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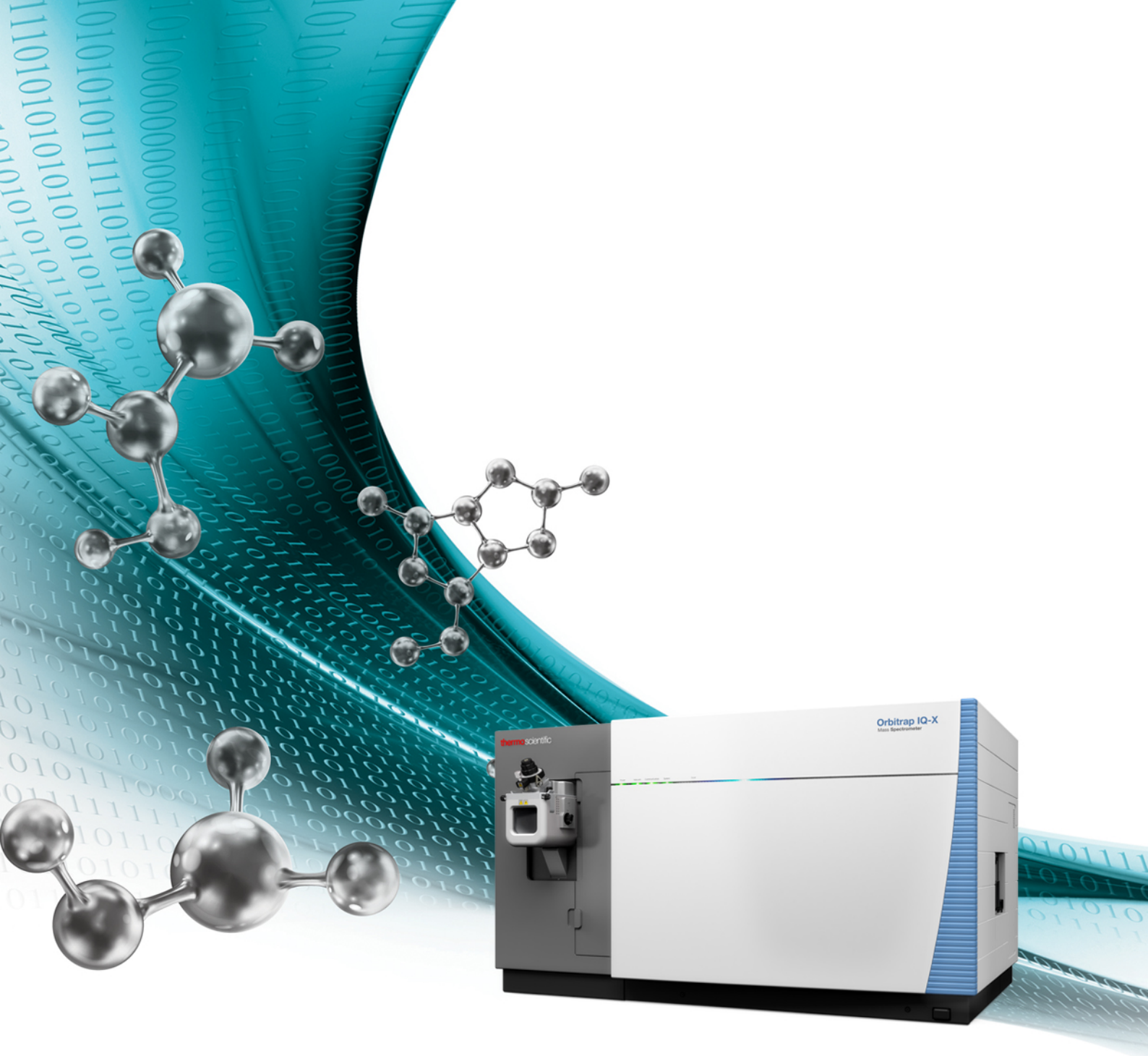
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Rapid point-of-need detection of bacteria and their toxins in food using gold nanoparticles

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Abstract

Biosensors need to meet the rising food industry demand for sensitive, selective, safe, and fast food safety quality control. Disposable colorimetric sensors based on gold nanoparticles (AuNPs) and localized surface plasmon resonance are low-cost and easy-to-perform devices intended for rapid point-of-need measurements. Recent studies demonstrate various facile and versatile AuNPs-based analytical platforms for the detection of bacteria and their toxins in milk, meat, and other foods. In this review, we introduce the general characteristics and mechanisms of AuNPs colorimetric biosensors, and highlight optimizations needed to strengthen and improve the quality of devices for their application in food matrices.

KEYWORDS

biosensing, foodborne and waterborne bacteria, localized surface plasmon resonance, meat, milk

1 | INTRODUCTION

Foodborne and waterborne diseases have become a major health issue worldwide, due to their high incidence that is in constant increase over the last 20 years (Law et al., 2015; Oliver et al., 2005; Vizzini et al., 2019). Foodborne diseases mainly occur through the consumption of foods contaminated with pathogenic bacteria, the most widespread being *Bacillus cereus*, *Campylobacter jejuni*, *Salmonella* spp., *Staphylococcus aureus*, *Listeria monocytogenes*, *Shigella* spp., *Clostridium botulinum*, *Clostridium perfringens*, *Cronobacter sakazakii*, *Escherichia coli* O157:H7, *Vibrio* spp., *Yersinia enterocoli*, and the Shiga toxin-producing *E. coli*. Additionally, food contaminated with bacterial toxins, including cholera, staphylococcal enterotoxin B (SEB), Shiga-like toxin, and ricin, represents high health risks as they may cause both acute and chronic foodborne illnesses. Some bacterial toxins, such as SEB or cereulide, are resistant to heat and persist in foodstuffs for long time periods (Ramarao et al., 2020). Foodborne infections cause diseases, when a bacterium establishes itself in

the human host after being ingested with contaminated food, or by foodborne intoxication, when the bacterium produces toxins in a food product, which is then ingested by the human host. Symptoms going from light and moderate (diarrhea, stomach ache, vomiting) to severe, such as kidney failure, and even death (Lund, 2015) can occur in the population at risk comprised immunodepressed or elderly people, newborns and children, and also in healthy people exposed to a very high dose of a microorganism.

Food contamination can occur at any stage in the food chain or under improper storage conditions if food safety issues are not taken into account. Meat and meat products, fish and mollusks, eggs and egg products, and finally milk and milk products are the most risky foods susceptible to bacterial contamination (Authority, Prevention, & Control, 2018). In 2017, the European Food Safety Authority (EFSA) reported 43,400 illnesses and 4541 hospitalizations caused by foodborne outbreaks in Europe (Authority et al., 2018). For the same year, the US Center for Disease Control and Prevention (CDC) reported 841 foodborne outbreaks that led to 14,481 illnesses and 827 hospitalizations

across the United State (Dewey-Mattia et al., 2018). These numbers are probably underestimated because many cases are not reported.

The global food industry, valued over US\$ 580 billion, concentrates its efforts on preventing food contamination with pathogenic bacteria and food recalls and avoiding huge economic losses. To ensure a safe food supply and to minimize the occurrence of foodborne diseases, it is essential to screen foods for the presence of pathogens. For this, several strategies have been used and improved over the decades. Traditional methods based on bacteria culturing are very sensitive and accurate but time-consuming, expensive, labor intensive, and unable to detect bacterial cells in viable but not cultivable (VBNC) status (Deisingh & Thompson, 2002; Nicolo et al., 2011). The possibility to detect and differentiate bacterial strains using molecular methods has emerged by means of the polymerase chain reaction (PCR)-based, and enzyme-linked immunosorbent assays (ELISA). Molecular methods are more rapid than traditional ones, and offer a highly sensitive, selective, and, in some cases, qualitative detection (Vidic et al., 2019). Nevertheless, major drawbacks of molecular methods include the need for trained personnel and sophisticated instrumentation for molecular analysis. They are high-cost and potential overestimation of the target microorganism can occur due to the detection of dead cells. Mass spectrometry, alone or coupled with MALDI, enables detection of bacterial cells and their toxins with a high specificity and sensitivity (Cao et al., 2020; Domínguez et al., 2020). However, the lack in portability due to the need for bulky instrumentation, complex chemical procedures and data analysis makes mass spectrometry unsuitable for point-of-need screening of foods for bacterial contaminations. The emerging miniaturized technologies may offer affordable, user-friendly, rapid and robust, but also sensitive and specific food safety monitoring at the point-of-need (Choi et al., 2019; Dincer et al., 2019; Vidic et al., 2019).

The need for fast, reliable, sensitive, cost-effective, user-friendly, and on-site pathogen detection to ensure food safety and prevent foodborne outbreaks in real time have pushed the agri-food sector toward nanotechnologies (Swierczewska et al., 2012). Biosensors based on gold nanoparticles (AuNPs) have been gaining importance as they enable robust and reliable detection of food contaminants. Due to the localized surface plasmon resonance (LSPR) phenomenon, AuNPs show tunable color change depending on their size, shape, and inter-particle distance (Balbinot et al., 2021; Sun et al., 2020; Verma et al., 2015). Thanks to this peculiarity, AuNPs-based assays allow a naked-eye visualization of the results.

In this review, we provide a brief introduction to the detection principles of biosensors based on the phe-

nomenon of LSPR of AuNPs and subsequently focus on the key parameters (ionic strength, pH, temperature, protein content, recognition elements) that affect the practical application of AuNP plasma sensors in food. The strategies on how to reduce these adverse effects in the detection of bacteria and their toxin in various foods are highlighted, including the application of direct and indirect target-mediated aggregation, enzyme-mediated detection, and lateral flow assays. Finally, a brief outlook on the current challenges and future development of LSPR sensors for food safety is given.

2 | BASIC CONCEPTS AND SENSOR PERFORMANCES

The term “plasmon” was first proposed by Pines and Bohm who described the resonance oscillation of free electrons at the surface of the particle in the presence of light as a surface plasmon resonance (Pines & Bohm, 1952). This phenomenon, also known as a local plasmon resonance (LSPR), based on the unique optic properties of noble metal nanoparticles, allows the color differentiation of aggregated and non-aggregated particles in a solution. LSPR sensors are commonly based on noble metals (such as gold, silver, platinum, and palladium) because they have an optical absorption band in the visible range of the electromagnetic spectrum. Gold is the most used noble metal in LSPR biosensors because gold can be easily and highly efficiently functionalized with biological molecules, and is compatible with chemically and biologically active molecules. Importantly, AuNPs biosensors can be integrated in various detection platforms (Balbinot et al., 2021; Sun et al., 2020; Zhengguo Wu et al., 2018). Dispersed spherical AuNPs (1–50 nm diameter) in a solution have a wine-red color (plasmonic band is at ~520 nm) while aggregated AuNPs have a purple color (plasmonic band is at ~630 nm) as illustrated in Figure 1a. The LSPR phenomenon reflects the collective oscillation of electron gas of AuNPs due to the interaction of free surface electrons with light. The charge polarization on the NPs surface establishes a dipolar field, which in turn, impacts the absorption and scattering of light, as illustrated in Figure 1b (Chang et al., 2019; Motl et al., 2014). The plasmon oscillation and the consequent color of AuNPs in a solution (dielectric medium) is highly affected by the inter-particle distance: the more the distance between AuNPs is reduced, the intensity of the change in color from red to purple is greater. AuNPs are also commonly used together with Raman spectroscopy for surface enhanced Raman spectroscopy (SERS) analysis. Raman and SERS analysis with AuNPs has shown the capability to analyze various food contaminants, such as toxins, pesticides, and

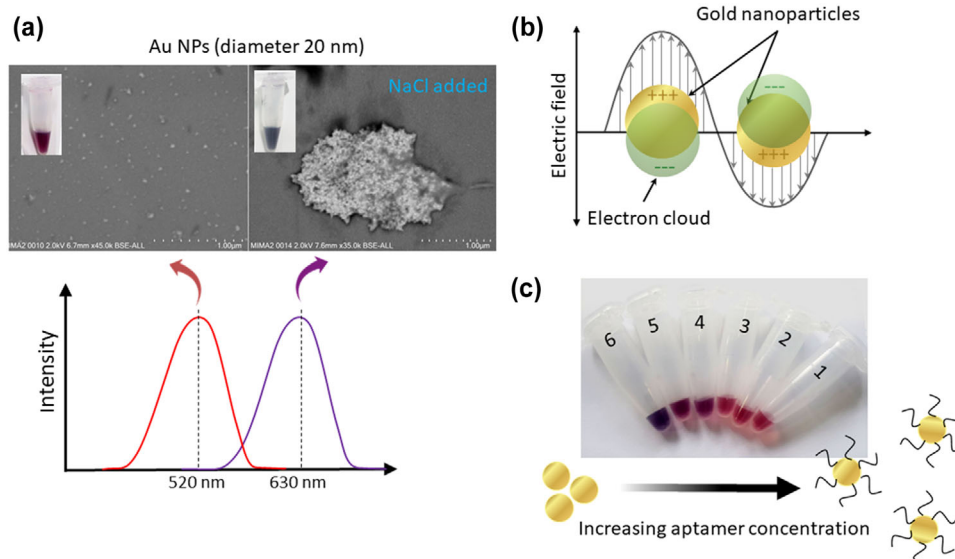


FIGURE 1 The mechanism for the detection of foodborne and waterborne bacteria and their toxins is mainly based on analyte-induced aggregation and disaggregation AuNPs. (a) A red color aqueous solution of AuNPs contains stabilized nanoparticles (diameter 20 nm), while upon salt addition, the solution changes color to blue and contains aggregated nanoparticles as observed by scanning electron microscopy. The two solutions have distinct adsorption maximums at 520 nm (red) and 630 nm (blue). (b) Schema of plasmon oscillation for a sphere, showing the behavior of metallic nanospheres in an external electric field. (c) DNA (aptamer) in a solution prevents AuNPs aggregation in a concentration-dependent manner

microorganisms. Some recent reviews have addressed the use of AuNPs for analysis in foods when coupled to Raman spectroscopy (Balbinot et al., 2021; Lin & He, 2019).

The simplest and most commonly used method to synthesize AuNPs is the citrate reduction method. First reports on AuNP synthesis by reduction of gold (III) salt (usually HAuCl_4) by trisodium citrate go back to the 1940s (Hauser & Lynn, 1940). The citrate reduction method was developed by Turkievich et al. (1951), and further optimized by Frens (1973) to enable control of the nanoparticle size by varying the trisodium citrate content. The role of sodium citrate is twofold: it functions as a weak reducing agent and a capping agent stabilizing nanoparticles. The ratio between the gold salt and citrate controls the particle size (Dong et al., 2020; Pong et al., 2007). Besides trisodium citrate, other reductants have been used, such as sodium borohydride (Jana et al., 2001), tannic acid (Slot & Geuze, 1984), ascorbic acid (Kimling et al., 2006), amine molecules (Niidome et al., 2004), or dextran (Y. Wang et al., 2010). Modifications of the synthesis protocol have resulted in AuNPs with different geometrical shapes as a result of controlling the pH and precursor to reductant concentration and room temperature synthesis (Tyagi et al., 2016). One modification is the “seed-mediated growth method” as initially formed small AuNP seeds grown in solution are used to synthesize AuNPs with controlled morphology and dimensions (Bastús et al., 2011). Systematic small manipulation of synthesis parameters can result in varied shapes

and sizes of AuNPs in aqueous solution at room temperature (Sau & Murphy, 2004).

To control the aggregation state of AuNPs for detection purposes, it is essential to manage their stability in the solution. The aggregation state of AuNPs depends on the equilibrium between the electrostatic repulsive force and van der Waals attractive force in a solution containing nanoparticles, recognition elements, and the target. Two main strategies, electrostatic and steric, are used to stabilize AuNPs. Electrostatic stabilization is achieved by the addition of molecules with a similar electrical charge as ions in the medium, in order to form a repulsive electric double layer and disperse AuNPs. Steric stabilization is obtained upon binding of ligands to the NPs to create a physical hindrance to particle aggregation (Aldewachi et al., 2018). To enable detection of a target, its addition to the solution has to alter the AuNPs aggregation state and consequently change the solution color as illustrated in Figure 1c.

The target may induce AuNPs aggregation by cross-linking or by a simple adsorption/desorption process (Zhengguo Wu et al., 2018). Upon cross-linking, specific bonds are created among aggregated AuNPs while in non-cross-linking the interaction occurs between the recognition element and a biomarker (Aldewachi et al., 2018). In the second case, the ionic strength of the solution controls the aggregation of AuNPs. Detection methods based on inter-particle cross-linking aggregation of AuNPs were

first developed by Mirkin and co-workers (Elghanian et al., 1997; Giljohann et al., 2010; Mirkin et al., 1996).

The most common recognition elements are ssDNA probes, antibodies, peptides, bacteriophages, and aptamers. DNA probes detect specific nucleic acid sequences of a pathogen. Storhoff et al., established that the aggregate size is crucial for optical properties of DNA-linked nanoparticle assemblies (Storhoff et al., 2000). Prasad et al., have developed a colorimetric genosensor for naked-eye detection of *Salmonella* spp. in food samples (Prasad & Vidyarthi, 2011). The biosensor detected PCR products using a complementary ssDNA probe immobilized onto AuNPs. Before addition of PCR products, the probe was adsorbed on colloidal AuNPs and prevented their aggregation. Upon probe hybridization with the target DNA, the formed dsDNA desorbed from AuNPs inducing color change of the solution from red to purple. The sensitivity of this colorimetric assay was higher than gel-based visualization of the same PCR products.

Antibodies, peptides, bacteriophages, and aptamers can target whole bacterial cells. Employment of such recognition elements drastically simplifies the test, by shortening sample preparation prior to analysis, which significantly reduces the time and the cost of the assay. For instance, thiolated chimeric phages displaying different specific receptor binding proteins that naturally target the desired bacterial species were incubated with bacteria, including *Pseudomonas aeruginosa*, *E. coli*, and *Vibrio cholera* and added to AuNPs colloidal solution (Peng & Chen, 2018). The covalent attachment of phages–bacteria complexes to AuNPs, due to the formation of thiol–gold bonds, induced aggregation of AuNPs and generated a colorimetric signal. This strategy demonstrated rapid and specific bacterial detection, with a limit of detection (LoD) of ~100 cells.

3 | CRITICAL PARAMETERS

The LSPR phenomenon reflects the size, composition, morphology, inter-particle distances, and orientation of plasmonic nanostructures. Performances of a LSPR colorimetric test in food matrices may be compromised by food components that alter these parameters. Ascorbic acid, ions, such as Cl^- , Ca^{2+} , Na^+ , K^+ , SO_4^{2-} and PO_4^{3-} , carbohydrates such as dextrose or sucrose, proteins and amino acids are all reported to interfere with the detection process (Paul et al., 2017). This is particularly the case in assays using non-modified AuNPs that are highly sensitive to the surrounding medium. The dynamics of physicochemical interactions between food matrix components and AuNPs has to be analyzed and predicted in order to design signal transducers for a visual readout.

The buffer plays a crucial role in LSPR colorimetric detection. The ionic strength of the buffer may modify the adsorption capacity of AuNPs and their aggregation state (X. Zhang et al., 2012). Water soluble salts, such as MgSO_4 , NaCl , or MgCl_2 , are usually used to adjust the ionic strength of the buffer and optimize the sensors' analytical parameters (H.-S. Kim et al., 2017; Y.-J. Kim et al., 2018; Ledlod et al., 2020). Salts neutralize the repulsive forces between AuNPs, which perturbs the equilibrium between van Der Waals attractive and electrostatic repulsive forces, and favors particle aggregation (Gao et al., 2012; Ledlod et al., 2020). A higher ionic strength results in faster aggregation and lower sensitivity (Hianik et al., 2007). For instance, Hianik et al. showed a decrease of the sensor sensitivity with the increase of salt concentrations (Hianik et al., 2007). Interestingly, Su et al. showed that the interferences of various common ions were not the same in the colorimetric test for *E. coli* O157:H7 detection (Su et al., 2012). No color change was observed upon addition 1 mM Al^{3+} , Mg^{2+} , K^+ , Cl^- , SO_4^{2-} , and NO_3^- , but the addition of 0.1 mM Ca^{2+} resulted in a color change. This indicated that Ca^{2+} from a food sample could bring out false-positive results for bacterial detection using the assay.

The pH of the solution is another critical factor because the pH influences the surface charge of AuNPs, and electrostatic interactions involved in binding processes (Su et al., 2012; A. Wang et al., 2016). Jiang et al. reported faster binding of non-thiolated DNA onto negatively charged AuNPs at pH 3 than at the neutral pH (Jiang et al., 2013). Similarly, Ma et al. showed that adsorption of DNA onto AuNPs at pH 3 required only a few minutes, while at neutral pH several days were needed (Requena et al., 2018), and Zhang et al. highlighted the decrease in adsorption of DNA at AuNPs for increasing pH (X. Zhang et al., 2013). The facilitation of DNA adsorption onto AuNPs at acidic pHs originates probably from the protonation of adenine and cytosine and reduction of the DNA negative charge. However, pH 3 was not found to be an optimal pH in the majority of publications. For instance, Kim et al. determined pH 5.5 as the most suitable pH since it promoted DNA adsorption and improved stability of conjugates, while other authors asserted a pH range from neutral to slightly basic (pH 7.3–8.2) as the most suitable due to the stable equilibrium between attractive and repulsive forces at the surface of AuNPs (Hianik et al., 2007; Ledlod et al., 2020). It appears, thus, that the most suitable pH of the solution cannot be standardized but should be optimized for each test and each food matrix. In addition, some variations of pH may denature proteins and oligonucleotides and block the recognition event.

The influence of the assay temperature on sensitivity was likewise stressed. The adsorption rate of a biomolecule onto AuNPs depends on the temperature (H. Li & L. J.

Rothberg, 2004; Vial et al., 2014). Ideally, a binding rate of about 50 % is achieved when a short oligonucleotide (<40 nucleic acid bases) is incubated with AuNPs at 37°C for 30 hr (Requena et al., 2018). However, the binding rate becomes lower upon temperature decrease, which may disable the point-of-care detection of pathogens at room or refrigerated temperatures applied for food storage. Feng et al. observed that the binding rate of about 40% was reached upon incubation of an aptamer with AuNPs at 37°C for 24 h, while the binding rate decreased to 32% and 20% at 15°C and 4°C, respectively (Feng et al., 2019). On top of that, it is better to perform assays at higher temperatures when possible. The downside risk in excessive temperature increase is a secondary structure modification of biomolecules, and loss in sensor sensitivity (H. Li & L. J. Rothberg, 2004).

The interactions between DNA and AuNPs have been extensively studied because the majority of LSPR colorimetric assays use the DNA detection probe. Although both ssDNA and dsDNA are negatively charged molecules, ssDNA adsorb faster than dsDNA onto AuNPs. Single and double DNA strands have different electrostatic properties in their native conformation due to the different exposition of negatively charge phosphate backbones to the solution (Bloomfield & Crothers, 2000). The uncoil capacity of ssDNA enables a higher exposition of its bases and facilitates adsorption, while the double helix of dsDNA presents negatively charged backbones to the negatively charged AuNPs (Y. S. Kim et al., 2011; F. Li et al., 2018; H. Li & L. Rothberg, 2004). The adsorption rate also depends on the sequence length, with short oligonucleotides (<40 nucleic acid bases) binding more rapidly to AuNPs (H. Li & L. J. Rothberg, 2004; X. Zhang et al., 2012). Short sequences are more stably adsorbed on AuNPs and protect them better from aggregation than long ones (F. Li et al., 2018; Y. Luo et al., 2015). Additionally, the adsorption rate is base discriminative, thus adenine has the highest affinity to Au surfaces, followed by cytosine, guanine, and thymine (Jiang et al., 2013; H.-S. Kim et al., 2017). The sensor stability can be increased by adding a short adenine base linker at one end of the DNA sequence (Y.-J. Kim et al., 2018; X. Zhang et al., 2013). Finally, to optimize analytical performances of a LSPR sensor it is necessary to adjust the DNA/AuNP concentration ratio as demonstrated in many publications (Q. Fang et al., 2019; H.-S. Kim et al., 2017; Y.-J. Kim et al., 2018; Y. S. Kim et al., 2010; Y. Luo et al., 2015; Ma et al., 2017; Requena et al., 2018; Yuan et al., 2014).

Oligonucleotides are commonly tagged with the thiol group at one end to enable their covalent binding to AuNPs via S—Au bonds to improve the stability of DNA/AuNPs complexes. The high stability of these complexes offers improved resistance to salts and other molecules from food

matrices, thermal treatment, or pH variations (Gao et al., 2012; Zhengguo Wu et al., 2018).

4 | PROTEIN ADSORPTION ON AuNPs

Proteins, as essential molecules, are present in almost any type of food. They interact readily with AuNPs and form a corona shell around particles. Its thickness and structure depends on the medium composition but also on the NPs' physicochemical properties and time of exposure (García-Álvarez et al., 2018; Piella et al., 2017). Wang et al., have shown that a protein corona created by albumin adsorption on AuNPs decreased the detection signal of the LSPR sensor by more than 20% compared to the detection signal observed in a buffer solution containing no protein (H. Wang et al., 2019). Most research on protein corona formed around AuNPs has been performed using biological fluids or cell media with only a very few dealing with this point using food matrices. Recently, Tao et al., selected milk as a model and showed that milk protein corona disturbed AuNP-aptasensors, AuNP-immunosensors, and AuNP-dichlorofluorescent sensors decreasing their sensitivity up to 80% (Tao et al., 2020). In addition, the polyethylene glycol backfilling strategy was ineffective in mitigating the protein corona negative effect. This demonstrates that AuNPs-based sensors should be calibrated in each food matrix to provide the test accuracy.

4.1 | Indirect target-mediated AuNPs aggregation

In direct LSPR assays, AuNPs aggregation is triggered by the stronger interaction between the stabilizer (aptamer, antibody) and target causing detachment of the stabilizer from the AuNP surface resulting in a color change, as illustrated in Figure 2a. Most label-free LSPR sensors function as direct assays. However, many molecules, especially proteins, present in food samples could additionally stabilize AuNPs and lead to detection failure by preventing AuNPs aggregation. Indirect target-mediated AuNPs aggregation, as a two-step procedure has been proposed to minimize potential interference from the matrix factors (Figure 2b). In the first step, aptamers/antibodies are mixed into the sample to allow their binding to the target bacterium. Then, aptamers/antibodies can be easily depleted from the solution using centrifugation. Using a supernatant in the second stage enables AuNPs to aggregate, resulting in a color change. In the absence of target bacteria, target-specific sensing elements cannot be removed by centrifugation in the first step. Freely diffused aptamer/antibodies in the supernatant adsorb onto AuNPs in the second step

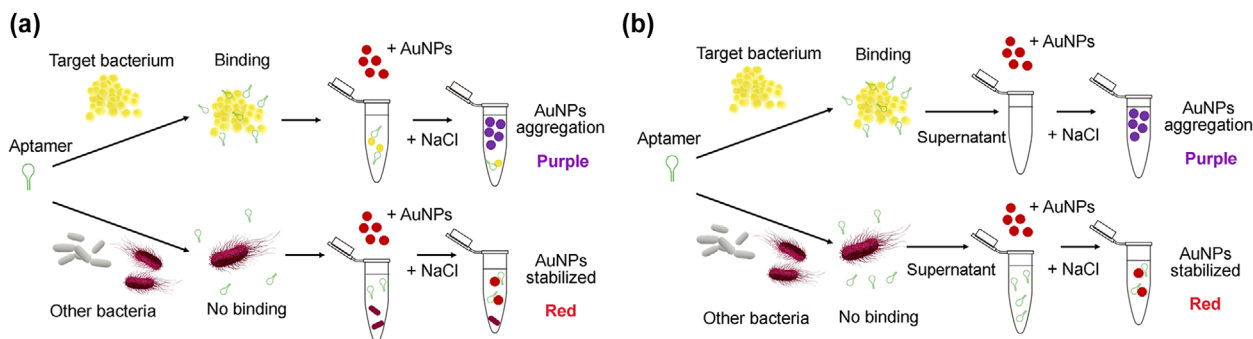


FIGURE 2 Schematic illustration of a (a) one-stage and (b) two-stage colorimetric platform designed to detect bacterial cells using AuNPs and aptamers

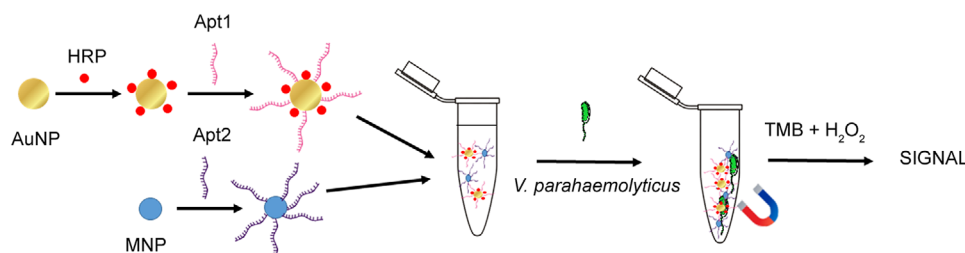


FIGURE 3 Schematic presentation of *V. parahaemolyticus* detection by a colorimetric aptasensor based on HRP enzymatic reaction (S. Wu et al., 2015). AuNPs modified with horseradish peroxidase (HRP) enzyme and the first specific aptamer (Apt1) together with magnetic nanoparticles (MNPs) carrying the second specific aptamer (Apt2) are added to the sample. Bacterial cells with attached AuNPs-Apt1 and MNP-Apt2 are collected using an external magnet and washed to eliminate the matrix. After addition of the HRP substrate TMB, and the activator H₂O₂ a blue colored reaction product is formed signaling the presence of the pathogen

and prevent salt-induced aggregation and solution color change. Indirect target-mediated tests have been successfully applied to bacterial detection in powdered infant formula (H.-S. Kim et al., 2017) and chicken meat (Y.-J. Kim et al., 2018).

4.2 | Enzyme-mediated detection

Sensitivity and specificity of LSPR assays can be improved by coupling AuNPs to an enzymatic reaction. Wu et al. have developed a colorimetric aptasensor for the detection of *Vibrio parahaemolyticus* cells (S. Wu et al., 2015). The aggregation of AuNPs occurred in the presence of *V. parahaemolyticus* due to a sandwich complex formation. Two different aptamers targeting bacterial whole cells were used: the first, Apt1, was thiolated and covalently linked to AuNPs via gold–thiol conjugation, while the second, Apt2, was biotinylated and attached by affinity to the avidin-modified magnetic nanoparticles (MNPs), as shown in Figure 3. In addition, horseradish peroxidase (HRP) was immobilized onto AuNPs-Apt1. After incubation of *V. parahaemolyticus* with AuNPs-HRP-Apt1 and MNPs-

Apt2 in a solution, a magnetic field was applied to collect the AuNPs-HRP-Apt1-Target-Apt2-MNPs complexes. Subsequently, addition of the HRP substrate, tetramethylbenzidine (TMB), in the presence of H₂O₂, generated a colorimetric signal proportional to the bacteria concentration. A LoD as low as 10 CFU/mL was reached. In the absence of targeted bacterial cells, free AuNPs-HRP-Apt1 were not collected by the magnet and no signal was observed upon TMB addition.

Bacterial toxins can be detected using their cleaving enzyme as recognition elements. For instance, a rapid and sensitive colorimetric assay for botulinum neurotoxins serotype A light chain (BoLcA), produced by *C. botulinum*, was developed by Liu et al. (X. Liu et al., 2014). Two specific peptides cleaved by BoLcA were used: Peptide1 carrying a biotin tag at one terminus and a thiol tag at the other, and bi-biotinylated Peptide2. In the first strategy, Peptide1-AuNPs aggregated upon the addition of neutravidin-functionalized AuNPs due to particle cross-linking. In the presence of BoLcA, Peptide1 was cleaved and no aggregation occurred. The LoD of this assay was 5 nM of BoLcA. In the second strategy, Peptide2 with two biotin moieties, one at each terminus was used to bridge

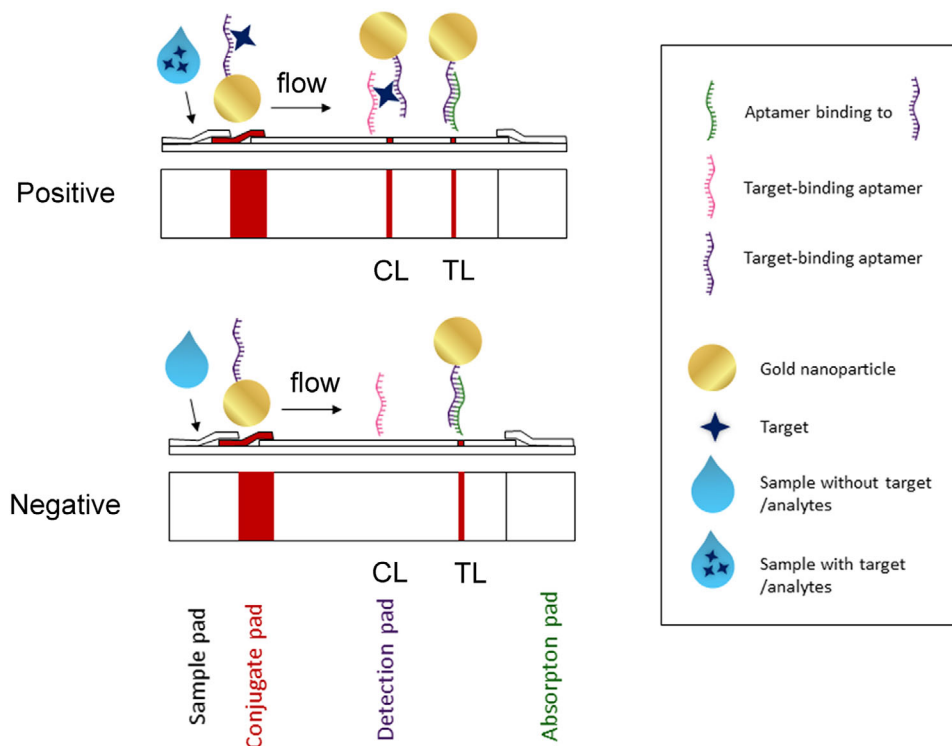


FIGURE 4 Schematic representation of the lateral flow test showing movement of a sample and aptamer-labeled AuNPs across the strip providing a positive or negative result

neutravidin-AuNPs. Again, cleavage of the peptide prevented nanoparticle aggregation. The LoD obtained with the second strategy was only 0.1 nM of BoLcA. Utilization of enzymes attached to AuNPs allows applications in various matrices. However, molecules such as proteins, or fats and ions from some foods may inhibit enzymatic reactions.

Some examples of AuNPs-based biosensors for bacteria and their toxin detection are given in Table 1.

4.3 | Lateral flow

Colorimetric methods may be performed on a flat substrate format enabling separation of some proteins from the target. Lateral flow assays performed on paper substrates, which use AuNPs as a color marker, are probably the most used point-of-need tests covering a variety of applications. In lateral flow assays, the sample is guided through capillary movement over different functional membranes (Sajid et al., 2015). As illustrated in Figure 4, a standard lateral flow strip has four main parts: sample pad, made of cellulose, where the sample is dropped; conjugate pad, made of glass fiber, containing AuNPs bioconjugated with the first recognition element (antibody, aptamer); detection pad, a nitrocellulose sheet where the result is revealed on the test line (TL), containing a second recognition ele-

ment for the target, and the control line (CL) containing a probe that binds to the first recognition element; and finally the absorption pad made of cellulose. The capillary movement provides target separation from surrounding proteins and other materials from the sample matrix (Quesada-González & Merkoçi, 2015). To improve the separation, additional filters can be integrated on the sample pad preventing migration of large particles. However, filters cannot be employed when whole bacterial cells are targeted. Alternatively, the sample pad may contain pre-stored reagents to stabilize pH and ionic strength in order to increase specific and decrease non-specific binding to AuNPs. Then, the solution flows from the sample pad to the conjugate pad, where the bioconjugated AuNPs recognize the target in the first recognition event. The solution then continues to flow along the detection pad, where the complex target/labeled-antibody(aptamer) binds to the capture element of the TL, during the second recognition event. Finally, the sample passes through the CL and arrives to the absorbent pad. The sensitivity of a lateral flow assay maybe improved by decreasing the flow rate and increasing the time of the test by engineering the pad structure (Sena-Torralba et al., 2020; S.-F. Zhang et al., 2019), by optimizing the concentration of recognition element on the surface of AuNPs (Byzova et al., 2017), or by increasing the amount of the capturing antibody on the TL (Pan et al., 2018).

TABLE 1 Target bacteria and their toxins, recognition elements, and AuNPs-based tests used for detection in milk

Target	Nanoparticles-type of test	Recognition element	Visualization	Limit of detection (LoD)	Reference
Bacteria					
<i>C. jejuni</i>	Au@Pd enzymatic reaction	Aptamer	Naked eyes	100 CFU/mL	(Dehghani et al., 2018)
<i>Cronobacter sakazakii</i>	AuNPs colorimetric test	Aptamer	Naked eyes	7.1×10^3 CFU/mL	(H.-S. Kim et al., 2017)
<i>Salmonella</i>	AuNPs-MNCs-LFI	Antibody	Image processing/Naked eyes	10^3 CFU/mL	(Hwang et al., 2016)
<i>Salmonella</i>	AuNPs-SYBR green	Aptamer	Naked eyes	10 CFU/mL	(Z. Fang et al., 2014)
<i>S. typhimurium</i>	AuNPs colorimetric test	Dual aptamers	Naked eyes	95 CFU/mL	(S. Chen et al., 2020)
<i>S. typhimurium</i>	AuNPs colorimetric test	Aptamer	Naked eyes	72 CFU/mL	(Ma et al., 2017)
<i>S. typhimurium</i>	MNPs-AuNPs sandwich assay	Aptamer	Naked eyes	1.9×10^2 CFU/mL	(Duan et al., 2016)
<i>S. typhimurium</i>	AuNPs ELAAS	Antibody; Aptamer	UV-vis	10^3 CFU/mL	(W. Wu et al., 2014)
<i>Salmonella</i>	AuNPs-LAMP-LPD	Antibody	Naked eyes	/	(Zhao et al., 2017)
<i>S. aureus</i>	AuNPs colorimetric array coupled with TSA	Aptamer	Plate reader	9 CFU/mL	(Yuan et al., 2014)
<i>P. aeruginosa, V. cholerae, E. coli</i>	AuNPs colorimetric test	Phage	Naked eyes	100 cells	(Peng et al., 2020)
<i>E. coli</i> O157:H7	Au ^{MBA} @Ag SERS-LFS	Antibody	Naked eyes/biosensor	5×10^4 CFU/mL	(H. b. Liu et al., 2019)
<i>E. coli</i> O157:H7	MNPs-AuNPs colorimetric test	Antibody	Naked eyes	41 CFU/mL	(X. Xu et al., 2017)
<i>E. coli</i> O157:H7	AuNPs	Aptamer	Strip reader	10 CFU	(W. Wu et al., 2015)
<i>S. aureus</i>	MNPs-AuNPs	Antibody	Naked eyes	1.5×10^3 CFU/mL	(Sung et al., 2013)
<i>E. coli</i> O157:H7	AuNPs-LFI	Antibody	Naked eyes	1.14×10^3 CFU/mL	(M. Chen et al., 2015)
<i>E. coli</i> O157:H7, <i>Shigella boydii</i>	AuNPs-LFI	Antibody	Naked eyes	4 CFU/mL	(Song et al., 2016)
<i>Cronobacter sakazakii</i>	AuNPs	Antibody	Naked eyes	10^3 CFU/mL	(Pan et al., 2018)

(Continues)

TABLE 1 (Continued)

Target	Nanoparticles-type of test	Recognition element	Visualization	Limit of detection (LoD)	Reference
Toxins					
Melamine	AuNPs colorimetric test	/	Naked eyes	0.5 mg/L	(Kumar et al., 2014)
<i>Staphylococcal enterotoxin A</i>	AuNPs colorimetric test	Antibody	Naked eyes	/	(Haddada et al., 2017)
<i>Botulinum neurotoxin</i> type A	AuNPs colorimetric test	Antibody	Microscopic imaging	10 pg/mL	(Cheng & Chuang, 2019)
<i>Staphylococcal enterotoxin B</i>	AuNR@Pt fluorescent test	Aptamer	Spectrophotometer	0.9 pg/mL	(Zhengzong Wu, He, & Cui, 2018)
<i>Staphylococcal enterotoxin B</i>	AuNPs colorimetric test	Aptamer	Naked eyes	0.5 ng/mL	(Mondal et al., 2018)
<i>Staphylococcal enterotoxin B</i>	Magnetic gold nanorod	Peptid	SERS	2.2×10^{-16} M	(Temur et al., 2012)

Abbreviations: AuNPs, gold nanoparticles; MNCs, magnetic nanoparticle clusters; LAMP, loop-mediated isothermal amplification; LDP, lateral flow dipstick; LFI, lateral flow immunoassay; MNPs, magnetic nanoparticles; SERS, surface enhanced Raman spectroscopy; TMB, 3,3',5,5'-tetramethylbenzidine.

Note: Studies presented are from the past 10 years.

Despite the many advantages of colorimetric methods performed on flat substrate format over those performed in solution there are still some technical drawbacks especially for samples containing high concentrations of proteins. A protein corona formed over AuNPs may prevent the binding event and the test may give a false-negative result, or the corona composition may non-specifically bind to some particles in the sample and provide a false-positive result. False-positive results may be removed by adding sucrose, tween or by nitrocellulose pretreatment (de Puig et al., 2017).

5 | BACTERIAL CELLS AND TOXIN DETECTION IN MILK

Milk is one of the most challenging food matrices for bacteria and toxin detection using colorimetric sensors. Milk is a colloidal solution composed of water, butterfat globules, carbohydrates, protein complexes, and various minerals (Quigley et al., 2013). It can support the growth of diverse microorganisms, because in addition to being highly nutritious, milk is of near neutral pH and has a high water activity. Due to bacterial ubiquitous presence in air, soil, water, and dairy plant environments, milk can be contaminated by pathogenic bacteria not only in farms but also during processing, storage, and distribution (Vidic et al., 2020). Thermophilic bacterial strains, such as *B. cereus*, sulfate-reducing clostridia, *Salmonella* spp., *Listeria* spp., coagulase-positive staphylococci, *E. coli*, and Enterobacteriaceae survive pasteurization, while psychotropic bacterial strains such as *Pseudomonas* and *Acinetobacter* spp. are frequently established in milk during cold storage (Quigley et al., 2013). Besides that, *S. aureus*, *E. coli* O157:H7, *C. sakazakii*, and *Campylobacter* are pathogens that contaminate milk if hygienic milking conditions are not fully respected.

Among milk ingredients fat, lipids, Ca^{2+} ions, and proteins are potent inhibitors of the LSPR phenomenon and may interfere in bacterial detection. Several strategies for milk treatment prior to analysis have been proposed in order to eliminate these inhibitory components from milk. For instance, fats can be easily scooped out from milk after sample centrifugation because they rest floating (Marathe et al., 2012). Proteins, such as casein and whey, precipitate upon addition of 0.5 M EDTA (Marathe et al., 2012). Similarly, proteins can be precipitated by decreasing the pH of skimmed milk (Haddada et al., 2017). A mixture of trichloroacetic acid and chloroform was shown to dissolve fats and other organic molecules and deposit proteins in a 1 min procedure (Y. Luo et al., 2015). Otherwise, subsequent 1 min vortexing of milk samples after addition of potassium hexacyanoferrate (II) trihydrate and

zinc sulfate efficiently precipitate proteins and fats (Kumar et al., 2014). Such procedures involve centrifugation steps to separate bacterial fractions from the assay inhibitors. *C. sakazakii* was successfully detected in milk and infant formula using an enhanced lateral flow assay but samples were centrifuged and re-suspended to remove lipids and proteins before being deposited on the sample pad (Pan et al., 2018). Such sample pretreatment limits point-of-need applications of the test. Using this strategy, the sensitivity of the enhanced lateral flow for detection of *C. sakazakii* in powdered infant formula was 10^3 CFU/mL and the time of analysis was 3 h. Traditional microbiological methods take 5 to 7 days to complete analysis of *C. sakazakii* and cannot be performed on-site.

In some cases, centrifugation steps can be replaced by portable separation methods like filtration (Requena et al., 2018), or magnetic separation (Cho & Irudayaraj, 2013; Duan et al., 2016; Kotsiri et al., 2019; Poshtiban et al., 2013; Quintela et al., 2019). For instance, Duan et al. applied MNPs as bacterial concentration elements and aptamer AuNPs as colorimetric probes for detection of *Salmonella typhimurium* in spiked milk (Duan et al., 2016). Two specific aptamers were employed, Apt1 modified with a thiol group (Apt1) was stability immobilized onto AuNPs and Apt2 modified with biotin was specifically bound to streptavidin coated MNPs. In the presence of *S. typhimurium*, AuNPs aggregated upon formation of MNPs-Apt2-*S. typhimurium*-Apt1-AuNPs complexes that were collected by an external magnet. Aggregation-induced fading of the solution red color visible to the naked eye. The assay enabled a quantitative detection of *S. typhimurium* because the peak intensity at 520 nm was proportional to the bacteria concentration. The LoD of only 10 CFU/mL was reached in milk. The sensitivity of standard molecular methods for detection of *S. typhimurium* was found to be around 10^3 CFU/mL in milk and meat samples (Perelle et al., 2004).

Kim et al. developed a two-stage label-free aptasensor for detection *C. sakazakii* in powdered infant formula (H.-S. Kim et al., 2017). First, the bacteria was incubated with the aptamer for a few minutes. Then the solution was centrifuged to precipitate bacterial-aptamer complexes and milk proteins. AuNPs were added to the supernatant, and their aggregation was induced with NaCl. This aggregation and the color change of the solution were dependent on the *C. sakazakii* concentration: more bacterial cells in the sample resulted in less aptamer molecules remaining in the supernatant. The color change from red to purple was the most pronounced in supernatants without aptamers because their adsorption onto AuNPs prevented nanoparticle aggregation after NaCl addition. The LoD of 7.1×10^3 CFU/mL was reached in the spiked infant formula with a total detection time of 30 min.

A sensitive colorimetric test for the detection of *C. jejuni* in milk was developed exploring aptamer binding to Au coated palladium nanoparticles (Au@PdNPs) (Dehghani et al., 2018). In this case AuNPs were synthesized using a modified Turkievich method, resulting in AuNPs of 50 and 58 nm. Au@PdNPs exhibited an enzyme-like activity. After sample incubation with a specific ssDNA aptamer followed by centrifugation, Au@PdNPs were added to the supernatant containing the unbound aptamers. The peroxidase activity of Au@PdNPs for TMB oxidation was used as a reporter to evaluate the concentration of *C. jejuni* in samples. Following an enzymatic reaction instead of AuNPs aggregation, makes the test less sensitive to the presence of milk proteins and fats and, thus, simplifies sample preparation. In the aptamer-free supernatant, showing evidence of the presence of target bacteria, the oxidative reaction of TMB by H₂O₂ occurred and the color turned from transparent to blue. On the contrary, in the presence of aptamers, in the absence of target bacteria, the oxidative reaction could not occur because aptamer binding to NPs inhibited their activity. Different concentrations of *C. jejuni* led to a different blue color shade. The LoD of the sensor was 100 CFU/mL. This aptasensor shows advantage over molecular methods, such as PCR-based methods, that may provide false-negative responses because of the sensitivity of DNA polymerase to inhibitors present in food matrices and enrichment broths (Vizzini et al., 2019).

Recently, a portable, and label-free gold nanodisk-based LSPR sensing chip was reported for sensitive detection of *S. aureus* in milk (Khateb et al., 2020). The sensor performance was optimized through different designs specifically addressing the role of the near-field and intrinsic refractive index sensitivity. By tuning the detection read-out from optical to the near-infrared, a good sensor performance was obtained by employing aptamers as recognition elements. The LoD of 10³ CFU/mL was obtained for *S. aureus* in artificially contaminated milk samples without a pre-enrichment step in less than 5 min. However, when the aptamer was replaced by an anti-*S. aureus* antibody a decrease in sensitivity was observed indicating the thickness of the sensing layer as a critical parameter.

Staphylococcal enterotoxin A (SEA) was quantitatively detected in milk using AuNPs-based LSPR immunosensors (Haddada et al., 2017). The citrate/tannic acid reduction method adapted from (Slot & Geuze, 1984) was used to synthesize AuNPs with an average size of 13.5 nm. Specific anti-SEA antibodies were treated by Traut's reagent to convert some of their primary amino groups to thiol groups to enable conjugation with AuNPs. In the direct washing-free detection, SEA was added to the solution containing AuNPs-antibody conjugates and color changes were monitored in real time. SEA binding to the anti-SEA antibodies attached to AuNPs changed the local refractive index in

NPs vicinity and turned the color of the solution from red to purple. The LoD of SEA was estimated to be 5 ng/mL suggesting that such a nanoplasmonic immunosensor is an attractive alternative to more bulky and expensive classical approaches for detection of SEA.

The detection sensitivity can be enhanced by coupling an enzymatic reaction to functionalized AuNPs. For instance, HRP-labeled immuno-gold particles were used for in situ detection of *E. coli* O157:H7, *Salmonella enteritidis*, *L. monocytogenes*, and *S. tphimurium* in reduced-fat milk (Cho & Irudayaraj, 2013). AuNPs on average 30 nm in diameter were synthesized using the citrate reduction method (Pong et al., 2007) and coupled with two types of antibodies. The immuno-magnetic separation using MNPs decorated with the bacterium-specific antibody1 was first performed to separate and concentrate the bacterial cells from milk. When AuNPs functionalized with the antibody2 that recognized and bound to a complementary bacterial surface epitope were added to the solution, AuNPs-antibody2-bacterium-antibody1-MNPs complexes were formed. To enable highly sensitive detection AuNPs carrying HRP-labeled secondary antibodies that bind to antibody1 and 2, were added to form a network structure that grew with time. The colorimetric signal produced upon addition of TMB and H₂O₂ enabled detection of different bacteria in milk with the LoD of 3–15 CFU/mL within only 2 h.

Another strategy to increase the sensitivity of bacterial detection in food consists in coupling LSPR with a PCR amplification (S. Chen et al., 2020; R. Luo et al., 2014; Prasad & Vidyarthi, 2011). For instance, Chen et al. specifically detected *S. tphimurium* in spiked milk samples using two different aptamer probes, Apt1 and Apt2 (S. Chen et al., 2020). After a specific enriching of *S. tphimurium* using MNPs-Apt1, Apt2 was added to create MNP-Apt1-*S. tphimurium*-Apt2 sandwiches as shown in Figure 5. Then, magnetic beads were collected, and heated to liberate Apt2, which was used as a PCR template. Generated PCR products hybridized with their complementary oligonucleotides attached to AuNPs and strongly prevented nanoparticle aggregation upon salt addition. In contrast, no PCR products were formed in the case of non-contaminated samples, and AuNPs aggregated. Due to the production of a large amount of PCR products this assay enabled a naked-eye read out with a detection limit of 95 CFU/mL *S. tphimurium* in spiked milk.

Recent results employing AuNPs-based detection strategies to detect bacteria and their toxins in milk are given in Table 1. AuNPs applied in these tests were generally in the range 10–50 nm, either purchased (Sung et al., 2013) or obtained using different modifications of the citrate reduction method (Haddada et al., 2017; Kumar et al., 2014) including seed growth (M. Chen et al., 2015; Hwang

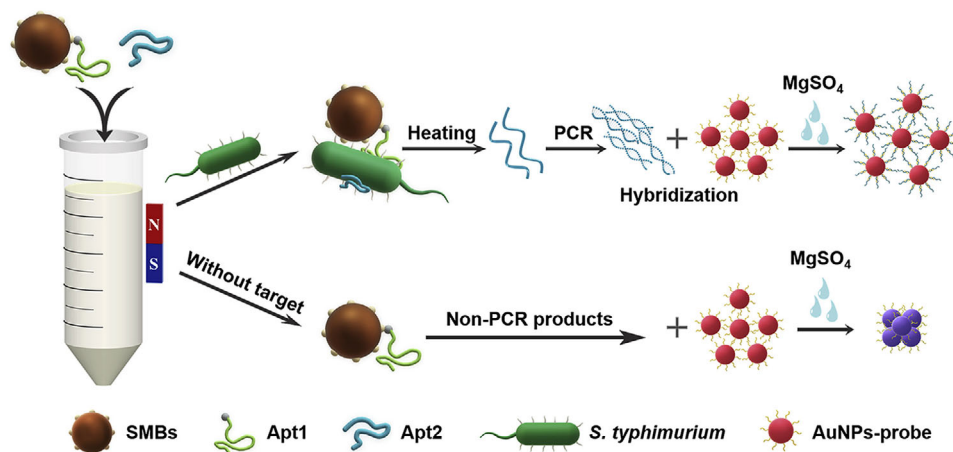


FIGURE 5 Schematic illustration of a streptavidin magnetic beads (SMBs)-aptamer sandwich based colorimetric sensor for detection of *S. typhimurium* in milk. Adapted with permission from S. Chen et al. (2020)

et al., 2016; H. b. Liu et al., 2019; Peng et al., 2020) and the modifications introduced by Grabar et al., (Grabar et al., 1995). The seed-mediated AuNP growth procedure of Bastus et al., (Bastús et al., 2011) was employed by (Peng et al., 2020) to synthesize 7, 20, 50, and 85 nm AuNPs. The smallest NPs were used as seeds for growth of larger NPs. The effect of AuNP size and colloidal stabilization was investigated, and showed that the assay remained stable to different sample media, but change in AuNP size and surface coating significantly influenced the sensitivity. Larger NPs that were citrate coated were overly stable rendering a stable colloid that resulted in no NP aggregation. PEG coating of all sized AuNPs also resulted in high stability bacteria detection.

6 | BACTERIAL CELLS AND TOXIN DETECTION IN MEAT

Meat is rich in proteins, poor in carbohydrates, and contains many micronutrients such as iron, selenium, vitamins A, B12, and folic acid. Meat structure is very complex containing repetitive myofibrillar protein systems with a high content of active water. Although important biotechnological advancements have been made to improve meat safety, meat-based foods are still under survey because of their contamination by pathogens, causing outbreaks, and economic losses. Indeed, meat has to be kept safe in sanitation at every step, starting from the farm. Fresh meat has to be controlled for *Salmonella* (pork, poultry, and turkey meat), *Campylobacter* (broiler meat), enterohemorrhagic *E. coli* including serotype O157:H7 (meat from ruminants), and other enteric pathogens (Sofos, 2008).

To counteract the persistent foodborne outbreaks caused by ingestion of contaminated meat, rapid colori-

metric assays that can be performed at any step of meat production could help the industry improve production management, reduce overheads, and prevent public health concerns. Kim et al. developed a LSPR test for *C. jejuni* and *Campylobacter coli* in a chicken carcass rinse with a sensitivity and specificity comparable to the culture method (Y.-J. Kim et al., 2018). A specific aptamer for live *Campylobacter* cells was truncated and tagged with adenine to minimize the incubation time with AuNPs to only 20 min. A two-stage procedure comprised of incubation of the aptamer and bacteria, and addition of AuNPs to the supernatant containing the unbound aptamers. The solution color varied from red to purple in tune with the aptamer and bacterial concentration ratios. The overall analysis was performed within 30 min but required a 48 hr enrichment step. However, the aptamer was shown to bind only spiral *Campylobacter* cells. This limits the sensor application for on-site chicken carcass screening because *Campylobacter* may change its cell shape from a spiral to a coccoid under unfavorable conditions like during cold storage (Duqué et al., 2019; Vizzini et al., 2019). However, the official ISO 10272-1:2017 method for *Campylobacter* detection may also provide false-negative results because *Campylobacter* may die during handling or enter in a VBNC status in food matrices, making its detection based on culturing impossible (Vizzini et al., 2020).

A highly sensitive and selective portable LSPR sensing chip was developed for detection of *S. typhimurium* in pork meat samples without a pre-enrichment step (Oh et al., 2017). Prior to functionalization with specific aptamers, AuNPs were self-assembled into a 20 nm monolayer on glass slides. This high-density deposition on a transparent substrate produced longitudinal wavelength extinction shifts via a LSPR phenomenon upon target binding. The LoD was of about 10⁴ CFU/mL for *S. typhimurium* in

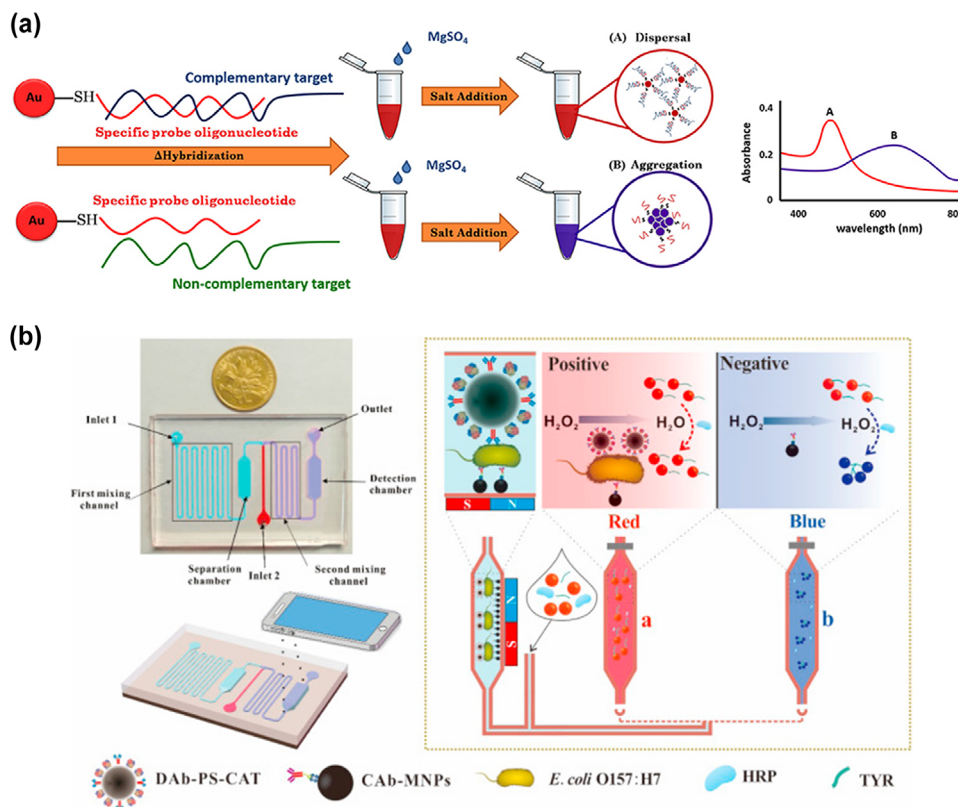


FIGURE 6 (a) Schematic illustration of a LAMP-AuNPs/DNA probe assay. Adapted with permission from Wachiralurpan et al. (2018). (b) The operating principle of a colorimetric biosensor for detection of *E. coli* O157:H7 based on AuNPs aggregation and smart phone imaging. Adapted with permission from Zheng et al. (2019)

the spiked pork meat samples with a total test time of 30–35 min. Moreover, the developed LSPR sensing chips were not susceptible to components of the food matrix or background contaminant microflora.

Wachiralurpan et al. developed a LAMP-LSPR assay for detecting *Listeria monocytogenes* in raw chicken meat samples (Wachiralurpan et al., 2018). After DNA extraction and isothermal amplification of the *plcB* gene of *L. monocytogenes*, the LAMP products were directly mixed with AuNPs carrying the complementary DNA probe. A thiolated probe was used to increase the robustness of the test. As illustrated in Figure 6a, after salt addition, the solution color changed from red to purple in the absence of LAMP products, but remained red when polymeric DNA networking was formed on AuNPs upon hybridization preventing AuNPs aggregation. The LoD of 2.82 CFU/mL was calculated for this test that took only 10 min for hybridization, which can be performed using only a heater block. An additional 1 min was needed for the observation of results. This suggested the possibility of user-friendly on-site sensor applications for chicken meat screening.

An UV-vis spectroscopic measurement of the solution color changing from red to purple can be replaced by smart phone imaging for quantitative on-site bacterial detection. Recently, Zheng et al. developed a microfluidic biosen-

sor based on AuNPs aggregation and smart phone imaging for simple, rapid, and sensitive detection of *E. coli* O157:H7 in chicken meat (Zheng et al., 2019). The detection sensitivity was increased using a HRP/H₂O₂/tyramine read out. Bacterial cells were concentrated by MNPs carrying the capture antibodies against *E. coli* O157:H7 and polystyrene microspheres functionalized with detection antibodies directed against *E. coli* O157:H7 (Figure 6b). In the first mixing channel of the microfluidic chip, *E. coli* O157:H7 cells were mixed with the catalases and functionalized MNPs. The MNP–bacteria–PS complexes were then captured and separated in another chamber by an external magnetic field. Then, H₂O₂ was injected and catalyzed by the catalases on the complexes. The obtained catalysate was mixed with the AuNPs and the cross-linking agent tyramine in the second mixing channel and incubated in the detection chamber. Aggregation of AuNPs was triggered through the cross-linking of phenolic hydroxyl moieties in tyramine which resulted in the color changing from blue to red. The color was imaged and analyzed by an imaging application on an Android smart phone. This automated assay exhibited a good specificity and sensitivity for detection of *E. coli* O157:H7 in chicken samples with a LoD of 50 CFU/mL. Some existing methods for detection of *E. coli* O157:H7, such as culture plating or PCR-based

methods, have high reliability and sensitivity, but all are time-consuming and generally need 2–3 days to provide results.

Recent results employing AuNPs-based detection strategies to detect bacteria and their toxins in meat are given in Table 2. AuNPs for detection of bacteria and toxins in meat were either purchased choosing an average size of 15–20 nm (Y.-J. Kim et al., 2018; Wachiralurpan et al., 2018), or synthesized using the citrate reduction method with an average size of 15–30 nm (Cho & Irudayaraj, 2013; Ledlod et al., 2020; H. b. Liu et al., 2019). Bu et al. (2019) synthesized two types of AuNPs: cysteamine and CTAB-modified AuNPs, with an average size of 26.4 and 38.7 nm, respectively, using the seed-mediated growth synthesis process (Jana et al., 2001; Niidome et al., 2004) focusing on diversely positive charge functionalized AuNPs that can be loaded on negatively charged bacteria leading to colorimetric labeling to target bacteria Wu and collaborators (Zhengzong Wu et al., 2018) designed a dual mode aptasensor for the detection of *P. aeruginosa* in chicken meat using a modification of the seed growth citrate reduction method (Xia, Xiahou, Zhang, Ding, & Wang, 2016). AuNPs 30 nm in diameter were used to carry the aptamer representing color signal probes, while cDNA-AuNPs 15 nm in diameter served as SERS signaling probes.

7 | OTHER FOODS

Most AuNPs colorimetric biosensors for the detection of pathogenic bacteria are reported for milk and meat but other foods and water have also been tested. The assays are particularly efficient when performed in water samples as shown for *Salmonella* (R. Luo et al., 2014), cholera toxin produced by *V. cholera* (Khan et al., 2015), enterohemorrhagic *E. coli* (Jyoti et al., 2010), *P. aeruginosa* (Das et al., 2019), and *S. flexneri* (Feng et al., 2019). Nonspecific bacterial detection can be achieved using unmodified AuNPs (Du et al., 2020). The assay is dependent on the electrostatic interaction between bacteria and negatively charged AuNPs. In this case by adjusting the pH of the test solution, the efficiency is improved to enable a naked-eye visualization of untreated bacteria as shown for *S. aureus*, *S. flexneri*, *P. aeruginosa*, *V. parahaemolyticus*, *B. subtilis*, *E. coli* O157:H7, and *S. typhimurium*.

Cho et al., have compared immuno-AuNPs-based in situ sensor performances for detection of *E. coli* O157:H7 and *S. typhimurium* in ground beef, milk, and pineapple juice (Cho & Irudayaraj, 2013). A low LoD of 3 CFU/mL was found in meat and milk while a LoD of 15 CFU/mL was found in pineapple juice. The lower sensitivity of biosensors in juice maybe due to its low pH that probably interfered with antibody–antigen interactions.

Recently, a low LoD of only 1 CFU/mL was obtained when *S. typhimurium* was detected in eggshell and egg white samples (Q. Chen et al., 2021). For this, bovine serum albumin (BSA) was used to stabilize gold nanoclusters (AuNCs). Obtained BSA-AuNCs complexes possessed a strong intrinsic peroxidase-like activity and were highly stable over a wide range of pHs and temperatures. Increased sensitivity was reached by a separate modification of clusters with two aptamers that recognize *S. typhimurium* cells. The capture of *S. typhimurium* by the dual-aptamers modified BSA-AuNCs (aptamers@BSA-AuNCs@*Salmonella*) was revealed upon addition of TMB as a chromogenic substrate. The intensity of the solution blue color was proportional to the pathogen concentration ranging from 10 to 10⁶ CFU/mL. In another study, peroxidase-like activity of AuNPs was obtained under UV irradiation (Xie et al., 2019). Sensitive detection of *S. aureus* and its enterotoxin B was obtained using aptamer-AuNPs complexes in a 96-well plate coated with chitosan-AuNCs. In the presence of *S. aureus* the solution changed from colorless to blue upon addition of TMB (Xie et al., 2019). In this assay colored AuNPs significantly amplified the response signal enabling a distinguishable color detection of enterotoxin B with the LoD of 10⁻¹² g/mL in corn, rice, and flour for naked-eye readout. Compared to the conventional ELISA for enterotoxin B quantification, the proposed colorimetric strategy seemed much easier for implementation in routine food screening in a facile and low-cost manner.

Some recent results employing AuNPs-based detection strategies to detect bacteria and their toxins in water and various foods are given in Table 3. As with meat and milk, detection in other foods used AuNPs either purchased or synthesized, most commonly using modifications of the citrate reduction method, rendering AuNPs with an average size of 13 (Quintela et al., 2019), 15 (S. Wu et al., 2015), 20 (Khan et al., 2015), or 30 nm (Cho & Irudayaraj, 2013) for different types of AuNP-based tests. The influence of particle size (16, 25, and 34 nm) and different surface modifications on the catalytic reaction of AuNPs synthesized using the Frens method used for fluorescence detection showed that smaller sized particles provided higher catalytic activity (X. Wang et al., 2015).

8 | CONCLUSIONS AND PERSPECTIVES

AuNPs are the most popular nanomaterial used in analytical assays providing visible signal readout. Low-cost AuNPs-based biosensors designed for rapid on-site detection of foodborne pathogens attract extensive attention in the field of food control because they remarkably simplify the procedure, and may potentially satisfy all demands

TABLE 2 Target bacteria, recognition elements, and AuNPs-based tests used for detection in meat

Bacteria	Type of test	Recognition element	Visualization	Limit of detection (LoD)	Reference
<i>L. monocytogenes</i>	LAMP-AuNPs colorimetric test	DNA probe	Naked eyes	2.82 CFU/mL	(Wachiraturpan et al., 2018)
<i>E. coli</i> , <i>L. monocytogenes</i> <i>Salmonella</i> spp.	AuNPs colorimetric test	Aptamers	Naked eyes	10 ⁵ CFU/mL	(Ledlöd et al., 2020)
<i>C. jejuni</i> , <i>C. coli</i>	AuNPs colorimetric test	Aptamers	Naked eyes	7.2 × 10 ⁵ CFU/mL	(Y.-J. Kim et al., 2018)
<i>C. jejuni</i>	RNase H activity AuNPs colorimetric test	RNase H	Naked eyes	1.2 pM	(McVey et al., 2017)
<i>Salmonella</i> spp.	IMS-AuNPs colorimetric test	DNA probe	Naked eyes	10 CFU/mL	(Quintela et al., 2019)
<i>E. coli</i> O157:H7S. <i>typhymurium</i>	IMS-AuNPs-ELISA	Antibodies	Microplate reader	15 CFU/mL ³ CFU/mL	(Cho & Irudayaraj, 2013)
<i>E. coli</i> O157:H7S. <i>enteritidis</i>	AuNPs@-LFS colorimetric assay	Antibody	Naked eyes	10 ³ –10 ⁴ CFU/mL	(Bu et al., 2019)
<i>E. coli</i> O157:H7	Au ^{MBA} @Ag-SERS-LFS	Antibody	Naked eyes/biosensor	5 × 10 ⁴ CFU/mL	(H. b. Liu et al., 2019)
<i>E. coli</i> O157:H7	AuNPs-GQDs	DNA probe	Spectrophotometer	1.1 ± 0.6 nM	(Saad et al., 2019)
<i>P. aeruginosa</i>	AuNPs colorimetric test/SERS	Aptamer/DNA probe	Naked eyes/spectrophotometer	/	(Zhengzong Wu, Deyun He, Bo Cui, et al., 2018)

Abbreviations: LFS, lateral flow strips; GQDs, graphene quantum dots.

Note: Studies presented are from the past 10 years.

TABLE 3 Target bacteria and their toxins, recognition elements, and AuNPs-based tests used for detection in water and other matrices

Target	Type of test	Recognition element	Visualization	Limit of detection (LoD)	Matrix	Reference
<i>E. coli</i> P. aeruginosa V. cholerae	AuNPs colorimetric test	Phage	Naked eyes	100 cells	Seawater	(Peng et al., 2020)
<i>V. parahaemolyticus</i>	MNPs-AuNPs enzymatic colorimetric assay	Aptamer	Naked eyes	10 CFU/mL	Ground water, sea water, waste water	(S. Wu et al., 2015)
<i>Salmonella</i> spp.	IMS-AuNPs colorimetric test	DNA probe	Naked eyes	10 CFU/mL	Chicken meat; blueberries	(Quintela et al., 2019)
<i>E. coli</i> O157:H7S. typhimurium	IMS-AuNPs-ELISA	Antibodies	Microplate reader	15 CFU/mL ³ CFU/mL	Fat milk; ground beef; pineapple juice	(Cho & Irudayaraj, 2013)
<i>E. coli</i> O157:H7	AuNPs colorimetric test	Antibody	Naked eyes	/	Yellow corn	(Ali et al., 2014)
<i>E. coli</i> O157:H7S. enteritidis	AuNPs@-LFS colorimetric assay	Antibody	Naked eyes	10 ³ -10 ⁴ CFU/mL	Water; lettuce; pork	(Bu et al., 2019)
<i>Shigella flexneri</i>	AuNPs colorimetric test	Aptamer	Naked eyes	1.50 × 10 ² CFU/mL	Smoked salmon	(Q. Fang et al., 2019)
<i>B. cereus</i>	AuNPs-LFA	Phage cell wall binding domain	Naked eyes	1 × 10 ⁴ CFU/mL	buffer	(Kong et al., 2017)
Shiga toxin-producing <i>E. coli</i>	AuNPs-LFA	Aptamer	Naked eyes	/	Bacterial medium	(Silva et al., 2019)
Toxins						
Melamine	AuNPs colorimetric assay	Antibody	Spectrophotometer	0.88 μM	Maize	(X. Wang et al., 2015)
Pyocyanin	AuNPs-gold coated zein film	/	SERS	25 μM	Drinking water	(Jia et al., 2019)
Shiga-like Toxin 1	AuNPs@PEW	/	MALDI	40 pM	Ham	(C.-H. Li et al., 2017)
Cholera toxin	AuNPs colorimetric aggregation	Antibody	UV-vis spectrophotometer	10 nM	Lake water	(Khan et al., 2015)

Abbreviations: LFA, lateral flow assay; PWE, Pigeon egg white.

Note: Studies presented are from the past 10 years.

of the food industry for screening tests at in-line and off-line levels. LSPR biosensors involve binding of bacteria or their toxins to AuNPs bioconjugated with recognition elements and transduction into colorimetric signals detectable to the naked eye, or a portable reader, thereby enabling extremely rapid analysis. However, actual applications of LSPR biosensors in food analysis are limited because of their low sensitivity (T. Xu & Geng, 2020). Compared to electrochemical biosensors that are reported to provide the LoD of 1 CFU/mL (Cesewski & Johnson, 2020; Vidic & Manzano, 2021), AuNPs-colorimetric biosensors are less sensitive. Tailoring the AuNPs size, shape, or inter-particle distance may increase the test sensitivity. Further, coupling of the LSPR phenomenon to an enzymatic reaction (such as H₂O₂ based, peroxidase like, HRP) is a signal amplification strategy that may enable direct test application to naturally contaminated foods. Finally, to increase test sensitivity, bacterial cells, or toxins can be pre-concentrated prior to analysis. Although signal amplification strategies we presented significantly increase the sensitivity of detection they increase experimental complexity and usually prolong the assay time and raise the price of analysis.

There are still some technical drawbacks to be solved to enable widespread application AuNPs-based tests. In some cases, food samples have to be pretreated using a multistep procedure before detection to eliminate the matrix effect. Furthermore, AuNP-based tests, including the most popular lateral flow assays, are not easily integrated in devices and can provide a single signal output. It is expected that future development will include novel highly sensitive detection without additional amplification steps, and integration of differently functionalized AuNPs into a multi-color biosensor for multiplex pathogen detection. Despite many technical challenges, rapid development of AuNPs based biosensors ensures future application of LSPR sensors in the food field.

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