Milk	56 to 5.6×10^8 CFU/mL	9 CFU/mL	–	Li, Chen, et al. (2017)
S. enterica	Label based (3-MPBA)	3-MPBA	–	–	10^2 CFU/mL	3 hr	Pearson et al. (2017)
S. Enteritidis	Label based (FAM)	Aptamer	Spinach leaf	1.4×10^3 to 1.4×10^7 CFU/mL	1.4×10^3 CFU/mL	≤3 hr	Gao and He (2019)
S. Enteritidis	Label based (AuNPs modified with Cy5)	DNA probe	Milk	6.6 to 6.6×10^6 CFU/mL	66 CFU/mL	–	Draz and Lu (2016)
S. Typhimurium	Label based (AuNPs modified with MBA)	Aptamer	Pork	10^2 to 10^7 CFU/mL	15 CFU/mL	–	Zhang, Ma, et al. (2015)
S. Typhimurium	Label based (AuNPs modified with MBA)	Aptamer	Pork	10 to 10^7 CFU/mL	5 CFU/mL	~3 hr	Ma et al. (2016)
S. Typhimurium	Label based (AuNPs modified with MGITC)	Antibody	–	–	–	–	Ko et al. (2018)
S. Typhimurium	Label based (AgNPs modified with DACITC)	Concanvalin A and antibody	–	–	10 CFU/mL	~1 hr	Kearns et al. (2017)
S. Typhimurium	Label based (Spiny AuNPs modified with MBA)	Aptamer	Pork	10 to 10^5 CFU/mL	4 CFU/mL	–	Ma et al. (2018)
S. Typhimurium	Label based (AuNPs modified with Cy3)	Aptamer	Milk	10^2 to 10^7 CFU/mL	35 CFU/mL	≤1 hr	Xu, Ma, et al. (2018)
S. Typhimurium	Label based (AuNPs modified with MBA/DSNB)	Antibody	Cottage cheese, egg white, and mixed fruit juice	10^3 to 10^6 and 10 to 10^7 cells/mL for MBA and DSNB	100 and 10 cells/mL for MBA and DSNB	–	Chattopadhyay, Sabharwal, Jain, Kaur, and Singh (2019)
S. Typhimurium	Label based (AuNPs modified with 4-MBA)	Antibody	Milk	10^2 to 10^7 CFU/mL	75 CFU/mL	–	Wu (2019)
S. Typhimurium	Label based (AuNPs modified with NBA)	Aptamer	Seafood	27 to 2.7×10^5 CFU/mL	27 CFU/mL	–	Duan et al. (2020)
S. Enteritidis	Label based (Au^{MBA}@Ag core–shell nanoparticles)	Antibody[b]	Milk, chicken breast, and beef	27 to 2.7×10^6 CFU/mL	27, 31, 35, and 35 CFU/mL in pure culture, milk, chicken breast, and beef	≤30 min	Liu, Du, Zang, Li, and Wang (2017)
S. Typhimurium and *S.* Kentucky	Label based (AuNPs coated with Raman dyes and encapsulated in glass)	Antibody	Raw ground beef and poultry	–	1 CFU/25 g in ground beef and poultry	–	Weidemaier et al. (2015)
Salmonella spp.	Label based (NAEBs)	Antibody	–	10^2 to 10^3 CFU/mL	30 CFU/mL	–	Su et al. (2019)

(Continues)

TABLE 3 (Continued)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
Fluorescent:							
S. Typhimurium	Sandwich (MNPs and QDs)	Antibody and aptamer	Ground beef	10 to 10^4 CFU/mL	160 and 750 CFU/mL in pure culture and ground beef	≤2.5 hr	Xu et al. (2015)
S. enterica	Sandwich (MBs and QDs)	Antibody	Milk	5×10^2 to 5×10^6 CFU/mL	60 CFU/mL	≤1 hr	Yin et al. (2016)
S. Typhimurium	Sandwich (MNPs and TRFL nanoparticles)	Aptamer	Milk	10^2 to 10^5 CFU/mL	15 CFU/mL	–	Wang et al. (2016)
S. Typhimurium	Sandwich (MNPs and FMSs)	Antibody	Apple juice	1.4×10^2 to 1.4×10^6 CFU/mL	58 CFU/mL	≤2 hr	Wang, Zheng, et al. (2019)
S. Typhimurium	Sandwich (MNPs and MnO_2 nanoflowers–QDs)	Antibody	Chicken meat	10^2 to 10^7 CFU/mL	43 CFU/mL	–	Hao et al. (2020)
S. Typhimurium	Sandwich (MNPs and ZnO capped mesoporous SiNPs loaded with curcumin)	Antibody	Chicken	10^2 to 10^7 CFU/mL	40 CFU/mL	1.5 hr	Huang et al. (2020)
S. Typhimurium	FRET (QDs and GO)	DNA probe	–	–	~4 nM	20 min	Guo, Chan, et al. (2017)
S. Typhimurium	FRET (UCNPs and AuNRs)	Aptamer	Milk	12 to 5×10^5 CFU/mL	11 CFU/mL	–	Cheng et al. (2017)
S. Typhimurium	FRET (QDs and CNPs)	Aptamer	Shrimp and chicken breast	50 to 10^6 CFU/mL	35 CFU/mL	–	Duan et al. (2015)
S. Typhimurium	FRET (ROX and CNPs)	Aptamer	Milk and salmon	10^2 to 10^6 CFU/mL	50 CFU/mL	–	Duan et al. (2016)
S. Enteritidis	FRET (QDs)	Antibody	Eggshells	75 to 5×10^5 CFU/mL	10 CFU/mL	1 to 2 hr	Wang, Wang, et al. (2015)
S. Typhimurium	FRET (FAM and MoS_2-Ns)	Aptamer	Tap water and skimmed milk	–	10 CFU/mL	–	Singh, Gupta, Sinha, Kumar, and Bhalla (2016)
S. Typhimurium	FRET ($NaYF_4$:Ce/Tb nanoparticles and FAM)	Aptamer	Chicken meat and eggs	10^2 to 10^6 CFU/mL	25 CFU/mL	–	Wang, Niazi, et al. (2017)

(Continues)

TABLE 3 (Continued)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Enteritidis	FRET (fluorescein and GO)	Aptamer	Milk	10^2 to 10^7 CFU/mL	25 CFU/mL	–	Chinnappan et al. (2018)
S. Enteritidis	FRET (FAM and NG)	DNA probe	Milk	10^2 to 10^6 CFU/mL	50 CFU/mL in milk	≤2 hr	He et al. (2017)
S. Typhimurium	Label free (SG); FRET (RB and AuNPs)	Aptamer	–	1,530 to 6,122 CFU/mL	733 CFU/mL;464 CFU/mL	2 hr	Srinivasan et al. (2018)
S. enterica	FRET (Texas red and MOF-NSs)	DNA probe	–	0.5 to 15 nM	28 pM	–	Qiu et al. (2019)
S. Typhimurium	Label free (assembly of fluorescent AgNCs)	Aptamer	Chicken meat	10^2 to 10^7 CFU/mL	50 CFU/mL	–	Zhang et al. (2017)
S. Typhimurium	Displacement (UCNPs and MBs)	Aptamer	–	50 to 10^6 CFU/mL	28 CFU/mL	–	Kurt, Yüce, Hussain, and Budak (2016)
S. Typhimurium	Displacement (UCNPs and MBs)	Aptamer	Drinking water and skimmed milk	10^2 to 10^6 CFU/mL	12 CFU/mL	–	Yüce, Kurt, Hussain, Ow-Yang, and Budak (2018)
S. Typhimurium	F_0F_1–ATPase aptasensor	Aptamer	Milk	10 to 10^4 CFU/mL	10 CFU/mL	–	Duan et al. (2018)
S. enterica	MCM–41 aptamer gate system	Aptamer	Milk	2×10^3 to 10^4 CFU/mL	2,336 cells in milk	<30 min	Bayramoglu et al. (2018)
S. Typhimurium	FMNPs-based aptasensor	Aptamer	Milk	63 to 10^8 CFU/mL	25 CFU/mL	≤1 hr	Li et al. (2018)
SPR:							
S. Typhimurium	Label free	Antibody	–	–	~10^7 CFU/mL	≤1 hr	Nguyen et al. (2016)
S. Typhimurium	Label free	Antibody	–	–	–	6 to 7 min	Lukose, Shetty, Ballal, Chidangil, and Sinha (2018)
S. Typhimurium	Label free	Antibody	–	10^5 to 10^8 CFU/mL	10^5 CFU/mL	10 min	Makhneva et al. (2018)
S. Enteritidis, *S.* Heidelberg, *S.* Javiana, *S.* Kentucky, and *S.* Typhimurium	Label free	Antibody	Chicken carcass rinse	2.1×10^6 to 4.1×10^8 and 7.6×10^6 to 5.1×10^7 CFU/mL in pure culture and chicken rinse	2.1×10^6 and 7.6×10^6 CFU/mL in pure culture and chicken rinse	~20 min	Chen and Park (2018)

(Continues)

TABLE 3 (Continued)

Serotype	Detection format	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium	Label free and sandwiched with antibody	Antibody	Romaine lettuce	4.7×10^5 to 9.5×10^6 CFU/mL	1.9×10^6,[c] 1.6×10^6,[d] and 4.7×10^5[e] CFU/mL in romaine lettuce	–	Bhandari, Chen, and Bridgman (2019)
Salmonella spp.	Label based (streptavidin)	DNA probe	–	10^2 to 10^7 CFU/mL	60 CFU/mL	–	Lei et al. (2015)
S. Enteritidis	Label based (MNPs)	Antibody	Eggshell	14 to 1.4×10^9 CFU/mL	14 CFU/mL	–	Liu et al. (2016)
Salmonella spp.	Label based (AuNPs)	Antibody	Cucumber and hamburger extracts	2.5×10^3 to 2.5×10^6 CFU/mL	7.4×10^3 and 11.7×10^3 CFU /mL in cucumber and hamburger extracts	<80 min	Vaisocherová-Lísalová et al. (2016)
S. Typhimurium	Label based (HRP)	Antibody	Powdered milk	10^2 to 10^6 CFU/mL	100 and 10^3 CFU/mL in pure culture and powdered milk	<60 min	Farka et al. (2016)
S. Typhimurium	Label based (AuNPs)	DNA probe	–	0.01 to 100 ng/mL	10 pg/mL	<1 hr	Melaine et al. (2017)

[a]For the mixture of *Escherichia coli*, *Listeria monocytogenes*, and *Salmonella* spp.
[b]Against digoxin labeled on the primers.
[c]Direct assay.
[d]Sequential two-step sandwich assay.
[e]Preincubation one-step sandwich assay.

Abbreviations: 3-MPBA, 3-mercaptophenylboronic acid; 4-MBA, 4-mercaptobutyramidine; AgNCs, silver nanoclusters; AgNPs, silver nanoparticles; Au@PtNCs, porous gold@platinum nanocatalysts; AuNPs, gold nanoparticles; AuNRs, gold nanorods; BSA-CUR, bovine serum albumin–curcumin; CNPs, carbon nanoparticles; Cy3, cyanine 3; Cy5, cyanine 5; DACITC, 7-dimethylamino-4-methylcoumarin-3-isothiocyanate; DSNB, 5,5′-dithiobis(succinimidyl-2-nitrobenzoate); FAM, carboxyfluorescein; FMNPs, fluorescent-magnetic multifunctional nanoprobes; FMSs, fluorescent microspheres; FNCs, Fe-nanoclusters; FRET, Förster resonance energy transfer; GNCs, glucose oxide-nanoclusters; GO, graphene oxide; HRP, horseradish peroxidase; MBA, mercaptobenzoic acid; MBs, magnetic beads; MGITC, malachite green isothiocyanate; MNPs, magnetic nanoparticles; MOF, metal–organic framework; MOF-NSs, metal–organic framework nanosheets; MoS_2-Ns, molybdenum disulfide nanosheets; NAEBs, nanoaggregate-embedded beads; NBA, Nile blue A; NG, nanographite; PBNPs, Prussian blue nanoparticles; Pt@ZIF-8, platinum loaded zeolitic imidazolate framework-8; PTAP, p-aminothiophenol; QDs, quantum dots; RB, rhodamine B; rGO, reduced graphene oxide; ROX, X-rhodamine; SG, SYBR Green I; SiNPs, silica nanoparticles; TRFL, time-resolved fluorescence; UCNPs, upconversion nanoparticles.

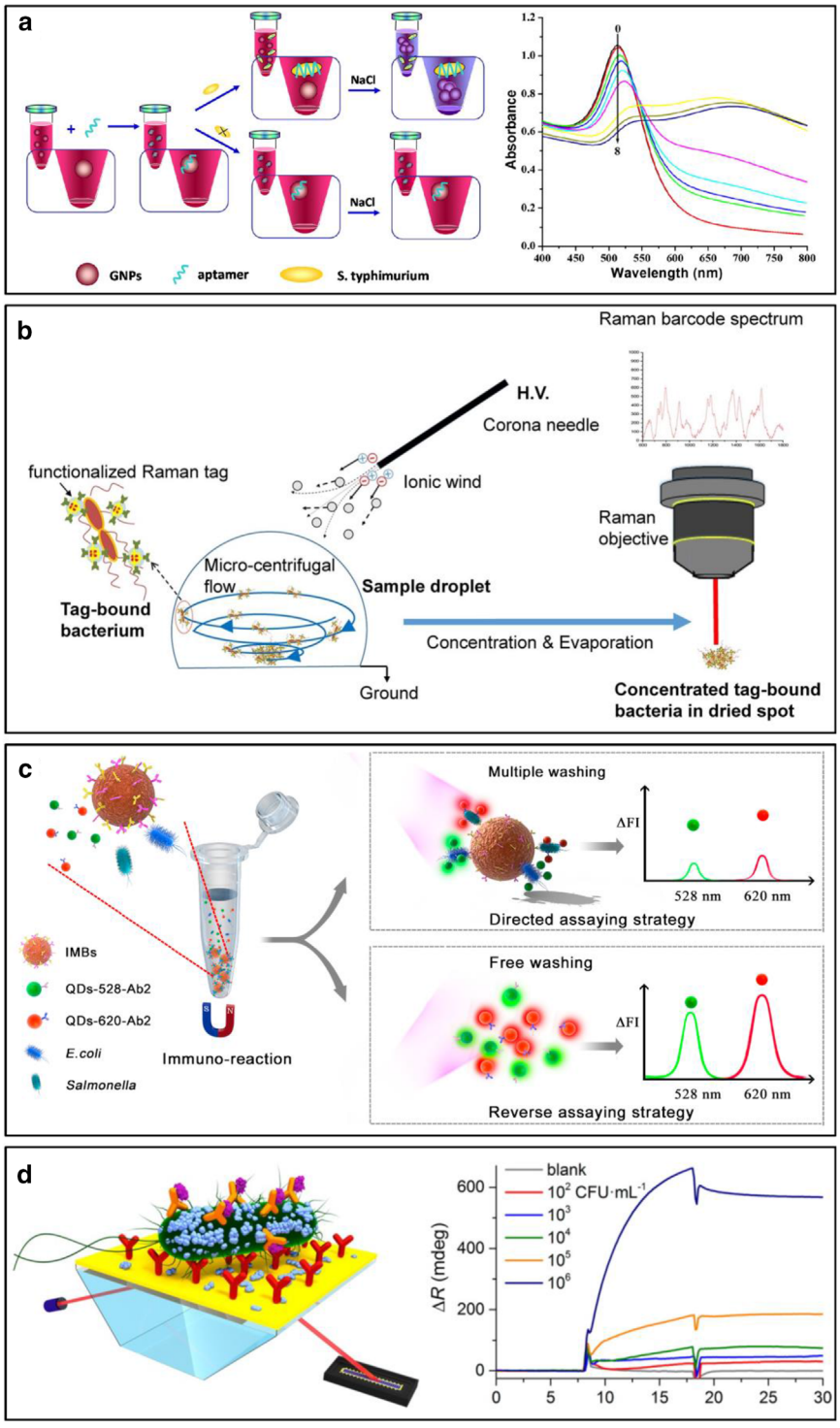

FIGURE 3 Examples of optical biosensors for *Salmonella* detection. (a) A colorimetric biosensor based on gold nanoparticles aggregation (Ma et al., 2017). (b) A label-based surface-enhanced Raman scattering biosensor using nanoaggregate-embedded beads as labels (Su et al., 2019). (c) Direct and reverse fluorescent biosensing strategies based on immunomagnetic beads and quantum dots (Yin et al., 2016). (d) A surface plasma resonance biosensor using biocatalyzed precipitation for signal enhancement (Farka et al., 2016). Figures 3a,3b, and 3c are reprinted with permission from Elsevier B.V. Figure 3d is reprinted with permission from American Chemical Society

photothermal effect of AuNPs, which could avoid the distribution of contaminated foods. The protective effect of aptamer for AuNPs stabilization was also utilized to detect *Salmonella* (Ma, Song, Zhou, Xia, & Wang, 2017; Wu et al., 2012). In these cases, the adsorption of aptamers on the surface of AuNPs kept the nanoparticles well dispersed in high-salt solution via electrostatic repulsion, whereas in the presence of the target cells of *Salmonella*, the aptamers preferentially bound to their targets and were consequently separated from AuNPs, resulting in AuNPs aggregation in high-saline environment.

AuNPs-based colorimetric biosensors are prevalent due to their high simplicity, but one limitation of most AuNPs-based methods is the instability of the nanoparticles.

Colorimetric biosensors based on enzymatic/enzyme-mimicking catalytic reaction

Another type of colorimetric biosensor is based on the color change originated from enzymatic or enzyme-mimicking catalytic reaction. HRP that can highly catalyze its substrate TMB changing from colorless to blue is most frequently used for *Salmonella* detection (Bayraç, Eyidogăn, & Öktem, 2017; Chen & Xie, 2015; Zeinhom et al., 2018). Besides, Zhu et al. (2016) incorporated catalase and AuNPs into an immunoassay for sensitive detection of *S*. Typhimurium based on enzymatic catalysis and AuNPs growth. *Salmonella* Typhimurium was sandwiched between two aptamers and labeled with catalase. Catalase consumed H_2O_2 in solution, slowing down the growth kinetics of AuNPs that induced AuNPs aggregation, whereas in the absence of the target, the reduction of gold ions took place at a rapid rate due to the high concentration of H_2O_2, leading to the formation of well-dispersed and spherical nanoparticles. The absorbance at 550 nm exhibited a linear correlation with *S*. Typhimurium concentrations in the range of 10 to 10^6 CFU/mL with a satisfactory LOD of 10 CFU/mL. Similar approach was also reported by Guo et al. (2020) in which *S*. Typhimurium was labeled with catalase and the etching of gold nanorods (AuNRs) was utilized for colorimetric signal output. Using moving immune MNPs for bacteria separation from a large volume and click chemistry for signal amplification, this biosensor allowed sensitive detection of *S*. Typhimurium with a LOD of 35 CFU/mL in 3 hr. Recently, a colorimetric sensor based on competitive binding of urease and bacterial cells toward antibody-modified silver nanoparticles (AgNPs) was reported for *S*. Typhimurium detection with a sensitivity limit of 100 cells/mL (Singh, Kakkar, Bharti, Kumar, & Bhalla, 2019). Urease lost its catalytic activity upon adhering to AgNPs, whereas in the presence of the bacteria, AgNPs bound to the bacterial cells, rendering urease active in solution.

Though enzymes show an unparalleled advantage of extremely high catalysis efficiencies, they are always expensive and susceptible to harsh environmental conditions. Since Fe_3O_4 nanoparticles were first reported to possess an intrinsic peroxidase mimetic activity in 2007 (Gao et al., 2007), the enzyme mimetic activity of nanomaterials/hybrid materials has been explosively explored. Nanomaterials/hybrid materials with enzyme-mimicking activities have been incorporated into colorimetric biosensors with improved stability, reproducibility, and reduced cost. Fe-based nanomaterials, such as Prussian blue nanoparticles, MNPs, $ZnFe_2O_4$-reduced GO nanostructures, and Fe-based MOF with excellent peroxidase-mimicking activities, were adopted as novel nanozyme labels for *Salmonella* detection (Cheng et al., 2019; Farka et al., 2018; Park, Jeong, Kim, & Park, 2015; Wu, Duan, Qiu, Li, & Wang, 2017). Furthermore, Zheng et al. (2020) labeled the captured *Salmonella* cells with porous gold@platinum nanocatalysts for signal output via catalysis of H_2O_2–TMB to achieve sensitive detection of *S*. Typhimurium with a LOD of 17 CFU/mL and demonstrated its application in chicken meat.

Colorimetric biosensors have attracted numerous attentions for quantitative and semiquantitative detection of target bacteria due to their unique advantages of naked-eye signal output. With the advance in image acquisition and processing by smartphones in recent several years, this type of biosensor holds great potential for in-field quantitation of *Salmonella* in the food supply chain. However, some issues such as the stability of the sensors and the interfering background color from food samples should be addressed in future research.

3.2.2 | SERS biosensors

SERS is a phenomenon of Raman scattering enhanced by rough metal surfaces or nanostructures (Li, Zhang, Ding, Panneerselvam, & Tian, 2017). Since first observed on electrochemically roughened silver in the 1970s, it has gained an explosion of interest for chemical and biological detection with high sensitivity, low cost, multiplexing ability, and high speed (Fleischmann, Hendra, & McQuillan, 1974; Hakonen, Andersson, Schmidt, Rindzevicius, & Käll, 2015). SERS provides unique fingerprint spectra furnished by molecular vibrations that can be used to characterize a variety of targets (Pang, Yang, & He, 2016). Detection of *S*. Enteritidis based on SERS technique was probably first reported by Montoya, Armstrong, and Smith (2003), using gold as SERS-active substrates. Generally, SERS biosensors for *Salmonella* detection can be classified into two types: label-free and label-based methods.

Label-free SERS biosensors

Label-free SERS biosensors along with whole-organism fingerprint information and simplified procedures are attractive for *Salmonella* detection. In order to improve the detection sensitivity, various gold- and silver-based nanomaterials/hybrid materials were studied and applied to SERS biosensors to provide field enhancement. For example, Chen, Park, Huang, Zhao, and Kwon (2017) modified aptamers on the silver nanorod array substrates for label-free SERS detection of *S*. Typhimurium. However, the LOD was still unsatisfactory (10^8 CFU/mL).

Label-based SERS biosensors

Despite the huge inherent advantages, label-free SERS methods always show limitations of unsatisfactory sensitivity and reproducibility. Label-based methods with

improved detection performance also have been well established. For example, a SERS aptasensor sandwiching target pathogens between Au@Ag core/shell nanoparticle substrates and X-rhodamine reporters was developed for the detection of *S*. Typhimurium with a LOD of 15 CFU/mL (Duan, Chang, Zhang, Wang, & Wu, 2016).

SERS tags/probes that contain metal nanostructures for signal enhancement, biological molecules for recognition, and Raman active dyes for signal output have gained increasing interest in the fabrication of novel SERS biosensors. One approach to construct such SERS tags is the direct attachment of recognition elements and Raman reporters on the surface of metal nanoparticles (Kearns, Goodacre, Jamieson, Graham, & Faulds, 2017; Ko et al., 2018; Ma et al., 2016; Ma, Xu, Xia, & Wang, 2018; Wang, Ravindranath, & Irudayaraj, 2011). Zhang, Ma, et al. (2015) used Raman molecule-modified AuNPs as Raman signal probes and Fe_3O_4 magnetic AuNPs as capture probes to simultaneously detect *S*. Typhimurium and *S. aureus* in both buffer and pork samples with a LOD of 15 CFU/mL for *S*. Typhimurium. Draz and Lu (2016) developed an integrated assay that combined loop-mediated isothermal amplification (LAMP) with SERS through the use of Raman active Au-nanoprobes to detect *S*. Enteritidis DNA in both buffer and artificially contaminated milk products. Target DNA was amplified by LAMP and then quantitatively detected by SERS using AuNPs modified with cyanine 5-labeled DNA as labels. The LOD of the developed LAMP-SERS method was 66 CFU/mL, which is 100 times more sensitive than the conventional PCR method.

One limitation of these SERS tags is their instability when exposed to an unfriendly environment. In practice, core–shell SERS tags that encapsulate nanoparticle aggregates and Raman reporter molecules into a protective silica shell, namely, nanoaggregate-embedded beads (NAEBs), can significantly improve the stability (Tay et al., 2012). Lin et al. (2014) combined the NAEBs-based SERS method with a microfluidic dielectrophoresis device for detection of *Salmonella* Choleraesuis and *Neisseria lactamica* within 2 hr. To further improve the detection sensitivity, an evaporation device that applied ionic wind flows to evaporate the droplet was developed for concentration of NAEBs-bound *Salmonella*. Single CFU of *Salmonella* could be detected when 30 μL of sample volume was used (Su et al., 2019).

Many studies indicate that SERS biosensors are considered as promising tools for on-line detection of pathogenic bacteria. Although the label-free one is less sensitive and susceptible to the interference from complex food matrices, the label-based one enables highly sensitive detection of the target bacteria via reporting the SERS spectra from the active labels. Even with these advances, it is still very challenging to apply SERS biosensors as routine detection tools for *Salmonella* in food. Future work may focus on the exploitation of high-performance SERS substrates, optimization of the fabrication and measurement conditions, and combination of the SERS technique with advanced sample pretreatment methods such as microfluidics, IMS, and so on, to facilitate its wide applications in actual foodstuffs.

3.2.3 | Fluorescent biosensors

Fluorescent biosensors with unique advantages of satisfactory sensitivity, high-throughput, fast response, ease of automation, and reduced background signals are one of the most prevalent types of biosensors for *Salmonella* detection (Bhardwaj et al., 2017). Currently, different sensing modes have been developed for *Salmonella* detection with excellent detection performance.

Fluorescent biosensors based on a sandwich format

Fluorescent biosensors based on a sandwich format are most commonly reported in the literature. Particularly, the simultaneous use of quantum dots (QDs) as fluorescent labels and IMBs as separation tools has obtained tremendous interest due to the distinctive optical properties of QDs (e.g., broad excitation spectra; narrow, size-tunable and symmetric emission; improved brightness; long fluorescence lifetime; and good photostability) and the capture, concentration, and separation abilities of IMBs (Moro, Turemis, Marini, Ippodrino, & Giardi, 2017). Early in 2005, our group reported a sandwich-type biosensor for detection of *S*. Typhimurium in chicken carcass wash water based on IMBs and QDs (Yang & Li, 2005). In this approach, *Salmonella* were first separated by antibody-functionalized IMBs and labeled with biotin-conjugated secondary antibodies. Streptavidin–QDs were then added and reacted with the secondary antibody, resulting in the formation of sandwich complexes. This biosensor showed a LOD of 10^3 CFU/mL with a linear range from 10^3 to 10^7 CFU/mL. Since then, we have presented a series of improved assays for simultaneous detection of *Salmonella* and other foodborne pathogens, reaching LODs ranging from 20 to 10^4 CFU/mL in pure culture and different food samples (Wang, Li, Wang, & Slavik, 2011; Xu et al., 2015; Yang & Li, 2006). Similar research was also conducted to simultaneously detect *S*. Typhimurium, *Shigella flexneri*, and *E. coli* O157:H7 using QDs and silica-coated γ-Fe_2O_3 MNPs that could detect *S*. Typhimurium at 6.0×10^3 CFU/mL (Zhao et al., 2009). Kuang et al. (2013) simplified the manipulations by coupling magnetic capture and QDs labeling into one step with less assay time of 30 min. Later, Yin et al. (2016) highlighted the elimination of the blocking effect of IMBs and multiple washing steps to develop a reverse assaying strategy using

the surplus QDs–antibody conjugates for signal output. The number of QDs–antibody probes added to the solution was kept constant and the remaining probes in the solution after removing the QDs–target–IMBs conjugates were used for fluorescence detection. This assay showed a LOD of 60 CFU/mL for *S. enterica* with detection time of 1 hr. Moreover, with the rapid development of nanomaterials, other fluorescent labels, such as upconversion nanoparticles (UCNPs), fluorescent nanospheres/microspheres, and time-resolved fluorescence nanoparticles, also have been incorporated into sandwich format–based biosensors for *Salmonella* detection (Duan et al., 2012; Wang, Zheng, et al., 2019; Wang et al., 2016; Wen et al., 2013).

Fluorescent biosensors based on Förster resonance energy transfer

Although well developed, the sandwich format–based methods always need multiple washing steps. Washing-free methods would be far more attractive. Among them, Förster resonance energy transfer (FRET) methods are promising, which are based on energy transfer from energy donors to acceptors via dipole–dipole interaction when these two species are in close proximity (Muhr et al., 2017). In FRET biosensors, "turn-off" mode, relying on sandwich binding events to dampen the fluorescent signals, has been demonstrated for the detection of *Salmonella*. Ma, Li, Xia, and Wang (2014) utilized FRET between UCNPs and AuNPs to determine the presence of target DNA in *S.* Typhimurium. Both the UCNPs and AuNPs were modified with ssDNA complementary to the target DNA and served as energy donor and acceptor, respectively. In the presence of the target DNA, a sandwich complex was formed, resulting in the occurrence of FRET. The proposed biosensor achieved a LOD of 3 CFU/mL under the optimal conditions. Similar strategy was proposed for *Salmonella inv*A gene detection using QDs as fluorescent donor and GO as quencher with a LOD of approximately 4 nM in 20 min (Guo, Chan, Chen, & Zeng, 2017).

Compared with fluorescence "turn-off," the "turn-on" mode is more preferable due to a better signal-to-noise ratio in a dark background (Cao, Guo, & Wang, 2017). Duan, Ning, Song, and Deng (2014) used carboxyfluorescein (FAM) and GO as FRET pair to detect *S.* Typhimurium with a LOD of 100 CFU/mL. FAM-labeled aptamers were absorbed onto GO surface through π–π stacking, resulting in the quenching of FAM emission. In the presence of *S.* Typhimurium, the aptamer preferred to bind to its target and released from GO, leading to the restoration of fluorescence. In another approach, UCNPs and AuNRs were chosen as a FRET pair, in which the electrostatic interaction between aptamer-modified UCNPs and AuNRs shorted the distance of these two nanomaterials, triggering FRET, whereas the added *S.* Typhimurium repelled the UCNPs–aptamers from the AuNRs, resulting in the restoration of fluorescence (Cheng, Zhang, Zhang, Wang, & Chen, 2017).

In order to improve the detection sensitivity, nucleases are commonly incorporated into the detection process. Song, Li, Duan, Li, and Deng (2014) used DNA nicking endonuclease to recycle nucleic acid hybridization and enzymatic cleavage, leading to the cleavage of numerous molecular beacons. The fluorescence of carbon nanoparticles modified on molecular beacons that was initially quenched by black hole quencher 1 could be restored and greatly amplified. The detection was finished within 2 hr with LODs of 10^2 and 1.5×10^2 CFU/mL for *S.* Enteritidis in water and milk, respectively. In another research, deoxyribonuclease I was used for recycling the target and continuously releasing FAM-labeled short sequences from nanographite surface with a LOD of 50 CFU/mL for *S.* Enteritidis detection in milk (He et al., 2017).

Fluorescent biosensors have been enormously exploited for *Salmonella* detection in food. They also hold great potential to be extended to in-field applications, particularly with the development of portable fluorescence detectors. However, their detection performance is always restricted by the inherent photophysical drawbacks of fluorophores such as instability in complex matrices and rapid photobleaching. The emerging of novel fluorescent materials would be largely beneficial for the fabrication of fluorescent biosensors with higher stability, reliability, sensitivity, and accuracy.

3.2.4 | SPR biosensors

SPR biosensors monitor the interaction between targets and ligands based on the changes in refractive index (Zhou et al., 2019). They have attracted extensive attention due to their simplicity, low cost, and most importantly, capability for label-free monitoring of the binding events in real time (Lan, Yao, Ping, & Ying, 2017; Mauriz, García-Fernández, & Lechuga, 2016). Large targets, such as *Salmonella*, with high molecular weight (>10 kDa) can be directly detected (Mahmoudpour et al., 2019).

The formation of well-ordered sensing interfaces with oriented immobilization of bioreceptors on a SPR surface is essential for better sensitivity. Covalent binding of recognition elements to gold chips/previously chemically modified substrates based on Au–S bond, amine coupling, and glutaraldehyde crossing-linking was most commonly employed (Koubová et al., 2001; Singh, Verma, & Arora, 2015; Waswa, Debroy, & Irudayaraj, 2006; Zhang et al., 2014). For example, Makhneva, Farka, Skládal, and Zajíčková (2018) deposited plasma polymers onto the gold surface to provide an excellent platform for stable immobilization of antibodies using glutaraldehyde activation. A

LOD of 10^5 CFU/mL with analysis time of 10 min was achieved for *Salmonella* detection.

Except covalent binding, antibody binding proteins, which can selectively capture the Fc region of antibodies, also play a vital role in antibody immobilization for *Salmonella* detection (Nguyen, Yi, Woubit, & Kim, 2016; Oh, Kim, Park, Lee, & Choi, 2004). The third efficient way to control the orientation of bioreceptors is biotin–avidin binding. A biotinylated single-stranded oligonucleotide probe that could target the *inv*A gene of *Salmonella* was designed and immobilized onto a streptavidin-coated dextran sensor surface. The *inv*A genes isolated from bacterial cultures were amplified by a modified semi-nested asymmetric PCR and hybridized with the complementary probes on the sensor surface to generate a SPR response. This genosensor had the ability to detect *Salmonella* as low as 10^2 CFU/mL within 4.5 hr (Zhang, Yan, et al., 2012).

The label-free methods are simple and rapid, but they are always less sensitive. Incorporation of metallic nanoparticles or other materials into a SPR biosensor can further improve the detection performance due to their large molecule weights and/or high refractive index values (Wang, Munir, et al., 2010). Lei et al. (2015) used DNA probes containing streptavidin aptamers for both target recognition and signal amplification that could detect *Salmonella* as low as 60 CFU/mL. Target DNA was sandwiched between DNA probe-1 and probe-2. Then the probe-2 that contained a segment of streptavidin aptamer bound to streptavidin to further amplify the biosensor response. Melaine, Saad, Faucher, and Tabrizian (2017) reported a SPR imaging biosensor for multiplex detection of bacterial 16S rRNA of *Pseudomonas aeruginosa*, *S.* Typhimurium, and *Legionella pneumophila* using AuNPs for signal amplification with a LOD of 10 pg/mL in less than 1 hr. Antibody-functionalized MNPs serving as both separation tools and SPR labels were incorporated into a sandwich format SPR biosensor with a LOD of 14 CFU/mL, which gave four orders of magnitude improvement in the sensitivity in comparison with the direct detection format (Liu et al., 2016). It is worth mentioning that Farka, Juřík, Pastucha, and Skládal (2016) innovatively proposed a SPR-based biosensor based on biocatalyzed precipitation that claimed to be able to detect *S.* Typhimurium with LODs of 100 and 10^3 CFU/mL in buffer and milk powder, respectively. *Salmonella* was captured by the antibodies immobilized on SPR surface, followed by the binding of detection antibodies conjugated with HRP. Then HRP catalyzed the conversion of 4-chloro-1-naphthol into insoluble benzo-4-chlorocyclohexadienone, resulting in a significant enhancement of SPR signals. The sensitivity of this method was increased 40 times in comparison to the label-free method.

In order to improve the detection performance in actual food samples, a low-fouling SPR biosensor was proposed for *E. coli* O157:H7 and *Salmonella* detection based on poly(carboxybetaine acrylamide) brushes and AuNPs (Vaisocherová-Lísalová et al., 2016). The poly(carboxybetaine acrylamide) brushes provided both surface resistance to fouling and functional capabilities. The LODs were found to be 7.4×10^3 and 11.7×10^3 CFU/mL for *Salmonella* in cucumber and hamburger extracts, respectively.

Compared with other biosensors, SPR biosensors enable real-time monitoring of the binding of target bacteria with less reagent consumption. They are probably the most successful examples of commercialized biosensors for *Salmonella* detection in food. In spite of some portable SPR biosensors emerging, however, most of them are still restricted to the laboratory. Furthermore, their LOD and sensitivity for *Salmonella* detection in food samples should be further improved.

3.3 | Piezoelectric biosensors

Piezoelectric biosensors are mass-sensitive devices that incorporate an oscillating piezoelectric resonator for signal transducing (Su et al., 2013). Quartz crystal microbalance (QCM) is the most commonly used piezoelectric device based on the principle that the shifts of quartz crystal resonant frequency are proportional to the mass deposited on the chip surface (Zhu et al., 2015). They can directly monitor the binding events in a label-free way with real-time signal output, simplified detection procedure, low cost, and potential portability (Jiang et al., 2011). Table 4 (2015 to 2020) and Table S3 (before 2015) summarize piezoelectric biosensors for *Salmonella* detection. An example of QCM biosensor for *Salmonella* detection is illustrated in Figure 4.

Wang, Wang, et al. (2017) immobilized aptamers, selected via SELEX, with high affinity and specificity toward *S.* Typhimurium onto a QCM surface to fabricate a label-free biosensor for *S.* Typhimurium detection with a LOD of 7.9×10^3 CFU/mL, in an assay time less than 1 hr. The results indicated that QCM acted well in both aptamer selection and pathogen detection. To improve the detection sensitivity, Ozalp, Bayramoglu, Erdem, and Arica (2015) incorporated magnetic separation into a QCM biosensor for sensitive and specific detection of *S.* Typhimurium with a LOD of 100 CFU/mL. *Salmonella* were separated and enriched by aptamer functionalized magnetic beads from milk samples, and the captured cells were eluted and anchored onto an aptamer-based QCM surface for detection.

TABLE 4 Summary of the piezoelectric biosensors reported for *Salmonella* detection (2015 to 2020)

Serotype	Label	Bioreceptor	Application	Linear detection range	Limit of detection	Assay time	Reference
S. Typhimurium	–	Aptamer	Milk	10^2 to 4×10^4 CFU/mL	100 cells	–	Ozalp et al. (2015)
S. Typhimurium	–	Bacteriophage	–	–	–	–	Olsson et al. (2016)
S. Typhimurium	–	Aptamer	–	7.9×10^2 to 7.9×10^6 CFU/mL	7.9×10^3 CFU/mL	<1 hr	Wang, Wang, et al. (2017)
S. Typhimurium	–	Antibody	Chicken meat	1 to 10^3 CFU/mL	<1 CFU/mL in chicken	<4 hr	Fulgione et al. (2018)
S. Typhimurium	–	Antibody	–	10^5 to 10^8 CFU/mL	10^5 CFU/mL	10 min	Makhneva et al. (2018)

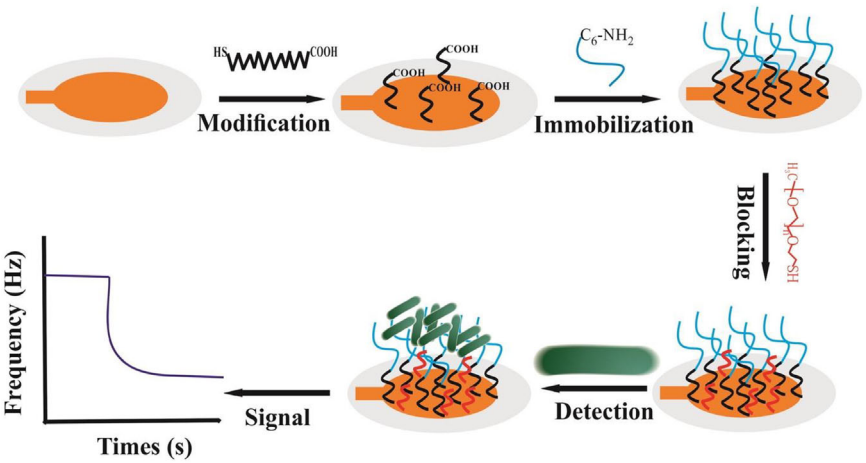

FIGURE 4 A label-free quartz crystal microbalance biosensor for *Salmonella* detection (Wang, Wang, et al., 2017). Reprinted with permission from Elsevier B.V.

Although QCM biosensors can directly measure the binding events without any labels, they always exhibit unsatisfactory sensitivities. For QCM, a change in frequency of 1 Hz is generally equivalent to a 10^{-9} g mass change (Shen et al., 2011). Therefore, it is definitely not reasonable for a single *Salmonella* bacterium (~10^{-12} g) (Zhu, Shih, & Shih, 2007) to trigger obvious shifts in frequency for a QCM biosensor. Consequently, mass-amplified QCM biosensors with improved sensitivities are investigated. A QCM biosensor coupled with AuNPs as mass amplifiers was developed for real-time and sensitive detection of *S.* Typhimurium (Salam, Uludag, & Tothill, 2013). Three detection approaches, that is, direct, sandwich without AuNPs, and sandwich with AuNPs amplification assays, were compared in this work. The results showed that the sandwich format with AuNPs amplifier exhibited the highest sensitivity with a LOD of 10 to 20 CFU/mL, compared with those of direct (1.83×10^2 CFU/mL) and sandwich without AuNPs amplification (1.01×10^2 CFU/mL) assays.

Though many QCM approaches that solely measure the changes in resonant frequency (Δf) have been demonstrated for *Salmonella* detection, in some cases, they may not be robust biosensing platforms for sensitive quantitation. The Sauerbrey equation is valid only to rigid, uniform, and thin films (Chen, Penn, & Xi, 2018). For *Salmonella* biosensors, the soft layer (e.g., the bacterial cells) on the sensor surface will not fully couple to the crystal oscillations, leading to the dampening of the oscillation (Poitras & Tufenkji, 2009). As a result, the adhered mass may not be determined accurately when only Δf is measured. Therefore, quartz crystal microbalance with dissipation monitoring (QCM-D) or resistance measurement will be more robust for biosensing of *Salmonella* because it can measure the changes in both frequency and energy dissipation (ΔD) or motional resistance (ΔR), corresponding to the changes in mass and viscoelastic properties of the adhered layer (Yongabi et al., 2020). Though Su and Li (2005a) reported a QCM biosensor for *S.* Typhimurium detection with simultaneous measurements of Δf and ΔR as early as 2005, unfortunately, relatively few efforts have been made to adapt QCM-D or QCM with resistance measurement for biosensing of *Salmonella*.

QCM-D and SPR are known independently as surface-sensitive analytical techniques with real-time and in situ detection capabilities. They have many features in common. Both of them are applicable for direct detection of

Salmonella in a label-free manner. Generally, SPR has a higher intrinsic mass sensitivity (Su & Zhang, 2004). However, as summarized in Tables 3 and 4, QCM biosensors usually exhibit comparable or lower LODs for label-free detection of *Salmonella*. This may be ascribed to the difference in the effective sensing thickness of a QCM sensor (up to several micrometers) and a SPR sensor (several hundred nanometers) (Su & Li, 2005b). Moreover, QCM may gain extra sensitivity because it measures the wet mass (including the mass of solvent between molecules) (Su, Wu, & Knoll, 2005). Both SPR and QCM-D can be applied in surface analysis to monitor specific interactions. SPR detects the changes on refractive index and can provide information about the changes on dry mass, thickness, and so on (Xing et al., 2017). And QCM-D measurements can reflect the changes on wet mass and viscoelastic properties of the adhered materials (Oh & Borrós, 2016). However, it is still a big challenge for SPR and QCM biosensors to be used outside of the lab as they are highly sensitive to external disturbances.

3.4 | Biosensors with other transducing methods

Recently, some novel signal-transducing mechanisms are also emerging for *Salmonella* detection. With magnetic signal output, magnetic biosensors, especially magnetic relaxation switching (MRS) biosensors with simple operation and high sensitivity, have been demonstrated to be useful for *Salmonella* detection (Jin, Li, et al., 2020; Wang, Zhang et al., 2015; Wu et al., 2020; Zou et al., 2019). Chen, Xianyu, et al. (2015) integrated MRS and magnetic separation into one method for one-step detection of *S. enterica*. They used lager magnetic beads for separation and the smaller ones for signal output. This MRS biosensor could detect 100 CFU/mL of *S. enterica* in spiked milk samples within 30 min. To further improve the sensitivity and stability, Wang, Xianyu, et al. (2019) employed Mn(VII)/Mn(II) interconversion into a MRS biosensor. It had low background signals because Mn(VII) ion has no T_2 relaxation rate ($R_2 = 1/T_2$). Then the ALP labeled on the captured *Salmonella* cells catalyzed the hydrolysis of ascorbic acid phosphate into ascorbic acid to reduce Mn(VII) into Mn(II), resulting in a strong R_2 signal output. This biosensor showed a LOD of 20 CFU/mL for *Salmonella* detection with recoveries ranged from 89.3% to 103.6% in milk samples.

Photothermal biosensors based on the photothermal effect of nanomaterials have been recently developed for *Salmonella* detection. Zhang, Wang, et al. (2018) integrated capture, photothermal detection, and sterilization of *S.* Typhimurium into one method through the use of immune-magnetic nanomaterials. After removing the free particles through membrane filtration, the magnetic nanomaterials on *Salmonella* that were trapped on the membrane were irradiated by a laser pen and produced a change in temperature. Using a thermal sensor to measure the change of temperature, this biosensor achieved a LOD of 300 CFU/mL. To further simplify the detection device, Du, Wang, Liu, Xu, and Zhang (2019) modified the mercury head of a common glass thermometer with antibodies to capture the target bacteria. After GO labeling and laser irradiation, the change of temperature was directly detected by the thermometer. The entire detection could be finished in 15 min with a LOD estimated to be 10^3 CFU/mL for *S.* Typhimurium. The authors also demonstrated that the matrix effects from tap water, milk, and grape juice almost had no influence on the detection.

Moreover, taking advantage of the produced oxygen that forms air gap in the capillary, Hou, Cai, Zheng, and Lin (2019) used electrical voltage as signal output for rapid detection of *S.* Typhimurium. The captured *Salmonella* was labeled with polystyrene microspheres modified with catalases. Catalases catalyzed the decomposition of hydrogen peroxide to produce oxygen and form air gap in the capillary, resulting in the change of electrical voltage. This biosensor was able to detect *S.* Typhimurium within 2 hr with a LOD of 33 CFU/mL. Wei et al. (2018) labeled target pathogens with platinum nanoparticles to generate oxygen and measured the pressure changes in a bar-chart SpinChip, achieving a LOD of 6.7 CFU/mL for *S. enterica*.

4 | RECENT TRENDS IN BIOSENSOR DEVELOPMENT FOR DETECTION OF *Salmonella* IN FOOD

Although multitudinous biosensors have enabled rapid and sensitive detection of *Salmonella* in food, their in-field applications are still limited by the unsatisfactory stability and reproducibility, high cost, and the necessary instrumentation. In recent years, the emerging of multifunctional nanomaterials and interdisciplinary advanced technologies offers a new and important direction for the development of on-site applicable and end user-accessible biosensors for rapid and sensitive detection of *Salmonella* in food.

4.1 | Nanomaterial-based biosensors

Nanomaterials with large surface area, remarkable optical, electrical, mechanical, and thermal properties (Kurbanoglu, Ozkan, & Merkoçi, 2017; Maduraiveeran, Sasidharan, & Ganesan, 2018) have been extensively

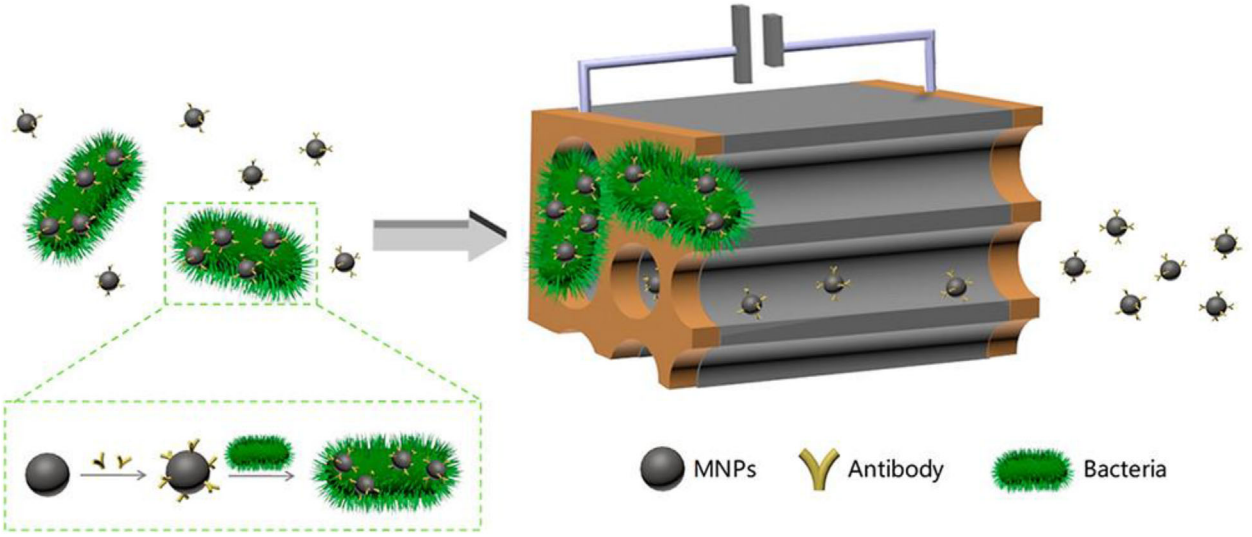

FIGURE 5 Illustration of the integrated nanochannel electrode-based biosensor for *Salmonella* detection (Zhu et al., 2020). Reprinted with permission from American Chemical Society

employed for the fabrication of novel biosensors. They are incorporated into biosensor design for better sensing performance, such as the improvement in sensitivity. In some cases, they also endow biosensors with extra features such as biocompatibility and magnetic properties (Silva et al., 2018). Nanomaterials have been applied to almost all the types of biosensors with various functions. Table 5 lists some common nanomaterials that have been extensively and successfully applied for the construction of *Salmonella* biosensors, including MNPs, AuNPs, QDs, UCNPs, carbon nanomaterials, and transition metal dichalcogenides (TMDs). Their properties and features, as well as the roles in biosensor fabrication, are also systematically summarized.

Moreover, we have also witnessed the rapid development of some new nanomaterials for *Salmonella* biosensing applications. Qiu et al. (2019) prepared an ultrathin MOF nanosheet based on a surfactant-assisted method and demonstrated its feasibility as a FRET quencher for multiplex detection of three pathogenic genes (*S. enterica*, *Listeria monocytogenes*, and *Vibrio parahaemolyticus*). Due to the high surface area and numerous accessible active sites on sheet surface that contribute to high quenching efficiency and reduced noise, this biosensor allowed sensitive detection of *Salmonella* genes at 28 pM.

Recently, Zhu et al. (2020) proposed a facile biosensing method for *S*. Typhimurium detection based on an integrated nanochannel electrode for both separation and detection. As illustrated in Figure 5, *Salmonella* was specifically captured by immune MNPs. Then the mixture of free immune MNPs and immune MNPs–target complexes was transferred to the surface of the nanochannel electrode. The free immune MNPs with smaller size than the pore size of the nanochannel penetrated through the channel, whereas the immune MNPs–target complexes were trapped. Finally, electrochemical impedance spectroscopy was employed for *Salmonella* detection with a LOD of 50 CFU/mL.

Though nanomaterials have been explosively and successfully employed in *Salmonella* biosensors for signal generation and/or amplification, several issues including their aggregation, heterogeneity, and instability should be explicitly solved in subsequent studies.

4.2 | Aptamer-based biosensors

Aptamers are recognized as "chemical antibodies" with unique advantages of high stability, ease of reproduction, and easy modification (Sabet, Hosseini, Khabbaz, Dadmehr, & Ganjali, 2017; Tan, Zhao, Du, Gan, & Quan, 2016). In most cases, they can replace antibodies for the fabrication of different types of biosensors for *Salmonella* detection. Moreover, they offer more flexibility due to their specific 3D structures. In this section, aptamers functioning differently from antibodies are discussed.

Aptamer-based FRET biosensors have been frequently reported for *Salmonella* detection as aptamers can spontaneously adhere to quencher materials via electrostatic interaction or π–π stacking. In these biosensors, fluorophore-labeled aptamers are adsorbed on quencher surface and thus bring the energy donor and acceptor in close proximity, leading to fluorescence quenching, whereas in the presence of the analytes, aptamers prefer to bind to their targets, resulting in the dissociation of aptamers from the quencher and the fluorescent

TABLE 5 Summary of commonly used nanomaterials and their main roles in *Salmonella* biosensors

Nanomaterial	Properties and features	Roles in biosensors	References
MNPs	Superparamagnetism; biocompatibility; large surface area; peroxidase-mimicking activity; ease of production	Separation and concentration tool; mass amplifier; catalytic label	Liu et al. (2016); Park et al. (2015); Xu et al. (2015)
AuNPs	Large surface area; biocompatibility; LSPR phenomenon; size-dependent color change; high electron transfer kinetics	SERS nanoprobe; colorimetric probe; FRET quencher; electrode modification; mass amplifier	Ma et al. (2014); Ma et al. (2017); Ma et al. (2018); Salam et al. (2013); Vaisocherová-Lísalová et al. (2016); Xiang et al. (2015)
QDs	Broad excitation spectra; narrow, size-tunable, and symmetric emission; improved brightness; long fluorescence lifetime; good photostability	Fluorescent and electrochemical probe; FRET donor and acceptor	Vijian et al. (2016); Wang, Wang, et al. (2015); Yin et al. (2016)
UCNPs	Capable of converting low-energy light to high-energy light; near-infrared excitation; large anti-Stokes shifts; long luminescence lifetime	Fluorescent probe; FRET donor	Cheng et al. (2017); Kurt et al. (2016)
Carbon nanomaterials (CNTs, GO, rGO, etc.)	Large surface area; capability of fluorescence quenching; excellent electron transfer capability; high mechanical strength; peroxidase-mimicking activity	FRET quencher; electrode modification; catalytic label	Duan et al. (2014); Jia et al. (2016); Singh et al. (2018); Singh, Iyer, and Giri (2012); Wu et al. (2017); Zhao et al. (2018)
TMDs	Large surface area; unique electrical, optical, and electrochemical properties; capability of fluorescence quenching	FRET quencher; electrode modification	Singh et al. (2018); Singh et al. (2016); Zhang, Zheng, et al. (2015)

Abbreviations: AuNPs, gold nanoparticles; CNTs, carbon nanotubes; FRET, Förster resonance energy transfer; GO, graphene oxide; LSPR, localized surface plasmon resonance; MNPs, magnetic nanoparticles; QDs, quantum dots; rGO, reduced graphene oxide; SERS, surface-enhanced Raman scattering; TMDs, transition metal dichalcogenides; UCNPs, upconversion nanoparticles.

emission is restored. These strategies are benefitted from the development of novel nanomaterials that can serve as quenchers for the aptamer-tagged fluorophore, such as GO, MOF, MnO_2 nanosheets, TMDs, and their composites in recent years. Satisfactory LODs down to 100 CFU/mL were obtained for *Salmonella* detection with different fluorescent labels and quencher materials (Chinnappan et al., 2018; Duan, Gong, Wang, & Wu, 2016; Duan et al., 2014).

As single oligonucleotides, aptamers can hybridize with their cDNA. Thus, displacement methods based on the affinity difference of aptamers toward cDNA and target analytes were reported (Wu, Duan, Shi, Fang, & Wang, 2014). MNPs–UCNPs probes were fabricated via DNA hybridization between cDNA modified on MNPs and aptamers conjugated on UCNPs to obtain background luminescence. With higher affinity toward the aptamers, target bacteria induced the dissociation of some UCNPs from MNPs–UCNPs probes, resulting in decreased luminescent emission. With this methodology, they obtained LODs of 25, 10, and 15 CFU/mL for *S. aureus*, *V. parahaemolyticus*, and *S.* Typhimurium, respectively.

Due to their specific 3D structures, conformational changes of aptamers may occur upon target binding. Bayramoglu et al. (2018) reported an aptamer-gated MCM-41 silica system to detect *S. enterica* in milk samples. Both the magnetic Fe_3O_4@SiO_2@poly(glycidyl methacrylate) and MCM-41 silica particles were modified with specific aptamers. *Salmonella enterica* was captured and separated by the Fe_3O_4@SiO_2@poly(glycidyl methacrylate), and mixed with the aptamer-gated MCM-41 silica nanoparticles, resulting in the conformational changes of aptamer gates to release previously loaded fluorophore molecules out of the MCM-41 particles. As low as 10^3 CFU/mL of *S. enterica* in milk samples could be detected without any culturing.

Despite being regarded as promising alternatives to antibodies, the application of aptamers for *Salmonella* detection is still challenging due to their relatively poor reproducibility in testing bacterial cells. Whole-cell SELEX has played an important role in the selection of *Salmonella* aptamers. Considering that bacteria may have different membrane properties in difference phases (Zou, Duan, Wu, Shen, & Wang, 2018), using *Salmonella* cells at different growth stages for aptamer selection may help improve the reproducibility. Moreover, because "bacteria" binding aptamers are likely specific to some entities on cell surface (Wu, Belmonte, Sykes, Xiao, & White, 2019), a deep understanding of these entities may also contribute to higher reproducibility of *Salmonella* aptamers. Furthermore, most of *Salmonella* aptasensors are still in a proof-of-concept stage, and the applications for real food samples should be further evaluated.

4.3 | Microfluidics-based biosensors

Integrating several laboratory functions into a miniaturized system is highly desirable for biosensors to be used on site. Microfluidics-based biosensors consisting of microchannels for fluids transportation with necessary components for immunoassay have received increasing attention (Bange, Halsall, & Heineman, 2005). Such devices are able to precisely control the flow of fluids in microchannels through pressure, electrokinetic, or other driving forces, and perform full analysis including sampling, separation, mixing, and detection in a single chip (Luka et al., 2015; Prakash, Pinti, & Bhushan, 2012). Benefiting from the advantages of microfluidics, they have some unique features such as capacities of automation and miniaturization, high-throughput analysis, reduced reagent consumption, less processing time, and high portability (Choi, Goryll, Sin, Wong, & Chae, 2011; Derkus, 2016; Sun, Xianyu, & Jiang, 2014; Weng & Neethirajan, 2017).

At present, optical and electrochemical detection are often integrated to microfluidic devices to develop microfluidics-based biosensors for *Salmonella* detection (Ghosh Dastider, Barizuddin, Yuksek, Dweik, & Almasri, 2015; Kim, Moon, Moh, & Lim, 2015; Li, Li, et al., 2017; Lin et al., 2014; Singh et al., 2018; Thiha et al., 2018). For example, Guo et al. (2015) designed a magnet-controlled microfluidic device that combined magnetophoretic separation with magnetic trap for selective and sensitive detection of *S.* Typhimurium in milk. The microfluidic chip consisted of a separation zone with nickel wires and a detection zone with nickel patterns. The target pathogens captured by immunomagnetic nanospheres were separated using a lateral magnetic force and later trapped between the nickel patterns as a result of the strong magnetic force between these nickel patterns. After labeled with QDs, *S.* Typhimurium with concentration of 5.4×10^3 CFU/mL could be detected in milk samples.

Recently, Jasim et al. (2019) reported a microfluidic impedance biosensor for rapid and simultaneous detection of different *Salmonella* serogroups in poultry products. As illustrated in Figure 6, the device consists of three microchannels, and each one involves a focus region to concentrate samples and a sensing region for bacterial cells detection. Poultry samples were injected into the biosensor via the main antigen inlet. Then the bacterial cells were focused into the centerline of the microchannel and pushed toward the sensing region using positive dielectrophoresis force. Finally, the binding of *Salmonella* to immobilized antibodies was detected using an impedance analyzer. This biosensor allowed sensitive detection of *Salmonella* at 7 cells/mL in 40 min.

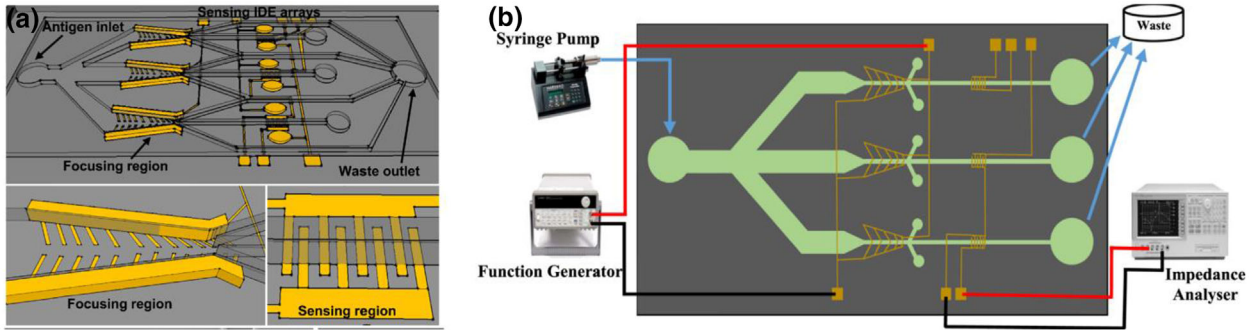

FIGURE 6 Illustration of the microfluidic biosensor for *Salmonella* detection (Jasim et al., 2019). Reprinted with permission from Elsevier B.V.

4.4 | Portable biosensor instruments

In view of in-field applications, it is necessary to integrate the biosensor into a portable device that has minimized size, light weight, and friendly interactive interface. Up to now, several efforts have been undertaken to construct portable biosensor instruments for *Salmonella* detection (Fronczek, You, & Yoon, 2013; Wen, Wang, Sotero, & Li, 2017).

A highly automated instrument system that consisted of a light-emitting diode light source, a spectrometer, and software based on LabVIEW was designed for rapid and high-throughput detection of foodborne pathogens (Lu, Zhang, et al., 2017). Integrating this portable device with fluorescent biosensing methodology, blind, in-field, and simultaneous detection of *E. coli* O157:H7, *L. monocytogenes*, and *S.* Typhimurium in different foodstuffs was accomplished in three different cities of China (Xu, Lu, et al., 2017). This portable fluorescent biosensing system produced comparable results with the conventional culture plating method in less than 60 min, demonstrating its feasibility for in-field and rapid detection of multiplex pathogens in real food samples. Such portable biosensors that enable rapid and in-field measurement of bacterial cells are in great demand as a significantly important element in building a fast-responsive and effective pathogen alert system for food safety.

4.5 | Smartphone-based biosensors

Equipped with build-in function modules such as operation systems, internal memory, high-quality cameras, communication modules, and GPS modules, smartphones can be converted into multifunctional sensing platforms for portable and in-field detection (Lu, Shi, & Liu, 2019). In recent years, they have gained ever-increasing interest to be integrated into *Salmonella* biosensors as they are more accessible and cheaper than laboratory devices (Roda et al., 2016).

In most cases, smartphones are integrated into optical biosensing systems, taking advantages of the embedded high-resolution camera. Especially, smartphones integrated with microfluidic biosensors endow great potential for in-field detection. Park, Li, McCracken, and Yoon (2013) reported a smartphone-based sensor for *Salmonella* detection on a paper microfluidic device. The system comprised two iPhone 4 smartphones. One was used as a light source, and the other was adopted as an image detector. The extent of immunoagglutination of polystyrene submicroparticles induced by antigen–antibody reaction was quantified by evaluating the Mie scattering from the digital images. The LOD for *S.* Typhimurium was found to be 10^2 CFU/mL. Furthermore, detection of *Salmonella* using a single smartphone under ambient light was also demonstrated.

Recently, Wang, Zheng, et al. (2019) established a smartphone-based fluorescent microscopic system and combined it with a microfluidic biosensor for online counting of *Salmonella*. As illustrated in Figure 7, the system is composed of a light source for fluorescent excitation, a microscope for optical amplification, and an APP for video processing. *Salmonella* were captured by immune MNPs and labeled with fluorescent microspheres. Then the labeled bacterial cells were injected into a microfluidic chip. Using the fluorescent microscopic system to monitor the fluorescent spots and the smartphone APP for video processing, this biosensor allowed on-line and sensitive detection of *Salmonella* with a LOD of 58 CFU/mL.

As discussed, smartphone facilitates simple and low-cost detection. Due to unparalleled availability, smartphone-based biosensors will in return boost the development of biosensing technology to be widely applied in *Salmonella* test, especially in the remote area.

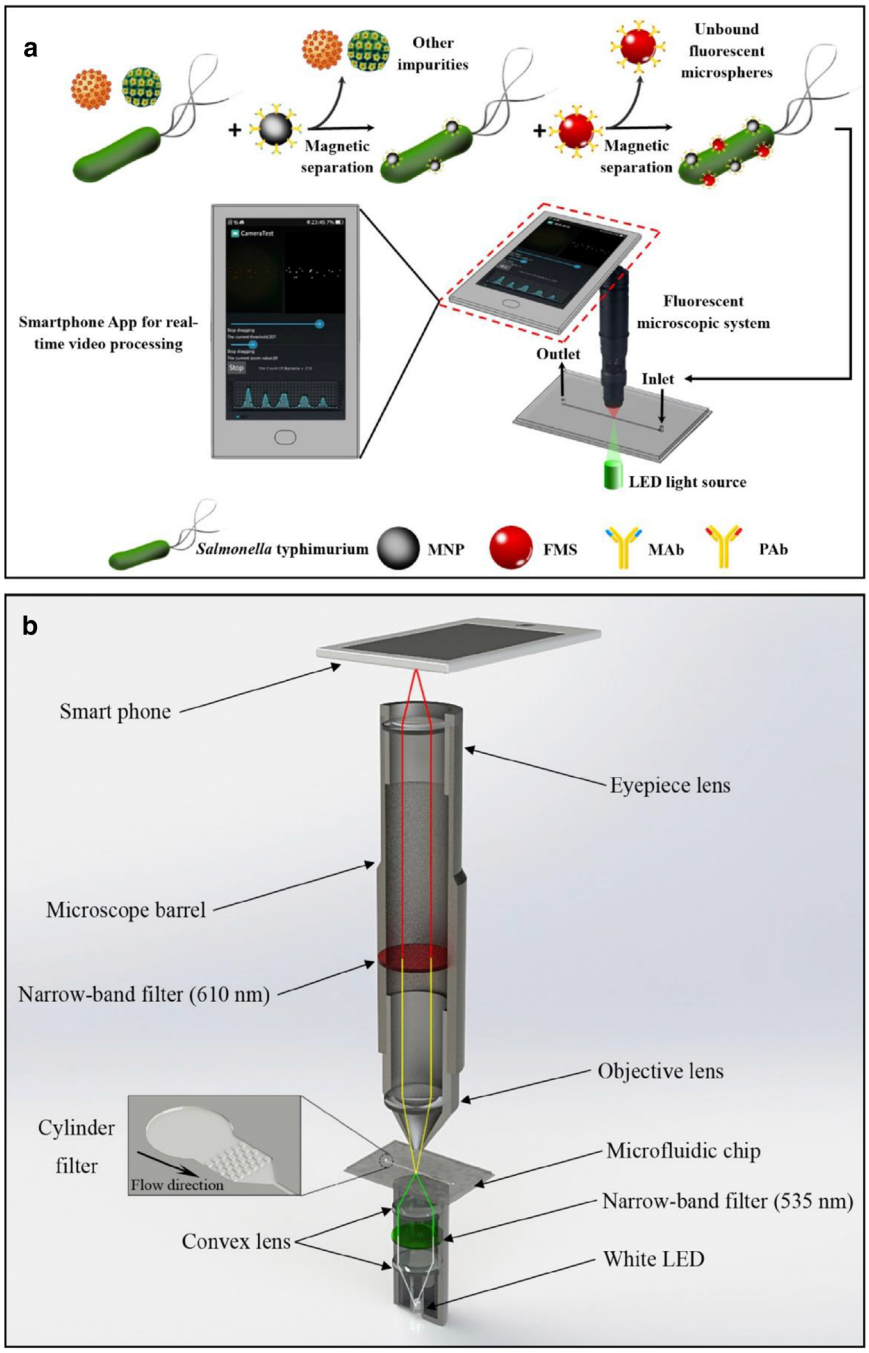

FIGURE 7 Illustration of the fluorescent biosensor based on smartphone video processing for *Salmonella* detection (Wang, Zheng, et al., 2019). (a) Principle of the smartphone-based biosensor for *Salmonella* detection and (b) structure of the fluorescent microscopic system. Reprinted with permission from Elsevier B.V.

4.6 | Commercialized *Salmonella* biosensors

Commercialization is the final goal of the development of *Salmonella* biosensors to be accessible to end users. Table 6 summarizes some commercialized biosensors for *Salmonella* detection in food.

Probably the most successfully commercialized applications are the SPR-type biosensors. One example is Biacore Q100 system (formerly Biacore AB, now part of GE Healthcare Sciences, Marlborough, MA, USA) that can provide high-throughput food safety analysis required in meat production. In combination with the Biacore HerdSense™ screening assays, this system enables serological screening of pathogens including *Salmonella* in pork. Currently, a number of SPR biosensors are available from commercial companies including GE Healthcare Sciences, Biosensing Instrument, Inc. (Tempe, AZ, USA), BioNavis, Ltd. (Tampere, Finland), IBIS Technologies, B.V. (Enschede, The Netherlands), Bio-Rad Laboratories, Inc. (Hercules, CA, USA), and Horiba, Ltd. (Kyoto, Japan). However, these SPR platforms are always designed for universal applications, and special sensor chips for *Salmonella* detection need to be customized. Furthermore, they are less

TABLE 6 Summary of commercialized biosensors for detection of *Salmonella* in food

Product model	Assay principle	Detection time	Limit of detection	Company
Biacore Q100	Surface plasmon resonance	–	–	GE Healthcare Sciences, Marlborough, MA, USA
Zephyr Pathogen Identifier[a] and PathSensors Navigator[b]	Cellular Analysis and Notification of Antigen Risks and Yields (CANARY) technology	2 min to result for Zephyr and 90 min for Navigator	1 CFU	PathSensors, Inc., Baltimore, MD, USA
Detex™ Pathogen Detection System	Electro-immunoassay	–	–	Molecular Circuitry Inc., King of Prussia, PA, USA
RAPTOR™	Fluorometric immunoassay	10 to 15 min	20,000 CFU/mL	Research International, Inc., Monroe, WA, USA
Early Warning™ Biohazard Water Analyzer	Genosensor based on DNA biomolecular probes and differential pulse voltammetry	2 to 3 hr	1 cell per 100 mL	Early Warning, Inc., Montreal, Quebec, Canada
HEATSENS_S[c]	Lab-on-a-chip microfluidic device based on plasmonic driven thermal nanobiosensing	–	–	NANOIMMUNOTECH, SL., Madrid, Spain
RapidScan™	–	≤90 min	–	ProteoSense, LLC., Columbus, OH, USA
Crystal Diagnostics AutoXpress™	Immunosensor based on disruption in an aligned liquid crystal matrix caused by aggregation of antibody covered microspheres binding to the target antigen	≤55 min	~10^4 CFU/mL	Crystal Diagnostics, Ltd., Broomfield, CO, USA
DESDEP	Genosensor based on carbon nanotube biochip with electrical signal output	≤90 min	–	Cubed Laboratories, South Bend, IN, USA

[a]For single-sample pathogen testing.
[b]For high-throughput sample testing.
[c]Prototype, and its commercial, technical, and financial viability has been proved.

automated and always restricted to the use in analytical laboratories.

In order for in-field applications, some transportable biosensors for *Salmonella* detection also have been launched. The RAPTOR™ (Research International, Inc., Monroe, WA, USA) with a physical size of 28 cm (L) × 17.3 cm (W) × 20.5 cm (H) and weight of 6.45 kg is a portable, automatic, and self-contained immunoassay-based biosensor that integrates optics, fluidics, electronics, and software into one compact system. It enables rapid detection of toxins and bacteria including *Salmonella* in 10 to 15 min. However, the LOD of this biosensor is 20,000 CFU/mL for *S*. Typhimurium so that extra pre-enrichment of the bacteria prior to detection may be necessary to detect *Salmonella* with lower concentrations. Zephyr Pathogen Identifier and PathSeneors Navigator (PathSensors, Inc., Baltimore, MD, USA) are two biosensing systems based on the Cellular Analysis and Notification of Antigen Risks and Yields (CANARY) technology from the MIT Lincoln Laboratory. These two methods can detect target pathogens such as *Listeria* and *Salmonella* with PCR levels of sensitivity and specificity. For the Zephyr Pathogen Identifier, test analysis can be finished once the sample is in the instrument in less than 2 min to results. And the Navigator takes 90 min to run but it will test 96 samples at a time. For these two instruments, necessary manual operations such as sample preparation and bacteria incubation are still required to detect an extremely low bacteria concentration (1 CFU), which may take 18 to 24 hr. Early Warning™ Biohazard Water Analyzer (Early Warning, Inc., Montreal, Quebec, Canada) is a fully automated biosensor that integrates an ultrasensitive electrochemical biosensor with automatic sample pretreatment components. It can automatically detect 1 cell per 100 mL of bacterium in water and get test results and pathogen alerts in 2 to 3 hr. Due to a different set of specific DNA probes on each working electrode, this biosensor can test for up to 25 specific bacteria, protozoa, and virus, including *Salmonella* at the same time. However, its application to complicated food samples may need to be further investigated. Therefore, there remains big challenges in the development of commercialized biosensors with high sensitivity, automation, and rapidity for *Salmonella* in complex food samples.

Although numerous *Salmonella* biosensors have been described in the literature, the commercially available ones for food industry are rather limited. Moreover, some commercialized *Salmonella* biosensors are spin-offs from research institutes. Their financial and technical viability may not be well validated. In future studies, some significant issues in *Salmonella* biosensors such as sensitivity, long-term stability, automation, minimization, detection time, and mass production must be well balanced to facilitate their commercialization.

4.7 | Biosensors for *Salmonella* surveillance of the food safety system

Salmonella can enter the food supply chain at different stages, such as contamination on farm, cross-contamination in the slaughterhouse, recontamination during transportation, and further contamination at wholesale and retail markets. Therefore, surveillance of *Salmonella* is urgently needed for the entire food supply chain. Conventional culture methods fail to provide instant information about *Salmonella* contamination because they require several days for verified results. Hence, contaminated foods cannot be controlled and recalled effectively. Biosensors are potential to provide quantitative information in a more rapid way. They are hopefully to be involved into a food safety surveillance system. By integrating with radio frequency identification (RFID) technology, GPS, as well as other advanced technologies, it is expected to provide rapid, quantitative, trackable, and sharable information about *Salmonella* contamination in the whole food supply chain, thus enhancing the food safety and reducing economic loss.

Furthermore, incorporation of biosensor data into a risk analysis model will be more beneficial for dynamic risk assessment. Quantitative microbial risk assessment (QMRA) has been regarded as an essential method to identify measures that can be taken to reduce or prevent microbial contamination, subsequently evaluate and mitigate the public health risk of the pathogens (Chen, Karanth, & Pradhan, 2020). Developed QMRA model for *Salmonella* was not dynamic feedback due to the existing problem of delayed and limited quantitative information about *Salmonella* contamination. This will need to develop the dynamic risk assessment model to predict the risk for early warning. The model is expected to be embedded to the project cloud platform and use the reliable biosensor data as the timely input.

Last but not least, biosensors are likely to enter a new stage by coupling with artificial intelligence (AI). AI biosensors and their future for healthcare application have been recently reviewed by Vashistha, Dangi, Kumar, Chhabra, and Shukla (2018) and Jin, Liu, Xu, Su, and Zhang (2020). This new concept also holds great potential to promote the surveillance and control of *Salmonella* for the food supply system. Biosensors together with other physical and chemical sensors are expected to be incorporated into the Internet of Things (IoT) to collect near real-time data. The resulted large datasets can be fed into

machine learning algorithms for prediction and decision-making, thus helping prevent *Salmonella* outbreaks. The integration of biosensors with AI technology will be a huge step toward improved food safety system.

5 | CHALLENGES IN THE DEVELOPMENT OF *Salmonella* BIOSENSORS

Biosensors have gained extensive attention for *Salmonella* detection with great potential of analysis in foodstuffs. However, as an emerging technology, they are still not ready for being used as routine analytical tools in the food industry. Some challenges are highlighted as the follows.

5.1 | Sample pretreatments

Sample pretreatments are inseparable parts of a *Salmonella* biosensor dedicated for food samples. They aim to reduce the complexity of the food matrices as well as to increase the concentration of target bacteria prior to detection. Conventional sample pretreatment methods are centrifugation and filtration (Che et al., 2000; Hoszowski, Fraser, Brooks, & Riche, 1996; McEgan, Fu, & Warriner, 2009). They enable physical enrichment of bacterial cells with simplicity and rapidity, but show limitations of non-specificity and loss of the target bacteria. Furthermore, they always fail to eliminate the matrix effects caused by soluble components.

Nowadays, much effort has been focused on novel sample pretreatment methods that are potential to be integrated into biosensors, including IMS (Du et al., 2018), microfluidic separation (He et al., 2013; Liu et al., 2019; Srbova et al., 2018), electrophoresis (Nguyen, Nguyen, Bui, & Seo, 2019; Zhang, Luo, et al., 2018), acoustophoresis (Ngamsom, Lopez-Martinez, et al., 2016), magnetophoresis (Ngamsom, Esfahani, et al., 2016), and magnetic ionic liquid-based extraction (Hice, Clark, Anderson, & Brehm-Stecher, 2019). Among them, IMS has been regarded as one of the most useful tools for selective capture, separation, and concentration of *Salmonella* prior to detection. Various nano- and micro-sized magnetic sorbents have been extensively investigated for *Salmonella* separation from different food samples (Brandão, Liébana, Campoy, Alegret, & Pividori, 2015; Xu et al., 2015). And their capabilities for large-volume sample treatment also have been demonstrated. For example, Wang, Huo, Zheng, et al. (2020) combined magnetic particle chains with magnetic flow separation to concentrate *Salmonella* cells from 50 mL of samples with a separation efficiency of approximately 70%. Even with these progresses, however, most of IMS methods are still restricted to small volume samples. Furthermore, the main challenges of most IMS techniques may include the aggregation of the particulate magnetic sorbents in complicated food matrices and the prolonged assay time, especially for MNPs with smaller sizes. Therefore, further efforts may focus on the optimization of MNPs modification and IMS (e.g., simulation of magnetic separation) in real samples and on a large scale. Additionally, magnetic materials with more interesting properties could also be investigated, such as the capacities for signal generation and amplification to realize separation/concentration signal amplification in one method.

5.2 | Detection of *Salmonella* at low concentrations

The commonly applied zero tolerance policy for *Salmonella* in ready-to-eat food (Bover-Cid, Belletti, Aymerich, & Garriga, 2017) requires detection methods to be extremely sensitive. Though some reported biosensors claim to lower their LODs down to 10 CFU/mL (Singh, Ali, Kumar, et al., 2018; Singh, Ali, Reddy, et al., 2018), most of *Salmonella* biosensors are still not sensitive enough when compared to standard culture methods and real-time PCR.

Moreover, it is always difficult to evaluate the actual analytical performance of some reported *Salmonella* biosensors in actual foodstuffs, as they are usually evaluated in optimized buffer conditions and validated in spiked food samples. Compared with these artificial samples, actual foodstuffs are more complicated, which may lead to severe matrix effects. Research has revealed that food matrices do have some adverse effects on detection performance. Xu et al. (2015) used a fluorescent aptasensor for simultaneous detection of four foodborne pathogens with a LOD of 160 CFU/mL for *S.* Typhimurium in pure culture. However, when applied it to ground beef, the LOD was increased to 750 CFU/mL. In other research, LODs in milk were also found 10 times higher in comparison to those in pure cultures (Farka et al., 2016; Srisa-Art, Boehle, Geiss, & Henry, 2018). Therefore, to detect extremely low concentrations of *Salmonella*, especially in actual food samples, is still a huge challenge. And it is also a complicated issue highly related to the choice of appropriate sample pretreatment methods, bioreceptors, and transducers.

Last but not least, LOD is commonly utilized in a *Salmonella* biosensor to describe the lowest concentration that can be reliably detected and differentiate from the assay background (González & Herrador, 2007). There exist several ways of determining the LOD of a *Salmonella* biosensor, such as calculation based on the mean of background (blank) signal plus three times of the standard deviation (Xu et al., 2016) and three times of signal-to-noise

ratio (Xiang et al., 2015). At the same time, in many reports, the LOD was determined based on the lowest bacterial concentration that could be detected. However, heterogeneous distribution of *Salmonella* cells becomes significant when the bacteria suspension is diluted to very low concentrations. In such cases, the concentration of bacterial cells determined based on the dilution may be untruthful (Wen et al., 2013), which leads to an unreliable LOD. Moreover, some reports did not present the microbial test method that they used in the experiment, which gave no solid evidence of the LOD. Therefore, it is difficult to compare the LOD values in different studies and further validation of those theoretical LODs is necessary.

5.3 | Discrimination of live and dead bacterial cells

Currently, most of the biosensors for *Salmonella* detection are based on the recognition of membrane components or DNA/RNA from bacterial cells. They always fail to discriminate between live and dead bacterial cells. The risk of infections maybe overestimated, leading to unnecessary product recalls and economic losses. Therefore, it is necessary to discriminate and detect live *Salmonella* cells from the dead ones as only the live cells are virulent and pathogenic (Fang et al., 2018).

There are several biosensors capable of detection of live *Salmonella*, among which some are based on bacterial growth and some utilize specific bioreceptors. A magnetoelastic biosensor that monitored the growth of *S*. Typhimurium in nutrient broths in real time was proposed for the detection of live cells (Horikawa et al., 2016). However, this approach is invalid for the detection of VBNC *Salmonella* cells. Bacteria in the VBNC state cannot multiply on routine culture media while are still alive and maintaining metabolic activity. The virulence of VBNC pathogens can be maintained or recovered after resuscitation (Zhao, Zhong, Wei, Lin, & Ding, 2017). It has been reported that several *Salmonella* species can enter the VBNC state and regain culturability once the environmental conditions are back to normal (Dong et al., 2020; Ferro, Amorico, & Deo, 2018). Hence, differentiating VBNC *Salmonella* from the dead ones is essential for prevention of outbreaks. A bacteriophage with the ability to distinguish viable and VBNC cells from dead *S*. Enteritidis was immobilized on a magnetoresistive biochip surface for viability assessment (Fernandes et al., 2014). Several aptamers were also selected and applied for discrimination of viable *S*. Typhimurium from the heat-killed cells (Labib et al., 2012; Zhang et al., 2017). However, their recognition capabilities toward VBNC cells may need to be further validated because VBNC cells show some differences in cell wall and membrane composition in comparison with the normal cells (Li, Mendis, Trigui, Oliver, & Faucher, 2014).

In conclusion, research in biosensors for the discrimination of live and dead *Salmonella* is still in its infancy and many technical hurdles need to be addressed including the prolonged detection time (bacteria culturing), the selection of appropriate bioreceptors, as well as the detection of VBNC cells.

5.4 | In-field applications

For in-field applications, the long-term stability and portability of biosensors, as well as food sampling, are common concerns. Biosensors always function well in the laboratory, but are instable outside of the lab as a result of the poor stability of bioreceptors. Antibodies, as the most commonly used bioreceptors, are always sensitive to temperature, pH, salinity, heavy metal ion, protease, and so on, making immunosensors not perform well in harsh environmental conditions. Therefore, robust bioreceptors should be developed to make biosensors more reliable outside of the lab. Aptamers with comparable or even higher affinity and specificity, as well as stability, are recognized as potential alternatives for *Salmonella* recognition. However, as the emerging ones, a lot of work needs to be done for a deep understanding of these recognition elements, including their selection and recognition mechanisms.

Besides, most of biosensors for *Salmonella* detection still depend largely on laborious manual operations, restricting their application to laboratory scales. Microfluidic technologies have opened new gates for the miniaturization of biosensing systems and enhanced the detection capacity. Compared with other transducers, optical and electrochemical techniques are most commonly integrated into microfluidic devices. Optical microfluidic biosensors always display desirable sensitivities. However, issues including high cost and complicated assembly process will need to be well addressed further (Kant et al., 2018). In the case of electrochemical microfluidic biosensors, their detection performance and reproducibility should be further improved. On the other hand, when compared with conventional lab-setting instruments, microfluidics-based biosensors may be less sensitive and accurate.

Last but not least, better sampling strategies are required for in-field detection of *Salmonella*. The International Organization for Standardization (ISO) has given recommended sampling methods for different types of food (e.g., ISO/TS 17728:2015 for food and animal feed, ISO 707:2008 for milk and milk products, and ISO 17604:2015 for carcasses). For example, excision, swabbing, and rinsing are three common methods for poultry carcasses sampling (Zhang, Ye, Xu, Zhou, & Cao, 2012). Generally, they are

applicable with acceptable bacteria recoveries. However, *Salmonella* can form biofilms on food contact surfaces or even the surface of food products for greater resistance to harsh conditions (Abeysundara et al., 2018; Shi & Zhu, 2009). Biofilms are hard to remove due to the strong biofilm–surface interactions (Keeratipibul et al., 2017; Merino, Procura, Trejo, Bueno, & Golowczyc, 2019) and subsequently decrease the bacteria recoveries and cause an underestimation of pathogen contamination. Keeratipibul et al. (2017) reported that the swab efficiency of bacterial biofilms was approximately 40% lower than those of recent cell inoculations in wet surfaces. Therefore, biofouling of *Salmonella*, especially in the form of biofilms, demands better sampling strategies. More fundamental studies on strategies for better removal of bacterial biofilms and their incorporation into food sampling methods are urgently needed.

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

This paper presents a comprehensive overview on biosensors for *Salmonella* detection with three main signal transducing mechanisms, including electrochemical, optical, and piezoelectric, and different bioreceptors such as antibodies, aptamers, nucleic acid probes, bacteriophages, and more. Compared with electrochemical and optical methods, piezoelectric biosensors are less studied for *Salmonella* detection due to their higher LOD ($>10^3$ CFU/mL) and their vulnerability to external disturbances that limits their in-field applications. Among optical biosensors, colorimetry, SERS, fluorometry, and SPR are four major signal transducing modes. Both SERS and SPR biosensors enable label-free detection of *Salmonella* with high simplicity and less reagent consumption. SERS can provide unique whole-organism fingerprint information. SPR biosensors have the ability for real-time monitoring of biomolecular interactions. However, the LODs of these two methods, especially for the label-free strategies, should be further improved. Generally, fluorescent biosensors can detect *Salmonella* at a lower concentration, but the background noise is high and a spectrophotometer is required. Colorimetric approaches can be used for qualificative and semiquantitative screening without the requirement of sophisticated equipment because the produced signals can be observed by the naked eyes or scanned by a smartphone. When very high sensitivity is required, electrochemical biosensors would be more appropriate. Although amperometric and voltammetric methods usually utilize extra labels for signal amplification, impedimetric biosensors have been extensively studied for label-free quantitation of *Salmonella*. Potentiometric biosensors are also very sensitive, but they need tedious sample pretreatments to eliminate other components in samples to minimize their interferences. As each type of biosensors has its own strength in a certain aspect, it is important to customize a suitable format for a specific application. For a *Salmonella* biosensor dedicated to applications in food safety, LOD, detection time, and in-field use are common concerns. Based on the literature discussed in this review, electrochemical biosensors can be potential for ultrasensitive detection of *Salmonella* with majority of publications in the past 5 years reporting LODs within 100 CFU/mL. Among electrochemical biosensors, the impedance method is known for its capability of label-free analysis. Its detection sensitivity can be further improved by using electrode-modified materials to improve electron transfer and surface area. Therefore, impedimetric biosensors coupled with novel electrode-modified materials are recommended as a candidate for ultrasensitive detection of *Salmonella*. In view of reduced assay time, "ideal" biosensors can be those that are capable of responding to the presence of *Salmonella* in food matrices without any extra labeling process. In this respect, one can choose SPR or QCM biosensors that allow label-free and real-time detection of the binding event. Moreover, the total detection time for *Salmonella* in food should be evaluated from food sampling to result report. Purification of *Salmonella* cells from complex food extracts will undoubtedly prolong the assay time, though sometimes it is inevitable to reduce severe matrix effects. Antifouling materials may provide surface resistance to fouling and help simplify sample purification, thus reducing the total assay time. Considering SPR is less sensitive to environmental disturbances in comparison with QCM, label-free SPR biosensors with antifouling coating can be a choice for *Salmonella* detection in food when rapidity is a major concern. From the aspect of in-field rapid screening of *Salmonella*, the minimization and automation of a sensing device or instrument are the major concerns. Colorimetric biosensors with naked eye or smartphone readout can be a potential candidate. At the same time, fluorescent biosensors with portable spectrometers are also applicable for in-field biosensing of *Salmonella* with high sensitivity. Moreover, IMS has been well developed for the separation and concentration of *Salmonella* cells from complex food samples. Hence, the integration of a biosensor with IMS or other sample pretreatment method is preferred for in-field detection of *Salmonella* in food.

Though the application of biosensors for *Salmonella* detection in the food industry is still immature, especially in comparison to other conventional methods, it is still a prosperous trend to develop robust biosensors for real application and commercialization. In the future, biosensing strategies in combination with nanomaterials and novel bioreceptors remain attractive with many exciting

possibilities. Increasing attention is focused on the implementation of innovative biosensing methods with portable and automated instruments such as microfluidic devices and smartphones to endow biosensors with more practical, integrated, automated, and portable features. Furthermore, with the development of information technology, biosensors in combination with big data analytics and AI are very likely to become a new trend to more effectively monitor and predict *Salmonella* contaminations in the whole food supply chain for food safety.

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AUTHOR CONTRIBUTIONS

Yafang Shen collected the literature and drafted the manuscript. Lizhou Xu critically revised the article. Yanbin Li conceptualized the idea, drafted the outline, and critically revised the article.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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