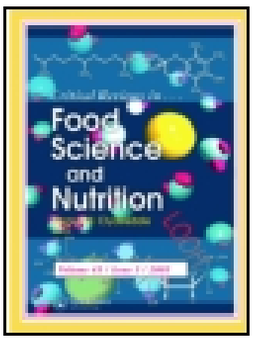

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REVIEW

Recent advancement in nano-optical strategies for detection of pathogenic bacteria and their metabolites in food safety

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ABSTRACT

Pathogenic bacteria and their metabolites are the leading risk factor in food safety and are one of the major threats to human health because of the capability of triggering diseases with high morbidity and mortality. Nano-optical sensors for bacteria sensing have been greatly explored with the emergence of nanotechnology and artificial intelligence. In addition, with the rapid development of cross fusion technology, other technologies integrated nano-optical sensors show great potential in bacterial and their metabolites sensing. This review focus on nano-optical strategies for bacteria and their metabolites sensing in the field of food safety; based on surface-enhanced Raman scattering (SERS), fluorescence, and colorimetric biosensors, and their integration with the microfluidic platform, electrochemical platform, and nucleic acid amplification platform in the recent three years. Compared with the traditional techniques, nano optical-based sensors have greatly improved the sensitivity with reduced detection time and cost. However, challenges remain for the simple fabrication of biosensors and their practical application in complex matrices. Thus, bringing out improvements or novelty in the pretreatment methods will be a trend in the upcoming future.

KEYWORDS

Nano optical sensor; pathogenic bacteria; bacterial metabolites; food safety; integrated platform

Introduction

In recent years, bacterial and their metabolites contamination during the processing of products in food has caused serious harm to human health and economics (Li et al. 2019; Xu et al. 2021). According to the Centers for Disease Control and Prevention (CDC), 70% of diarrhea is related to various pathogenic microorganisms generally present in food, such as *Staphylococcus aureus* (*S. aureus*), *Salmonella typhimurium* (*S. typhimurium*) and *Escherichia coli* (*E. coli*) (Majdinasab et al. 2018). And these bacteria can generate toxin that usually have strong chemical stability in the food matrix. Meanwhile, over the period of time, several strains of bacteria have started showing resistance toward commonly used antibiotics, which posed a severe threat to global public health (Hu et al. 2021).

Till now, conventional detection methods based on culture systems are unable to meet the rapid requirements of bacteria (You et al. 2020). Although some rapid methods like polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and nucleic acid-based molecular biology methods have reduced the detection time compared with culture methods (Trnčíková et al. 2009; Vasilopoulos et al. 2010; Zhang et al. 2014), they still have limitations for on-site detection and relied on trained personnel.

Fortunately, with the rapid expansion of nanotechnology, several optical and colorimetric detection techniques have begun to show advantages (Sharifi et al. 2020). Surface-enhanced Raman spectroscopy (SERS) serves as a unique biometric fingerprint recognition technique offering significant advantages of label-free, simple operation, fast, and small sample size (Garcia-Rico, Alvarez-Puebla, and Guerrini 2018; Xu et al. 2020). Rich structural information of analyte adsorbed on noble metal (gold (Au), silver (Ag) or copper (Cu)) nanostructures or sol-gel can be easily obtained through SERS. Due to the above reason, it is widely used in the field of food safety, pharmaceutical analysis, etc. (Lenzi, Jimenez de Aberasturi, and Liz-Marzán 2019).

Fluorescence technology based on upconversion nanoparticles (UCNPs), carbon dots (CDs), fluorochrome, and aggregation-induced emission luminogens (AIEgens) has also attracted attention in the detection of bacteria in different matrices (Potara et al. 2020). Colorimetric sensor arrays based on colorimetric reagents, catalytic reactions, or plasmonic nanoparticles for monitoring bacterial activities have been studied (Burklund et al. 2019; Li et al. 2020; Sun, J. et al. 2019a). In some cases, these three techniques are utilized either with the support of other techniques, such as microfluidic, electrochemical, and nucleic acid amplification methods, or the integration of each other for better sensing performances. Taken together, the optical detection techniques discussed above are promising analysis platforms for direct or indirect detection of pathogenic bacteria. Besides, the direct detection of bacteria in food samples, the metabolites of bacteria, including gas, liquid, toxin, etc., are other desired ways for indirect monitoring of bacteria.

Therefore, this review is focused on the recent advances in optical (SERS, fluorescence, and colorimetric) techniques and their integration with other platforms used for the detection of pathogenic bacteria and their metabolites in food samples in the past four years (Figure 1).

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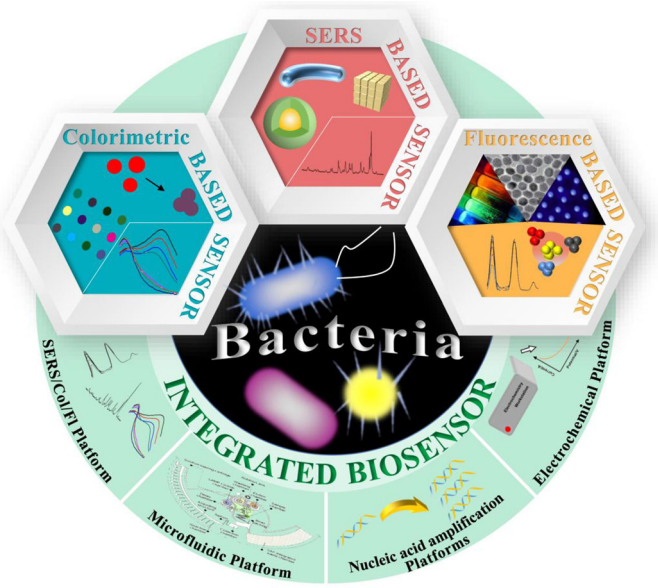

Figure 1. Scheme of bacteria detection biosensors based on SERS, fluorescence, colorimetric and integrated techniques.

Basic tools for identifying bacteria

The development of capture units with higher efficiency and specificity for bacteria are in great demand. Up to now, several capture units such as aptamers, antibodies, phages, antibiotics, and antimicrobial peptides are widely applied in optical biosensors (Shan et al. 2020; Zhao et al. 2021). Antibody is the most commonly used tool for capturing bacteria due to its outstanding specificity and strong binding ability (Wu et al. 2021). Aptamers are a class of oligonucleotides synthesized by in vitro exponential enrichment of ligand system evolutionary combinatorial chemistry or polynucleotide short sequence (Wu, W. et al. 2020). Owing to the specificity and higher affinity toward a variety of targets, aptamers have been widely used in biosensors. Phage is a kind of virus that can recognize and infect the host bacteria. It does not only cause the host bacteria to split but also produces a large number of viruses (Peng and Chen 2019). Considering the advantages, phage can be used to identify and distinguish different types of bacterial strains; additionally, it can distinguish dead and live bacteria at a low cost. Antibiotics are secondary metabolites secreted by microorganisms or higher animals and plants in the process of growth and development (Zhang, A et al. 2018). Some of them can inhibit the activity of specific bacteria, in some cases, it is also used as capturing units for bacterial detection. Antibacterial peptide, a kind of peptide with antibacterial activity, is produced by the immune system after the induction of bacteria into the host system, which can bind on the surface of bacteria (Chen et al. 2018).

SERS-based sensor

SERS has shown great promise in bacteria detection and can provide fingerprint signals about their nucleic acids, proteins, or pigments, which represent bacterial phenotypes

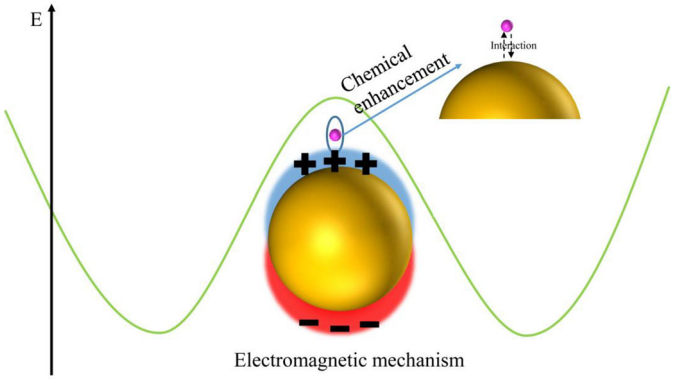

Figure 2. Two mechanisms (electromagnetic mechanism and chemical enhancement) contributed to SERS.

(Liu, S. et al. 2021). The enhancement factor (EF) of this technique is mainly dependent either or both on electromagnetic enhancement (EM) and chemical enhancement (CE) mechanisms (Wang, J. et al. 2020); it is believed that both of the effects generate together (Figure 2). The interests in quantitative or qualitative analysis of bacteria based on SERS have been steadily increasing due to the advantages of its ultra-sensitivity through the strong electromagnetic effect generated by exciting localized surface plasmon resonance (LSPR) of Au, Ag, or Cu based nanomaterials (Cui, L. et al. 2019). On the one hand, more creative and effective SERS-based detection systems have been explored to improve analysis sensitivity and stability. However, these researches are mainly focusing on the establishment of novel SERS-based substrates and novel principles (Franco et al. 2020; Prakash et al. 2020; Zhu et al. 2021). On the other hand, portable systems coupled with SERS probes and multiple analysis methods have been developed to meet the demand for in-situ detection in the food process industry, biomedical research, and clinical diagnostics (Rodríguez-Lorenzo et al. 2019). Herein, the recent advances related to the detection of pathogenic bacteria and their metabolites in food samples using the SERS technique are summarized in Table 1.

Strategies for SERS-based sensor

SERS-based biosensors for fast and specific detection of pathogenic bacteria have drawn grave attention recently (Akanny et al. 2020; Liao et al. 2019). The detection strategies can be divided into two ways: 1) the direct expression of SERS signals related to specific bacterial species and 2) indirect detection based on the Raman reporter molecules, the SERS intensity of the reporter molecules are directly dependent on the concentration of the target bacteria and their metabolites.

Direct sensing strategy. The use of suitable substrates with SERS based system can directly assist in the detection of bacteria. Such a direct detection strategy ultimately helps in achieving intuitive analysis. In general, Raman signals from a complex mixture of samples can give rise to overlapping peaks. In such cases, the use of chemometric methods such as principal component analysis (PCA), partial least squares (PLS), and hierarchical clustering analysis (LDA) can serve

Table 1. SERS-based biosensor for detection of pathogenic bacteria and bacterial metabolites.

Bacteria/metabolites	Matrix	SERS substrate	C&R unit	Reporter	LOD (cfu/mL)	D/InD	RC (%)	Ref.
B. thermosphacta, *E. coli*, *M. luteus*, *P. fluorescens*, *S. Enteritidis*, *L. monocytogenes, and B. thuringiensis*	Meat	AuNPs	–	–	–	D	–	Breuch et al. (2020)
S. aureus	Orange juice, pure milk, milk beverage	Au NPs	M13 phage	DTNB	10	InD	103.3 – 110.0	Wang et al. (2021)
E. coli O157:H7	Drinking Water and romaine lettuce	GNRs	Aptamer	RhB	3	InD	96.95 – 105.88	Zhou, Lu, et al. (2020)
S. typh	Egg white, Cheese, and packaged juice	AuNPs	Antibodiy	DSNB	10	InD	82 – 114	Chattopadhyay et al. (2019)
S. aureus	Milk and orange juice	Fe_3O_4@Au	Aptamer; vancomycin	MBA	3	InD	95 – 106.4	Pang et al. (2019)
S. sonnei	Chicken breast and milk	AuNPs	Aptamer	$[Eu(phen)_2(MBA)_2]$ Cl	10	InD	92.6 – 103.8	Wu, Duan, et al. (2020)
E. coli and *S. aureus*	Drinking water	Au@Ag	Aptamer	–	$8.6 - 5.5 \times 10^6$	InD	–	Liao et al. (2019)
Gaseous metabolites from *E. coli, S. aureus,* and *P. aeruginosa*	Pork	AuNSs	–	–	–	D	–	Guo et al. (2020)

Note: C & R unit, capture and recognition unit; LOD, detection limit; RC, recovery rate; D/InD, direct/indirect; PATP, *p*-aminothiophenol; 4,4′-DP, 4,4′-dipyridyl; RhB, rhodamine B; DSNB, 5,50-dithiobis(succinimidyl-2-nitrobenzoate); MBA, 4-mercaptobenzoic acid.

as reliable and simple analysis tools to deal with complex SERS spectra of different pathogenic bacteria and their metabolites (Akanny et al. 2020; Dina et al. 2018; Gong et al. 2019; Prakash et al. 2020; Xu et al. 2021). In addition, analysis of pathogenic bacteria and their metabolites in food samples is not free from interference. In fact, most of the interference arises from their own complex matrix, thus, sample preparation is an essential step to improve the accuracy and reliability of SERS detection (Viehrig et al. 2020). Moreover, quick separation is always a concerning step because it saves time and cost (Wang, C. et al. 2018). Therefore, enormous studies have been explored for convenient and straightforward separation methods to establish an accurate bacteria detection system (You et al. 2020; Zhou et al. 2021). However, liquid SERS substrate becomes aggregate and occurs discrepant distribution in the solution during the storage, which leads to the poor SERS signal. In order to improve SERS signal reproducibility, three-dimensional (3 D) SERS-based sensing platforms have gained more attention, especially in practical applications (Ko et al. 2018; Tahir et al. 2019). Compared with traditional SERS-based sensors, they have the advantages of large surface area to provide more binding sites and hotspots. Some novel systems based on 3 D-SERS substrate such as black phosphorous-Au (BP-Au) filter paper (Huang et al. 2019), mesoporous Au films (Kim et al. 2021), and SERS adhesive tape (Guo, J. et al. 2019) have been reported. The above-mentioned cases demonstrated that the fabrication of a facile, low-cost, and label-free 3 D SERS-based detection system has great potential in real food sample analysis. Furthermore, a direct detection system for bacteria and their metabolites has great room for improvement with the development of nanomaterials and analysis tools.

Indirect sensing strategy. The indirect detection system (also called SERS tags) is more complicated compared with the direct one because of the introduction of specific organic Raman reporter molecules, such as 4-mercaptobenzoic acid (4-MBA), 4-aminothiophenol (4-ATP), 4,4′-dipyridyl (4,4′-DP) and 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB) (Shan et al. 2020; Zhang, C et al. 2018; Zhou et al. 2021). However, it gives more sensitive signals due to their C = C bonds and symmetrical structure. Novel noble metallic nanoparticles with various compositions, sizes, and shapes have been developed for better SERS signals (Langer et al. 2020). Simultaneously, the application of Raman reporter molecules also evolved to a greater extent. They are not only simply function as reference molecules for signal output but can also serve as a connection bridge between SERS substrates and analytes or as catalytic medium or pH and temperature indicators in the SERS-based sensors (Wu, S. et al. 2020). The most commonly used SERS tags can directly combine on the surface of the noble metallic nanoparticles through S-Au, S-Ag, N-Ag, or N-Au bonds. One obvious drawback in the design of the SERS-tag is that its stability gets easily affected by outer environmental factors (temperature, pH, or humidity). Accordingly, researchers have paid increased attention to achieve a highly stable SERS tag embedded with reporter molecules (Yuan et al. 2018). Moreover, the SERS reporter molecules that are used to modify the substrate can serve as an effective bridge in connecting the substrate surface and the capturing or recognition unit, such as aptamer, antibody, or vancomycin. Another interesting strategy has focused on the exploration of novel compounds that will serve both as SERS substrate and Raman reporter molecules. In recent years, some novel molecules such as 4-mercaptophenylboronic acid (4-MPBA) (Bai et al. 2019), near-infrared (NIR)-absorbing organic fluorophores (OTPA-TQ3) (Qi et al. 2019), and 4-MBA ligand of the Eu-complex ($[Eu(phen)_2(MBA)_2]Cl$) (Wu et al. 2020) have been developed to establish more functional SERS platform.

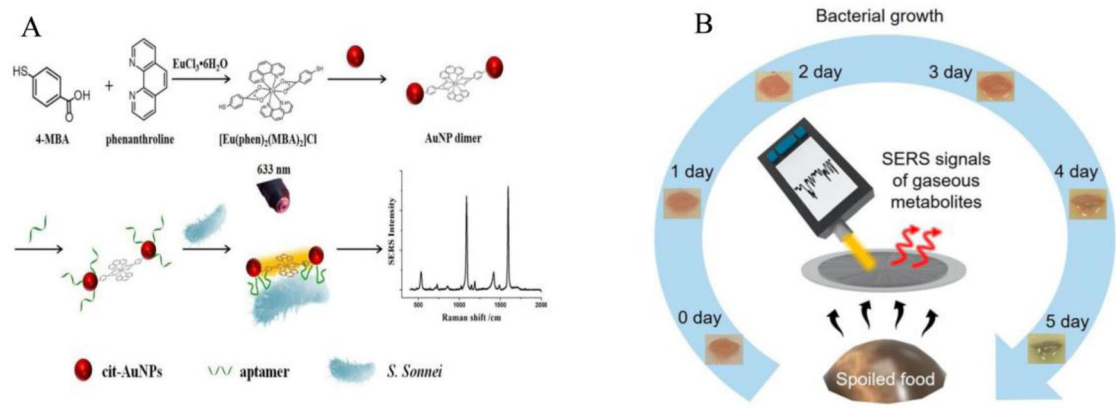

Figure 3. (A) Schematic representation of $[Eu(phen)_2(MBA)_2]$ Cl-ligated AuNPs dimer-based aptasensor for *S. sonnei* detection. © 2020. Shijia Wu, Nuo Duan, Chuxian He et al. All Rights Reserved. Reproduced with permission from Elsevier. Wu et al. (2020). (B) Principle of AuNSs-based SERS 'nose' for morning of gaseous metabolites from pork samples. © 2020. Jingxing Guo, Ying Liu, Yuanjiao Yang, et al. All Rights Reserved. Reproduced with permission from American Chemical Society. Guo et al. (2020).

Application of SERS-based sensors in food samples

SERS sensing of pathogenic bacteria in food. As a typical case of using direct method for sensing bacteria, Breuch et al. differentiated meat-related microorganisms through a combination of paper-based SERS substrate and multivariate statistical analysis (Breuch et al. 2020). The SERS spectra of seven important meat-associated microorganisms were collected based on commercial paper-supported SERS substrate and classified successfully through principal component analysis and discriminant analysis with 97.5% cross-validation. For the indirect method of detection of bacteria, Wang's group reported M13 phage-based SERS sensor with DTNB as SERS active molecule for detection of *S. aureus*. M13 phage was chosen for specific binding of target *S. aureus*, and meanwhile Au NPs-based SERS probe was built through in situ growth on M13 phage surface followed by DTNB modification. This work achieved a linear range of $10-106$ cfu/mL for *S. aureus* detection, and exhibited good application ability in orange juice, pure milk and milk beverage (Wang et al. 2021). The use of magnetic nanoparticles was found to play a crucial role in the rapid isolation of target bacteria from the complex matrix. Zhou et al. synthesized the multifunctional gold nano-bones (NBs) with modification of aptamer and Raman reporter Rhodamine B (RhB) as the SERS sensor, and aptamer modified magnetic nanoparticles as capture probe for sensing *E. coli* O157:H7 in Romaine Lettuce with the recovery ratio ranging from 96.95 to 105.88% (Zhou, S. et al. 2020). In a similar way, Chattopadhyay et al. has effectively demonstrated the detection of *S. typhimurium* in food samples by exploring the combination of magnetic separation technique and Raman reporter molecule 5,5' - dithiobis (succinimidyl-2-nitrobenzoate) (DSNB) (Chattopadhyay et al. 2019). As reported in Pang's group, they developed a dual-recognition magnetically assisted SERS biosensor for *S. aureus* detection in fresh milk and orange juice based on aptamer and vancomycin. 4-MBA was used in this study as a SERS signaling molecule, as well as to direct conjugation with vancomycin to improve the specificity. This method showed a LOD of 3 cells/mL, and the whole process can be finished within 50 min (Pang et al. 2019). Zhouping Wang et al. prepared metal complex-ligated gold nanoparticles (AuNPs) dimer using $[Eu(phen)_2(MBA)_2]Cl$ and cit-AuNPs for SERS-based detection of bacteria (Wu et al. 2020). They demonstrated that with the help of a suitable aptamer, the prepared SERS substrate could selectively detect *Shigella sonnei* (*S. sonnei)* in chicken breast and milk (Figure 3A). The above-mentioned pathogenic bacteria sensing SERS platform based on various Raman reporter molecules exhibited high specificity and stability and is promising for further application in food safety and infectious disease point-of-care diagnosis.

SERS-sensing of pathogenic bacteria metabolites in food. Bacteria have the ability to produce glucose, amino acids, and fatty acids with the aid of various enzymes when their living environment contains nutrients, such as carbohydrates, fat, and protein (Thrift et al. 2019). Subsequently, a part of these produced materials is transformed into structural components of bacteria themselves, and another part is used to generate energy and a series of complex metabolites, include volatile metabolites and toxins (Nguyen et al. 2018; Zhang et al. 2018; Zukovskaja et al. 2019). The monitoring of bacterial metabolites is crucial in developing an analytical method besides real-world applications.

Bacteria can utilize nutrition in the surrounding environment to generate a series of complex volatile metabolites which is served as important gaseous biomarkers to indicate the species and viability of bacteria (Thrift et al. 2019). Therefore, it is possible to monitor these gaseous metabolites from food samples for evaluating the degree of food spoilage, which reduces the probability of food poisoning. As a typical case, Guo et al. designed a flat filter supported gold nanostars as a SERS 'nose' (Figure 3B) to monitor bacteria metabolites from common foodborne bacteria, such as *E. coli*, *S. aureus,* and *Pseudomonas aeruginosa* (*P. aeruginosa)* in spoiled pork, and demonstrated this sensor has much higher sensitivity than that of human sense (Guo et al. 2020). This interesting study showed great potential as a promising tool for monitoring volatile organic compounds (VOCs) that are produced by pathogenic bacteria contaminated food samples.

Table 2. Fluorescence-based biosensor for direct detection of pathogenic bacteria and bacterial metabolites.

Bacteria/metabolites	Matrix	Fluorescence materials	C&R unit	Principle	LOD (cfu/mL)	RC (%)	Ref.
E. coli O157:H7	Tap water and tea powder	$NaYF_4$:Yb, Er@$NaYF_4$	Aptamer	FRET: WS_2 as acceptor and UCNPs as donor.	17	98.2 – 101.6	Wang et al. (2020)
E. coli, Salmonella, C. sakazakii, S. Flexner, V. parahaemolyticus, S. aureus, and Listeria	Water, milk and beef	$NaYF_4$:Yb,Er	Guanidine	The positively charged guanidine group with two parallel hydrogen donor sites can bind with bacteria through electrostatic interaction and hydrogen bond interactions.	130	70 – 118.2	Yin et al. (2019)
S.aureus, Listeria, E. coli, Salmonella, C. sakazakii S. Flexner and *V. parahaemolyticus;*	Tap water, milk, and beef	$NaYF_4$:Yb,Er	Phenylboronic acid; phosphate groups and imidazole ionic liquid	The prevalent spotlight effect of microorganism and the electrostatic interaction between modified UCNPs and bacteria.	10^6	92.1% accuracy	Yin et al. (2020)
MC-LR from cyanobacteria	Water	CQDs	MIP	electron transfer process between MC-LR and CQDs	0.0093 μg/L	91.8 – 100.4	Qi et al. (2021)
E. coli O157:H7 and *S. typh*	Milk	CdSe/ZnS QDs	Aptamer	–	16 and 25	84.9 – 101.6	Li et al. (2018)
S. aureus	Milk and orange juice	CDs	Antibody	–	30	95 – 105	Yang et al. (2018)
E. coli O157:H7	Milk	Au NCs	Antibody	–	1	96 – 103.3	Cheng et al. (2018)
B. cerius, E. faecalis, E. coli, and *P. aeruginosa*	Water sources	Au NCs	–	–	634 ± 16 and 740 ± 14 cfu/mL for Gram-positive and Gram-negative bacteria	–	Goswami et al. (2018)
E. coli	Water	Au NCs	–	–	89	–	Rong et al. (2018)
S. aureus	Peanut milk	Magnetic nanoparticles	Aptamer	–	10	–	Shrivastava, Lee, and Lee (2018)
S. typh	Chicken	GOx-nanoclusters	Antibody	–	16	85.2 – 110	Guo et al. (2019)

Note: C & R unit, capture and recognition unit; LOD, detection limit; RC, recovery rate; FRET, fluorescence resonance energy transfer; IEF, inner filter effects.

Fluorescence-based sensor

The principle of fluorescence-based sensors is based on light emission generated by some specific molecules or nanoparticles that return from the excited state to the ground state (Martynenko et al. 2019). Biosensors based on fluorescence techniques have attracted much attention due to their ability to detect trace amounts of analytes even at a very low concentration (Baig and Chen 2019; Wang et al. 2019). In general, there are three kinds of strategies applied in fluorescence-based sensors for detection of bacteria or their metabolites: (1) bio-imaging to differentiate bacteria; (2) the fluorescence property of the sensor enhances or changes upon the analyte binding; (3) by quenching of fluorophore signals with the help of energy receptor (quencher). On the basis of the above-mentioned strategies, enormous efforts have been made on the development of various biosensors for bacteria detection using different fluorescence-based materials, including UCNPs, quantum dots (QDs), AIEgens, etc (Feliciano Crespo et al. 2018; Yang, J. Y. et al. 2019). A summary of the fluorescence-based sensor for the detection of pathogenic bacteria and their metabolites is listed in Table 2.

Strategies for UCNPs-based sensor

The fluorescence mechanism of lanthanide ions doped UCNPs is based on a kind of nonlinear optical phenomenon referring to 4f-4f electronic transitions (Wang et al. 2019). In brief, it converts two or more low-energy photons into one photon of higher energy, which is featured with the absorption of NIR radiation and then followed by radiative emission through the near-ultraviolet, visible, or NIR ranges through a series of complex pathways (Wang, P. et al. 2020). UCNPs convert lower energy NIR excitation light into higher energy visible or ultraviolet emission light leading to a large anti-Stokes shift. Because of their excellent photo-stability, narrow emission spectrum, less toxic elements multicolor tunable property, and low background fluorescence (Zhang, Z. et al. 2019), UCNPs-based biosensors have been widely used to detect single or multiple bacteria in many research (Yin et al. 2020).

Basically, sensing strategies of UCNPs can be divided into four: 1) Förster resonance energy transfer (RFET), generated by the effect of UCNPs and receptor fluorescent material (AuNPs, reduced-graphene-oxide (RGO), QDs, and

dyes, etc.); 2) labeling based UCNPs (usually with the aid of magnetic separation technology); 3) inner filter effect (IFE), produced by UCNPs in the presence of absorbent; and 4) label-free strategies coupled with exploratory and supervised statistical methods.

For FRET, the distance between the acceptors (luminescence quencher) and donors (UCNPs) must be less than 10 nm, while, the absorption spectra of acceptors should have a clear overlapping with the emission spectra of donors. Upon the addition of a suitable analyte, the FRET process gets initiated, resulting in quenching or enhancement of fluorescence signal take place, which directly reflects the concentration of analytes (Liu, Y. et al. 2018). Strategies based on labeled UCNPs for bacteria detection usually rely on specific recognition elements or various UCNPs with different emission peaks to indicate target bacteria (Liu, R. et al. 2021). As compared to FRET, IFE could take place irrespective of the distance between the donor-acceptor pair. Simple spectral overlapping between the absorption or emission spectra of the analyte and the emission spectra of the UCNPs is enough to evoke IFE-induced quenching (Chen et al. 2019). Further, some label-free strategies commonly need surface chemistry modification of materials that can capture bacteria including boronic acid, quaternary ammonium salt, and phosphate groups (Yin et al. 2020).

Strategies for QDs/CDs-based sensor

QDs are usually prepared from semiconductor nanocrystals composed of elements from groups II–VI or III–V of the periodic table. The size-dependence of QDs decides their photo-physical properties with emission wavelength ranging from ultraviolet to near-infrared light. For example, the size of CdTe QDs is in the range of $2.5-4.0$ nm, and their emission wavelength varies between 520 and 650 nm. The advantages of QDs such as wide excitation range, large Stokes shift, and long-term photostability have gained increasing engagement in tackling bacteria in many fields (Aruna et al. 2018). Semiconductor-based QDs are composed of heavy metal elements, which make them less compatible with the biosystems. Enormous work was conducted to improve the performance of these probes. Besides, the search for new fluorescent probes that have multifunctional abilities and devoid of commonly observed paucity (such as low quantum yield, toxicity, etc.) is currently underway (Rong et al. 2020; Wang, C. et al. 2020).

As one of the recently developed fluorophores, CDs are a new class of carbon-based nanomaterials with sizes typically in the range of $1-10$ nm (Cui et al. 2020). Exceptional optical and electronic properties of CDs make them suitable in various applications, such as optoelectronic devices, biological labeling, and biosensors. Carbon-based quantum dots exhibit many noticeable advantages compared to rare-earth doped materials, such as up-conversion photoluminescence, aqueous solubility, functionalization ability, biocompatibility, and high affinity to bacteria (Han et al. 2020). For CDs with large-size π conjugation, their fluorescence phenomenon attributes to the quantum confinement effect that occurs from conjugated π electron, which is considered the luminescent center of carbon core (Fang, Huang, and Chen 2019). Another luminescence mechanism of CDs is the surface defect state, which is caused by surface oxidation. These defects can serve as a capture center of excitation to realize luminescence (Zheng, Qi, and Zhang 2019). Besides, the interaction of band gap fluorescence and molecular fluorescence can also lead to CDs luminescence. Owing to high fluorescence yield, CDs have been used in fluorescence imaging applications, which also explored to identify and trace bacterial contamination in real samples. In addition to detection, CDs with inherent ease of functionalization are able to combine with antibacterial agents easily for the inactivation of bacteria (Cui, F. et al. 2019; Fang, Huang, and Chen 2019; Yang et al. 2018). Due to the nonspecific binding of non-target molecules by biological recognition molecules like antibodies, etc., in complex medium, the array-based fluorescence method has been widely explored (Zheng, Qi, and Zhang 2019).

Strategies for AIE-based sensor

Aggregation-induced emission (AIE) as an opposite effect to aggregation caused quenching (ACQ) was first proposed by Tang et al. in 2001 (Luo et al. 2001). Normally, AIEgens are non-emissive or weakly emissive when they are in the dissolved state, but they induce to emit intensely in the aggregates due to the restriction of intramolecular motions (RIM), thus they exhibit high fluorescence efficiency and extraordinary photo-stability at higher concentrations (Zhang,H. et al. 2019; Naik et al. 2018). Notably, water-soluble AIEgens have emerged as outstanding fluorescence materials with great potential for effective bacterial discrimination and anti-bacteria activity owing to their features of non-washing procedures, high signal-to-noise ratio in bioimaging, efficient photosensitization ability in the aggregation state, and the ability to generate reactive oxygen species (ROS) generation (He, X. et al. 2019). For this reason, a handful of AIEgens has been used in anti-bacterial and imaging applications in recent years. In the year 2018, Tang et al. proposed a novel AIEgens-based sensing strategy involving metal-free click bioconjugation assay based on activated alkynes at different levels, and it was successfully applied in quick differentiation and staining of Gram-positive bacteria, which carried forward the research on AIEgens in bacterial fluorescence sensing (Lee et al. 2020; Hu et al. 2018). Although some positive charged AIEgens can realize bacteria imaging, it is difficult to differentiate live bacteria from dead bacteria just through electrostatic adsorption between the positively charged fluorescent probe and negatively charged bacteria. Therefore, chemically specific mechanisms have been proposed to develop AIEgens for the detection of live bacteria (Kong et al. 2018; Donnier-Maréchal et al. 2018).

Strategies for nanocluster-based sensor

Nanoclusters (NCs) are composed of a small number of atoms with a size of < 2 nm. Notably, NCs show an obvious difference between physiochemical and optical properties compared with larger nanoparticles, such as bright

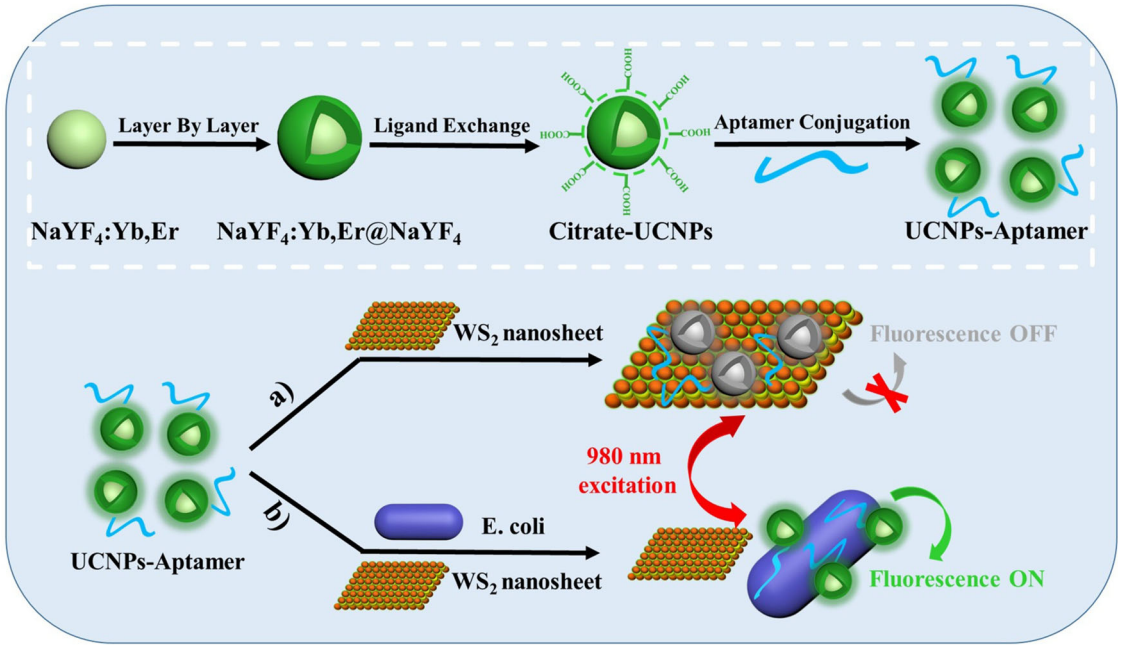

Figure 4. Schematic description of UCNPs-WS_2 nanosheet sensing platform for *Escherichia coli* detection. © 2020. Pingyue Wang, Ancheng Wang, and Md Mehedi Hassan et al. All Rights Reserved. Reproduced with permission from Elsevier. Wang et al. (2020).

luminescence and catalytic properties (Li et al. 2019). These differences are mainly caused by the quantum confinement effect, size of particles, discrete energy levels, and so on. The emergence of NCs greatly overcome the inherent limitations of conventional fluorescent organic dye and provide a new way for bacteria sensing. Currently, the smartphone has offered an on-the-spot detection platform for faster and easier bio-imaging of bacteria. Thus, smartphone-based fluorescence detection platform has been widely applied for imaging of bacteria.

Application of fluorescence-based sensors in food samples

Fluorescence sensing of pathogenic bacteria in food. Most fluorescence-based sensors are designed through the FRET principle. As a representative strategy, our group designed a biosensor based on the FRET between aptamer modified UCNPs as donors and layered tungsten disulfide (WS_2) nanosheets as the effective acceptor for the detection of *E. coli* in tea powder (Figure 4). The potent van der Waals force between the nucleobases of aptamer on the UCNPs and the basal plane of WS_2 led to the distance between them was less than 10 nm, thus the spectral overlap between WS_2 absorption and UCNPs fluorescence emission led to quenching of fluorescence. When *E. coli* was present, its specific binding with aptamer could dissociate UCNPs probe away from the surface of WS_2 nanosheets, which made parts of the quenched fluorescence of UCNPs retrieve. The obtained biosensor exhibited a concentration range from 85 to 85×10^7 cfu/mL for *E. coli* in tap water and tea powder (Wang et al. 2020).

IFE-based fluorescence sensors have also been widely applied in the sensing of bacteria in food samples. For instance, Wu et al. designed a fluorometric aptasensor for the detection of Vibrio parahaemolyticus (*V. parahaemolyticus*) based on IFE utilizing platinum-coated gold nanorods (AuNR@Pt) and UCNPs. This work got a linear detection range from 50 to 107 cfu/mL under optimal conditions and was extended for sensing in food products like tap water and fresh shrimp (Wu 2019).

The label-free detection strategy has attracted numerous attentions to researchers due to its simple design principle. As an example, Yin's group designed a straightforward UCNPs-based sensing approach comprising of guanidine-functionalized UCNPs (UCNPs@GDN), tannic acid, and hydrogen peroxide (HP). Strong interaction between UCNPs@GDN and bacteria via guanidine group made the light propagate and distribute along with bacteria. This phenomenon led to the light be focused on by bacteria and further enhance the fluorescence intensity of the developed biosensor (Li et al. 2017). In the presence of bacteria, the luminescence of UCNPs could be strengthened, thus it could quantify seven pathogenic bacteria in a nonspecific way (Yin et al. 2019). Under a similar design principle, they further established a UCNPs fluorescent sensor array by modifying the surface functional group of UCNPs with phenylboronic acid, phosphate groups, and imidazole ionic liquid. The sensor array showed excellent recognition ability of bacteria due to their prevalent spotlight effect and the electrostatic interaction. The results showed that seven foodborne pathogenic bacteria were identified accurately with 100% accuracy in pure solution and 92.1% accuracy in real samples (tap water, milk, and beef) by linear discriminant analysis (LDA) (Yin et al. 2020). In another interesting case, Goswami et al. introduced a novel synthesis method of Au NCs on the surface of bacteria. The intensity of Au NCs enhanced with the increasing number of bacteria, thus the prepared Au NCs were used to detect and count bacteria (Goswami et al. 2018). Yan et al. developed an on-off-on Au NCs-based fluorescent probe for *E. coli* sensing, differentiation, and

screening. The Au NCs stabilized with serum albumin (BSA) were capable of undergoing coordination interaction with Cu^{2+}. In the absence of *E. coli,* this could result in the fluorescence quenching of Au NCs. On the contrary, the fluorescence of Au NCs recovered in the presence of *E. coli* owing to their copper-binding and redox pathways with Cu^{2+} (Yan et al. 2018).

Actually, there are multiple bacteria that live in polluted food, thus simultaneous detection of multiple bacteria makes sense for food safety. In order to improve the existing separation and collection method, Li et al. combined magnetic γ-Fe_2O_3 with CdSe/ZnS QDs as a sensitive probe for multiple pathogens sensing in milk (Li et al. 2018). The use of magnetic nanoparticles played a vital role in biosensing owing to their higher surface-to-volume ratio and the ability to get separated under an external magnetic field.

Recently, nanocapsules are used for the amplification of fluorescence signals and improving sensing sensitivity. For an instance, Cheng et al. prepared Au NCs-embedded chitosan (CS) nanocapsules as a fluorescence signal amplification system to detect *E. coli* O157:H7 in milk and drinking water with a LOD of 1 cfu/mL. The prepared nanocapsules contained a large number of Au NCs, which greatly amplify fluorescence signals of the system compared with the conventional Au NCs-based fluorescence method (Cheng et al. 2018).

In order to realize more conventional fluorescence detection of bacteria, smartphone-based bio-sensing systems have been developed. As a representative strategy, Shrivastava et al. used fluorescent magnetic nanoparticles to capture *S. aureus* and then used a smartphone camera equipped with a light-emitting diode as the excitation source to image the fluorescence. This method showed a LOD of 10 cfu/mL and have been successfully applied in peanut milk within 10 min (Shrivastava, Lee, and Lee 2018). Similarly, Guo et al. combined monoclonal antibodies modified magnetic nanoparticles, polyclonal antibodies and glucose oxidase (GOx) modified nanoclusters, peroxide test strips, and the smartphone APP as a portable biosensor for rapid detection of *S. typhimurium* (Guo, R. et al. 2019).

Fluorescence sensing of pathogenic bacteria metabolites in food. Microcystin-LR (MC-LR) is a representative toxin generated from cyanobacteria, which has posed a serious threat to water safety. Thus, Qi's group creatively developed a fluorescence sensor based on imprinted polymer-coated quantum dots (MIP@CQDs@SiO_2) for sensitive detection of MC-LR in water samples. The target MC-LR could be adsorbed through the specific recognition sites on the polymer layers of MIP@CQDs@SiO_2, and then caused fluorescence-quenching of CQDs because of the electron transfer process. This work showed great detection stability in real water samples with the linear range of 1–1000 μg/mL (Qi et al. 2021).

Colorimetric-based sensor

Colorimetric-based sensors, as one of the oldest analytical methods, refers to the color change of the sensor due to the intermolecular interactions between the chromophore and analytes, aggregation mechanism, or localized surface plasmon resonance (LSPR) (Ma et al. 2019). The main advantage such as its cost-effectiveness, simplicity of operation, straightforward readout, and digital color imaging of colorimetric method has made it a potential technique for bacteria sensing (Choi, Hwang, and Lee 2018). Normally, some organic dyes were first used to establish colorimetric sensors (Duan et al. 2021). With the development of nanotechnology, various noble metal nanoparticles with higher extinction coefficients and unique LSPR properties as well as some with catalytic properties have been prepared to achieve functional colorimetric sensors (Ma et al. 2019).

Strategies for colorimetric-based sensor

There are mainly two strategies used in colorimetric-based sensors:1) catalysis or structural change caused the color change (Sun, J. et al. 2019); 2) aggregation and morphology transition of nanoparticles (Santopolo et al. 2019). A summary of the colorimetric-based sensor for the detection of pathogenic bacteria is listed in Table 3.

The catalysis mechanism is based on the chemical reactivity between the probe and analytes, and this reaction leads to color changes. In colorimetric sensing, several kinds of catalysis reactions are utilized (Ziyaina et al. 2019). Another mechanism related to aggregation or morphology transition of nanoparticles, such as AuNPs and AgNPs, and the color generation is mostly based on the strong plasmon between the nearby particles, which is caused by the morphology, size, or distance variation of these nanoparticles (Ma et al. 2019). In addition, their morphology, size and distance variation lead to plasmon band shift and obvious color change (Singh et al. 2018).

Application of colorimetric-based sensors in food samples

Colorimetric sensing of pathogenic bacteria in food. Wang et al. designed a kind of solid mimic peroxidase - hemin-concanavalin A hybrid nanoflowers (HCH nanoflowers), which was capable of catalyzing the oxidation of 2,2′-azinobis (3-ethylbenzthiazoline-6-sulfonic acid) diammonium salt (ABTS) in the presence of H_2O_2 and generated visible green-colored final product. The colorimetric sensor developed based on HCH nanoflowers could detect *E. coli* O157:H7 with a good linear range from 10 to 106 cfu/mL and LOD of 4.1 cfu/mL, which is promising for point-of-care detection of foodborne pathogenic bacteria in food (Wang, K. Y. et al. 2018). Dehghani et al. unitized peroxidase activity of Au@Pd NPs to establish a colorimetric detection system for *Campylobacter jejuni* (*C. jejuni)*. Free DNA aptamer was coated on the surface of Au@Pd NPs to prevent its catalytic capacity, however, in the presence of *C. jejuni*, the aptamer bound to *C. jejuni* preferentially, thereby recovered the catalytic effect of Au@Pd NPs toward 3,3′,5,5-tetramethylbenzidine (TMB) and generated a blue product. This label-free colorimetric biosensor gave a LOD of 100 cfu/mL in milk (Dehghani et al. 2018). Liu et al. prepared nonapeptide-fusion proteins pVIII as a specific element to

Table 3. Colorimetric-based biosensor for direct detection of pathogenic bacteria and bacterial metabolites.

Bacteria/metabolites	Matrix	Colorimetric materials	C&R unit	Principle	LOD (cfu/mL)	RC (%)	Ref.
VOCs from microbial growth	Milk	SiO_2 and Schiff's reagent	–	VOCs can react with Schiff's reagent and lead to color change from colorless to magenta.	$5-7$ $\log_{10}$c fu/mL	–	Ziyaina et al. (2019)
E. coli O157:H7	Milk	HCH nanoflowers	–	HCH nanoflowers enables to catalyzing the oxidation of ABTS in the presence of H_2O_2 followed by a green-colored product.	4.1	99 – 105.1	Wang et al. (2018)
C. jejuni	Milk	Au@Pd NPs	Aptamer	The catalytic effect of Au@Pd NPs toward TMB to generate a blue product.	100	98 – 113	Dehghani et al. (2018)
V. parahaemolyticus	Seawater, clam, and Spanish macherel	MnO_2 NSs	Phage	MnO_2 NSs can catalyze TMB and H_2O_2 to produce a colorimetric change.	15	98 – 102.5	Liu et al. (2018)
S. typh	Whole milk	β-gal	Antibody	β-gal was performed to generate color with CPRG.	100	–	Srisa-Art et al. (2018)
Fecal-indicating *E. coli* and *E. coli* O157:H7	Milk	S-β-gal and X-β-gluc	–	Enzymes β-glucuronidase and β-galactosidase can serve as indicators of FIB and O157 strains of *E. coli*	10	–	Kim, Kwon, and Noh (2019)
E. coli, E. coli O157:H7, *Listeria,* and *V. vulnificus*	Milk	Magenta-β-gal, Aldol-MIP, X-β-gluc, and X-β-glu	–	Magenta-β-gal, aldol-MIP, X-β-gluc, and X-β-glu have the ability to react with specific bacterial enzymes with color change.	10	–	Kim et al. (2019)
E. coli, *S. typh* and *K. pneumoniae;*	Lake and tap water	AuNPs	Colistin	Colistin functioned as aggregator of Au NPs with blue color, and if it exists bacteria, colistin bound with bacteria causing Au NPs becomes free in solution with red color.	10	–	Singh et al. (2018)
Sh. flexneri	Smoked salmon	AuNPs	Aptamer	Aptamer modified AuNPs have high binding affinity to *Sh. Flexneri*, thus the addition of it led to the aggregation of AuNPs.	80	88.51 – 110.2	Feng et al. (2019)
E. coli	Tap water	AgNPs	MPBA	MPBA-AgNPs could form aggregation with the color from yellow to brownish and the presence of bacteria can prevent it because MPBA can react with the cis-diol groups contained in saccharides on the bacteria cells.	0.9×10^4	93.4 – 107	Zheng, Qi, and Zhang (2018)
19 *Salmonella spp.*	Chicken	Au NPs	Oligonucleotides	In the absence of target bacteria, cannot form stable structure which led to the aggregation of probe (purplish-blue color).	10	–	Quintela et al. (2019)

Note: C & R unit, capture and recognition unit; LOD, detection limit; RC, recovery rate; VOCs, volatile organic compounds; MNPs, magnetic nanoparticles; HCH nanoflowers, hemin-concanavalin A hybrid nanoflowers; ABTS, 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) diammonium salt; TMB, 3,3,5,5′-tetramethyl-benzidine; CPRG, chlorophenol red-β-D-galactopyranoside; MPBA, 4-mercaptophenylboronic acid.

identify *V. parahaemolyticus via* a high-throughput way and combined it with MnO_2 nanosheets (NSs) templated from protein to form a catalysis type colorimetric sensor. MnO_2 NSs can catalyze TMB in the presence of H_2O_2 to produce a colorimetric change. This research showed a LOD of 15 cfu/mL and proved reliability in marine samples (Liu, P. et al. 2018). Srisa-Art et al. designed a colorimetric test paper to detect *S. typhimurium*. Paper-based analytical device (PAD)

coupled with immunomagnetic separation (IMS) was used for rapid capture and separation of *S. typhimurium*; in this sensor, β-galactosidase (β-gal) was used to generate color with chlorophenol red-β-$_D$-galactopyranoside (CPRG). This method showed a LOD of 100 cfu/mL in the culture solution, 10^5 cfu/mL in inoculated bird feces samples, and 10^3 cfu/mL in inoculated whole milk (Srisa-Art et al. 2018).

Singh et al. first used electrostatic interaction of the positively charged colistin and negatively charged AuNPs to design visual sensors for pathogen detection. In the absence of bacteria, colistin induced the aggregation of individual AuNPs to give blue color; whereas, in the presence of bacteria, colistin selectively bound to bacteria causing the redispersion of aggregated AuNPs to give red color. The color change within 5 min was an indication of the concentration of bacteria as low as 10 cells/mL (Singh et al. 2018). A similar strategy was performed by Feng's group, they utilized aptamer and Au NPs to form colorimetric aptasensor for the detection of *Shigella flexneri (Sh. Flexneri)*. Aptamer modified AuNPs have high binding affinity to *Sh. flexneri* thus the addition of bacteria led to the aggregation of AuNPs (Feng et al. 2019). Zheng et al. proposed a 4-mercaptophenylboronic acid functionalized Ag NPs (MPBA-AgNPs)-based colorimetric method for the detection of Gram-negative bacteria. In the presence of MPBA, AgNPs underwent aggregation with a visible color change from yellow to brownish. In the presence of bacteria, the aggregated AgNPs caused by MPBA get re-dispersed in the system to yield visible color change, owing to the selective binding of MPBA with the cis-diol groups that are afforded by the saccharides present on the bacteria cells. Thus, a series of color changes were observed via both naked eye and UV-Vis spectrometer depending on the concentration of bacteria. *E. coli* was chosen as a model of Gram-negative bacteria to verify the feasibility of this design and it showed a LOD of 900 cfu/mL within 20 min (Zheng, Qi, and Zhang 2018).

Chen's group engineered phage M13 to obtain the receptor-binding protein toward targeted bacteria, and then further prepared thiolated chimeric phage through 1-ethyl-3-(3-dimethy-laminopropyl) carbodiimide (EDC) chemistry, which allowed the binding of AuNPs as signal amplifier. In the detection system, the engineered phage M13 was used to capture bacteria, and then free phage was removed through centrifugation, the remaining page-bacteria complexes were added to AuNPs solution to obtain a color change from red to purple due to the aggregation induced by the thiolated phage. This strategy proved the ability to rapidly and specifically sense two strains of *E. coli*, *Vibrio cholerae* (*V. cholerae)*, two strains of *Xanthomonas campestris* (*X. campestris)*, and *P. aeruginosa* with a LOD of 100 cells (Peng and Chen 2019). *Salmonella* spp. as one of the major causative agents of foodborne sickness and death, has about 2000 serotypes, which pose a great challenge to simultaneously detect multiple strains. Quintela et al. attempted to design a highly sensitive colorimetric biosensor for simultaneous detection of 19 strains of *Salmonella* spp. by oligonucleotide-modified AuNPs. In this study, they designed a pair of new single-stranded oligonucleotides with 30-mer and connected them on the surface of AuNPs with a diameter of 13 nm, that can hybridize with a conserved genomic region (192-bases) of *ttrRSBCA,* which exists in most of *Salmonella* spp. strains. The formed sandwich structure is highly stable even in salt concentration showing red color; on the contrary, in the absence of target bacteria, the sensing system cannot form a stable structure, which leads to the aggregation of the probe (purplish-blue color). Finally, results showed the developed colorimetric biosensor had the ability to identify 19 kinds of *Salmonella* spp. strains with 100% specificity and a LOD of less than 10 cfu/mL or 10 cfu/g in both pure culture and real samples (Quintela et al. 2019) (Figure 5A).

Colorimetric sensing of pathogenic bacteria metabolites in food. Ziyaina monitored the VOCs generated from spoilage bacteria in milk by Schiffs reagent coated SiO_2 particles. The chemical reaction between the volatile organic compounds and Schiffs reagent resulted in an obvious color change from colorless to magenta within the storage temperature of 7 to 19 °C. It was found that the response of this nanosensor is correlated well with microbial growth in milk and could be applied to predict the remaining shelf-life of food packaging (Ziyaina et al. 2019). Bacterial metabolism as gene markers usually reflects the features of bacteria strains, thus more study on it will help to explore more accurate methods to tell different bacterial strains. Kim et al. developed a multifunctional paper-based platform for the detection of fecal indicator bacteria (FIB) and O157 strains of *E. coli* using two chromogenic substrates β-glucuronidase and β-galactosidase as indicators, respectively. Thus, the mixture of these chromogenic agents is a promising enzymatic probe for the detection of two kinds of *E. coli* strains (Kim, Kwon, and Noh 2019). Furthermore, they integrated four kinds of chromogenic substrates into a 3 D paper-based device for one-step detection of foodborne pathogens (Figure 5B). 5-Bromo-6-chloro-3-indoxyl-β-D-galactose (Magenta-β-gal), aldol® 518 myoinositol-1-phosphate(Aldol-MIP), 5-bromo-4-chloro-3-indoxyl-β-D-glucuronic acid (X-β-gluc), and 5-bromo-4-chloro-3-indoxyl-β-D-glucose (X-β-glu) have the ability to react with specific bacterial enzyme, namely,β-D-galactosidase, myoinositol mono-phosphates, β-glucuronidase and β-D-glucosidase, which leads to corresponding colors (sky blue, light pink, burgundy, and strong blue). Thus, one drop (50 μL) of sample fluid generated desired colors, and quantification analysis was carried out through a commercial imaging device. Four bacteria strains - *E. coli, E. coli* O157:H7, *Listeria monocytogenes* (*L. monocytogenes), Vibrio vulnificus (V. vulnificus)* in milk were detected with 8 hours of enrichment even at the concentration of 10 cfu/mL (Kim et al. 2019).

Integrated dual model-based sensor

Nowadays, more and more attention has been paid to integrate techniques for improving detection sensitivity, stability, and selectivity, as well as obtain multiple functions for bacteria sensing (Tok et al. 2019; Zhao et al. 2020). The above

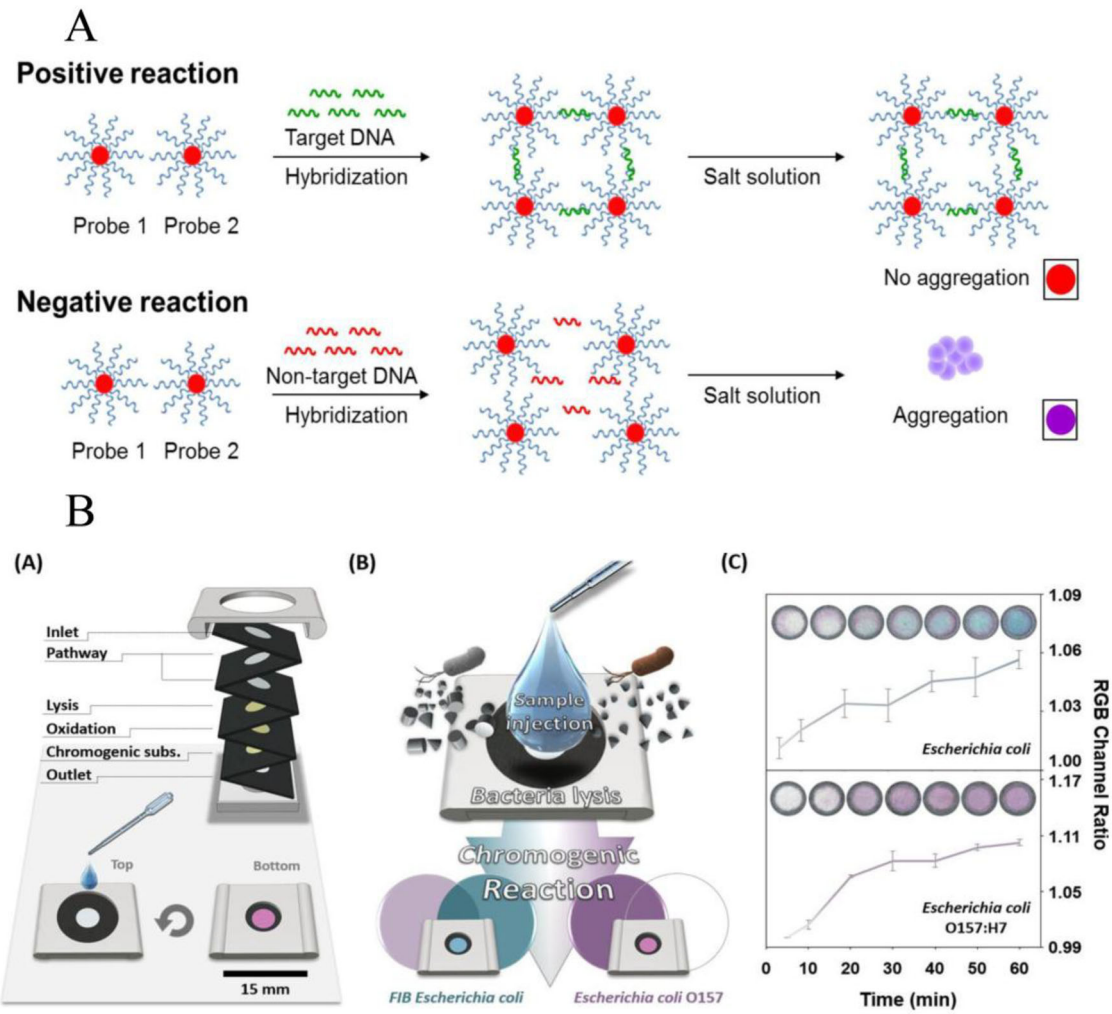

Figure 5. (A) Description of behind AuNPs-based optical biosensor for detection of *Salmonella* spp. Reproduced with permission from Quintela et al. (2019). (B) Process of color paper-based sensor for sensing of *E. coli*. © 2019. Hyeok Jung Kim, Chanho Kwon, and Hyeran Noh. All Rights Reserved. Reproduced with permission from American Chemical Society. Kim et al. (2019).

mentioned three types of sensors have also been designed as dual models, such as SERS/colorimetric, SERS/fluoresce, and fluoresce/colorimetric-based detection platforms for bacteria sensing in different views (Do et al. 2019; Rodríguez-Lorenzo et al. 2019; Nguyen et al. 2019). In addition, some other techniques, such as microfluidic technology, electrochemical technology, and nucleic acid amplification technology, and so on have been integrated with the above three techniques to improve the detection performance (Hsieh et al. 2018; Rodríguez-Lorenzo et al. 2019; Lynk, Sit, and Brosseau 2018; Ronspees and Thorgaard 2018; Sun, J. et al. 2019b). A summary of the integrated dual model-based sensor for the detection of pathogenic bacteria is listed in Table 4.

Application of SERS/colorimetric/fluoresce integrated platform

Wu et al. proposed a SERS/colorimetric-based aptasensor for the detection of *P. aeruginosa* in food products (Figure 6A). Two kinds of AuNPs with 30 nm and 15 nm were prepared as color signal probes and SERS signal probes, respectively. The aptamer that can selectively target *P. aeruginosa*; however, horseradish peroxidase was modified on the surface of 30 nm-AuNPs, and its corresponding complementary DNA fragment (cDNA) and Raman reporter were modified on the surface of 15 nm-AuNPs. The two probes could form the duplex structure when there was no target bacterium in the system; contrarily, this structure could be destroyed in the presence of target bacteria because of the stronger interaction between the aptamer and *P. aeruginosa*. With the increasing concentration of *P. aeruginosa,* the SERS signal decreased because of the lack of electromagnetic effect. Meanwhile, the color signal probe was generated green color with the addition of TMB and hydrogen peroxide. The absorption intensity at 640 nm indicated the bacteria concentration. This strategy obtained average recoveries of 88 – 112% in spiked tap water and chicken samples (Wu et al. 2018).

Deng et al. proposed a colorimetric/fluorescent-based immunoassay sensor for the detection of *S. aureus* in milk samples (Figure 6B). L-cysteine (Cys) encapsulated liposome (Cys@liposome) nanocapsules were prepared to label *S. aureus*, and immunomagnetic nanoparticles were prepared to capture and isolate *S. aureus* from the matrix. After separation, tween-20 was used to destroy liposomes to release Cys molecules, and then Cys could react with 4-chloro-7-

Table 4. Integrated dual model-based sensor for direct detection of pathogenic bacteria and bacterial metabolites.

Bacteria/metabolites	Matrix	Techniques	C&R unit	LOD (cfu/mL)	RC (%)	Ref.
P. aeruginosa	Water and chicken	SERS/colorimetric	Aptamer	20 for SERS and 50 for color mode.	88 – 112	Wu et al. (2018)
S. aureus	Milk	Colorimetric/ fluorescent	Antibody	10 for color mode and 1 for fluorescence.	93 – 105	Deng et al. (2019)
C. jejuni	Milk	SERS/colorimetric	Antibody	75 for color mode and 50 for SERS.	89.33 – 107.62	He et al. (2019)
E. coli, Salmonella spp. and *V. cholera*	Chicken	Microfluidic/ colorimetric	Antibody	2.7×10^4	–	Sayad et al. (2018)
Salmonella spp., E. coli O157:H7, and *S. aureus*	Milk	LAMP/colorimetric	Genomic DNAs	30 – 300	–	Trinh, Trinh, and Lee (2019)
Salmonella spp. and *E. coli* O157:H7	Milk	LAMP/colorimetric	Genomic DNAs	100	–	Trinh, Trinh, and Lee (2019)
V. parahaemolyticus	Codfish, Shrimp, milk, oysters, clams, squid and jellyfish	CA-RCA/colorimetric	Aptamer	10	–	Song et al. (2019)
E. coli O157:H7	Drinking water and apple juice	RCA/fluorescence	DNAzyme	1.57	–	Zhou et al. (2020)
E. coli O157:H7	Milk and sewage water	MALDI-TOF MS/ fluorescent	–	1	92.3 – 101.5	Yang et al. (2019)

Note: C & R unit, capture and recognition unit; LOD, detection limit; RC, recovery rate; LAMP, loop mediated isothermal amplification; CA-RCA, cut-assisted rolling circle amplification; RCA, rolling circle amplification.

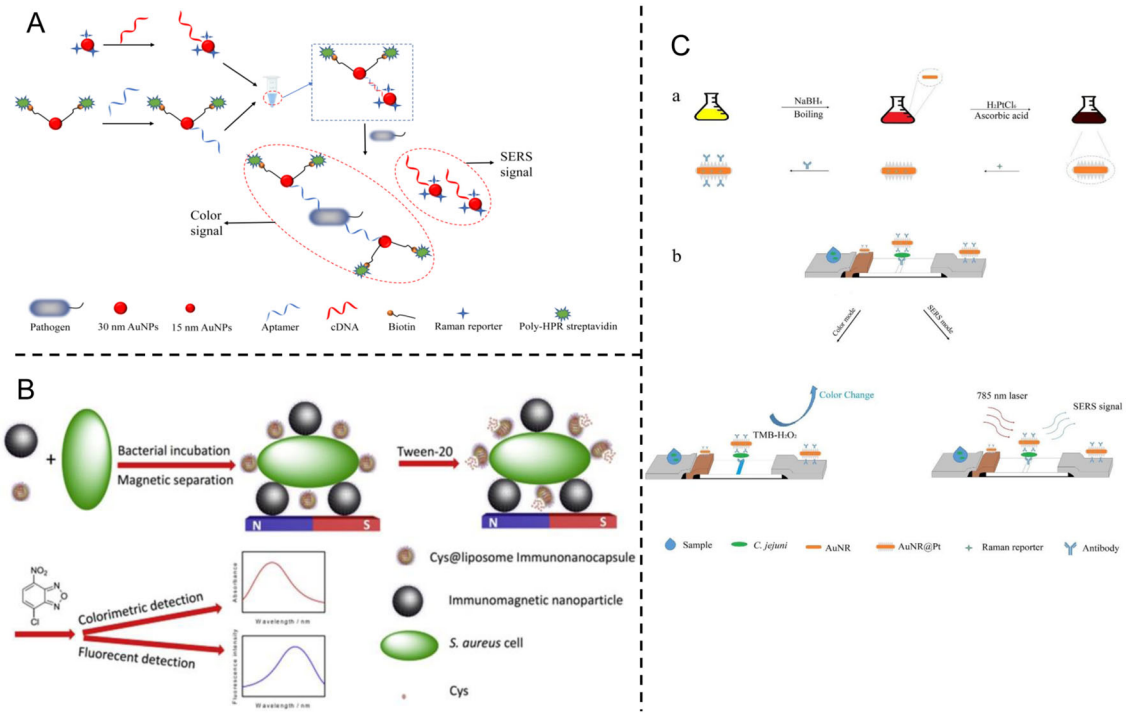

Figure 6. (A) Schematic illustration of a SERS/colorimetric-based aptasensor for detection of *P. aeruginosa*. Reproduced with permission from Wu et al. (2018). (B) Schematic illustration of colorimetric/fluorescent-based immunoassay sensor for detection of *S. aureus* in milk samples. © 2019. Wenfang Deng, Chang Cheng, Hui Yang et al. All Rights Reserved. Reproduced with permission from Elsevier. Deng et al. (2019). (C) Operating principle of SERS/colorimetric-based lateral flow assay for detection of *Campylobacter jejuni*. © 2019.Deyun He, Zhengzong Wu, Bo Cui et al. All Rights Reserved. Reproduced with permission from Elsevier. He et al. (2019).

nitrobenzo-2-oxa-1,3-diazole (NBD-Cl), which generated both colorimetric signals and fluorescent signals. It is noted that liposome nanocapsules used here were efficiently amplified signals and improved the sensitivity of detection. The results showed that the LOD of the colorimetric probe and fluorescent probe for *S. aureus* were 10 and 1 cfu/mL, respectively (Deng et al. 2019). Compared with natural enzymes, nanozyme is more stable and recyclable, and a typical case of nanozyme-based dual model detection platform was reported by He et al. They developed a SERS/colorimetric-based lateral flow assay for the detection of *C. jejuni* using platinum coated gold nanorods (AuNR@Pt) as a peroxidase mimicking agent to guarantee detection accuracy (Figure 6C) (He, D. et al. 2019).

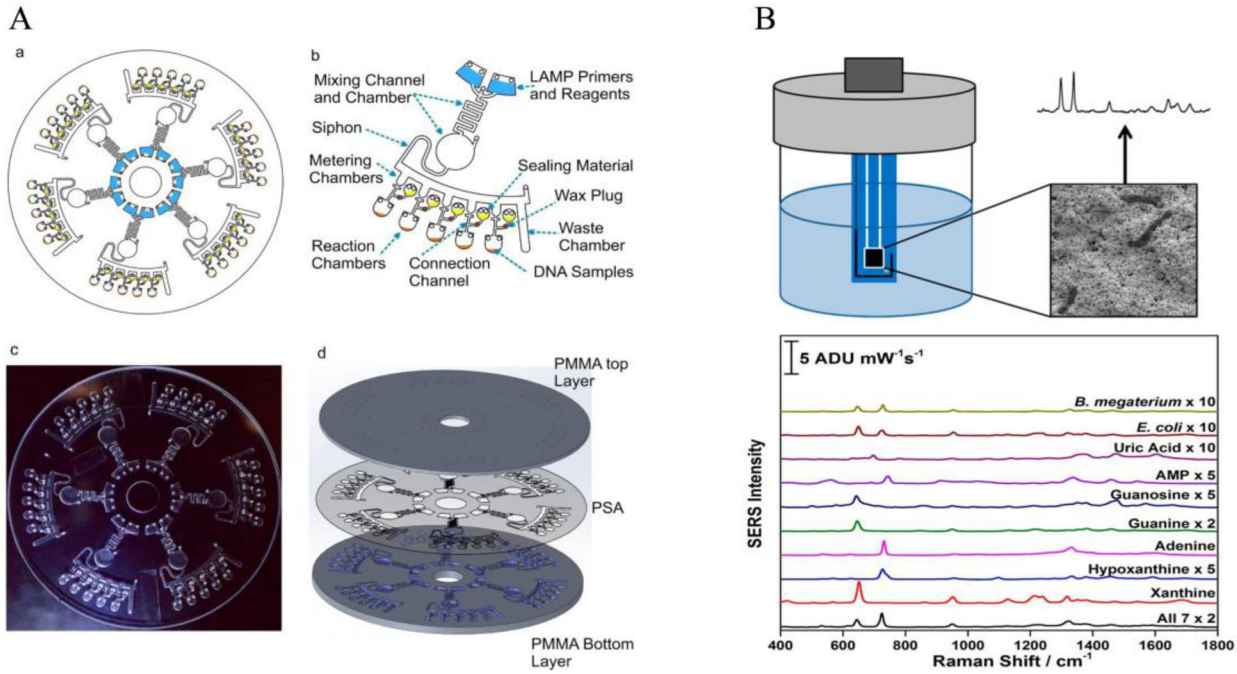

Figure 7. (A) Scheme of micro-device based colorimetric probe for detection of 24 strains of pathogenic bacteria from *Escherichia coli, Salmonella spp.,* and *Vibrio cholera*. © 2018. Abkar Sayad, Fatimah Ibrahim, Shah Mukim Uddin et al. All Rights Reserved. Reproduced with permission from Elsevier. Sayad et al. (2018). (B) Description of EC-SERS-based platform for detection of bacteria. © 2018. Taylor P. Lynk, Clarissa S. Sit, and Christa L. Brosseau. All Rights Reserved. Reproduced with permission from American Chemical Society. Lynk, Sit, and Brosseau (2018).

Application of microfluidic platform integrated optical-nano-sensors

With the emergence of microfluidic technologies, the development of point-of-care testing (POCT) for bacteria has improved rapidly. It is an analytical system with only little size that integrated all the operations of traditional experiments, including sample pretreatment, preparation, reaction, separation, and detection. Compared with conventional counterparts, it is highly effective, portable, low cost, and needs lower amount of sample and reagent, which can minimize human interferences. Hence, the development of microfluidic assisted SERS/fluorescence/colorimetric biosensors will offer a user-friendly detection system.

Sayad et al. fabricated a micro-device that integrated the function of centrifugal microfluidic automatic wireless end-point and loop mediated isothermal amplification (LAMP) and used calcein dye as a colorimetric probe for the detection of 24 strains of pathogenic bacteria from *E. coli*, *Salmonella spp.,* and *V. cholerae*. The microfluidic process includes loading of LAMP assay (a total of 62.5 μL for 5 reactions in one set of each identical sets), mixing, metering, valving, amplification, and detection. As stated in Figure 7A, at the beginning of detection, the LAMP reagents and primers were first injected into the loading chambers, and transferred into the sealing chambers, amplification chambers and square-wave mixing channel with corresponding reagents in sequential. And the filling of the mixing chamber channel activated the siphon valve which made enough LAMP reagents flow into the metering chambers, and then excessive liquid flowed into the waste chamber. Then, the LAMP reagents were transferred into the amplification chambers to initiate the sealing process and the DNA amplification in sequential. The results were observed by the color change to yellowish green of calcein dye (Sayad et al. 2018).

Application of electrochemical platform integrated optical-nano-sensor

Electrochemistry has the advantages of simple operation, rapid, sensitive, and easy miniaturization and integration, which has been coupled with SERS (EC-SERS) for the application of bacteria sensing. EC-SERS has been proved to provide more intense spectra when compared with the normal SERS technique, and it allows a more biologically relevant electric field environment for bacteria sensing. A typical case is first reported by Lynk et al., who used EC-SERS biosensor platform to detect and identify bacteria. They manipulate the surface charge of the SERS substrate to obtain good electrostatic condition for better bacteria adhesion, and this operation is helpful to screen wide variety of different bacteria owing to their difference in surface charge (Figure 7B). The SERS spectra of bacteria are mainly attributed to the 7 kinds of nucleotide breakdown products (namely, adenine, hypoxanthine, xanthine, uric acid, guanine, guanosine, and AMP), and their reference EC-SERS spectra were first established as a database. Then the screening of Gram-negative *E. coli* K-12 and Gram-positive *Bacillus megaterium (B. megaterium)* were investigated by EC-SERS, the results demonstrated the improvement of SERS performance; hence an EC-SERS-based sensor is a promising tool for quantitative analysis of bacteria (Lynk, Sit, and Brosseau 2018).

Recently, the integration of electrochemical-based platforms and colorimetric nano-sensor has received widespread attention due to their combination can overcome individual

disadvantages. Moreover, the integration made the detection system simpler and more sensitive. For instance, Sun et al. proposed a dual-model colorimetric and electrochemical detection strategy for *E. coli* sensing using p-benzoquinone (BQ) as a redox mediator. Glucose can react with an intact redox enzyme through catalytic reactions during *E. coli* respiration and the obtained reductase offer electrons to the BQ (electron acceptor). In this strategy, *E. coli* serves as electrodes, and BQ serves as electron mediator that can reduce to hydroquinone (HQ), and the remaining BQ further reacts with HQ to produce a red complex - quinhydrone. Thus, the color change was an index of the concentration of *E. coli*, meanwhile, the remaining BQ was reduced on the surface of the working electrode and generated a current flow for quantitative analysis. This method obtained a good linear detection range from 1×10^3 to 1×10^9 cfu/mL, with a LOD of 1×10^3 cfu/mL (Sun, J. et al. 2019b).

Although different researches focus on exploring the combination of the electrochemical platform with nano-optical sensors, most of these studies are stay on the simple matrix. Thus, there is great explore space for researchers to develop more sensitive and stable electrochemical-based nano-optical sensors to detect bacteria and their metabolites in food samples.

Application of nucleic acid amplification platform integrated optical-nano-sensor

Nucleic acid amplification-assisted nano-optical biosensors have been widely employed in recent foodborne pathogen sensing due to their excellent stability, sensitivity in complex food matrices. The most commonly used nucleic acid amplification technology is PCR, and following emerged isothermal amplification technology, such as LAMP, rolling cycling amplification (RCA), and the hybridization chain reaction (HCR) is an advanced development of PCR. When it was coupled with the colorimetric sensor, researchers focused on establishing a relationship between the target genes from bacteria and chromophore for the detection (Song et al. 2019; Zhan et al. 2020). In Lee's group, they utilized the characteristic reaction between fuchsin, sodium sulfite, and acid-hydrolyzed DNA amplicons to develop a series of LAMP-assisted colorimetric sensors for the detection of foodborne pathogens in milk (Trinh et al. 2019; Trinh and Lee 2019). Song et al. proposed a cut-assisted rolling circle amplification (CA-RCA) coupled colorimetric sensor for rapid visual detection of *V. parahaemolyticus* in food samples. The target bacteria were first captured and separated from food metrics by the anchoring aptamer and then bound with the detecting aptamer (D-Apt). CA-RCA was then introduced to amplify the D-Apt, which can further generate the monomeric G4 sequence to catalyze the oxidation of $ABTS^{2-}$, leading to the coloration visible to the naked eye (Song et al. 2019). Many efforts are also focusing on combing nucleic acid amplification with a fluorescence sensor (Zhou, Z. et al. 2020). For example, Xu's group used *E. coli*-specific RNA-cleaving DNAzyme for specific identification of target protein in a crude intracellular mixture (CIM) and then induced RCA to generate copper nanoclusters (CuNCs) with fluorescence signal (Zhou, Z. et al. 2020). The integration of SERS and nucleic acid amplification strategy also greatly improved the sensitivity of bacteria. As a typical case, Li's group explored the combination of SERS and RT-PCR for bacterial phenotype detection. They designed nucleic acid-based SERS probes to identify target pathogens and introduced IS into the SERS system for self-calibrating analysis to realize sensitive and specific detection of bacteria with LOD nearly to a single bacterium (Yu et al. 2020).

Application of other platforms integrated optical-nano-sensor

There are also some other techniques spring up to couple SERS or fluorescence or colorimetric sensor to obtain excellent performance of detection. Liao's group fabricated a 3 D silicon nanowires bio interface decorated with Au@Ag nanoparticles without complex chemical modifications coupled with laser-induced breakdown spectroscopy (LIBS) and SERS. LIBS showed direct element information of *E. coli* and *S. aureus* and the uniform Au@Ag nanoparticles on the biointerface provided more attachment sites for capturing bacteria and SERS signals for detection. This system obtained a range of $8.6 - 5.5 \times 10^6$ cells/cm^2 when detected *E. coli* and *S. aureus* in drinking water (Liao et al. 2019). Yang et al. synthesized pH-sensitive CDs as fluorescent probes to detect *E. coli* O157:H7 in milk and then identify it coupled with MALDI-TOF mass spectrometry (MALDI-TOF MS). This kind of ratiometric nanoprobe enables *E. coli* O157:H7 detection in milk and sewage water with a LOD of 1 cfu/mL (Yang, Q. et al. 2019).

Conclusions

Pathogenic bacteria have caused many hardships to human health, and it is necessary to develop simple, rapid, and sensitive approaches to detect them beforehand. This review has summarized the methods that are widely used for the detection of pathogenic bacteria and their metabolites by three types of optical-based biosensors, namely SERS, fluorescence, colorimetric-based sensors, and their integration with other techniques. Strategies established based on SERS or fluorescence techniques are mainly categorized into two types, one is specific sensing with assisted specific recognition units, such as antibody, aptamer, phage, and antimicrobial peptides, to capture target bacteria from the matrix and then build a quantitative model with standard curves; in addition, some specific strategy utilize physiological properties to generate a particular reaction, leading to the signal changes; another type is label-free ways with some broad-spectrum capture tools, such as positively charged materials, 4-MPBA, and glutaraldehyde, which can bind with most of the bacteria. And chemometric methods, like PLS, PCA, LDA, and so on, can be applied for further effective quantitative or qualitative analysis. The colorimetric sensor is generally developed based on the color changes of specific catalytic reactions or particle motion properties related to target bacteria. It should be noted that the mentioned

biosensors have their own distinctive properties, and the ability to sense bacteria depends on their goals and condition. Therefore, it is foreseeable that further development of nano-optical detection platforms has great potential to be applied in real food industry and improve the detection efficiency of food safety.

Future perspectives

The developed optical-based sensors have greatly improved the detection time and sensitivity and saved detection costs compared with the traditional techniques. However, challenges remain for the simple fabrication of biosensors and their practical application. For example, most of the cases have reported the application of bacteria sensing in real food samples, yet some of them require complex sample pretreatment, which extended the whole detection time. Moreover, tedious pretreatment operations may increase the chances of error in final results. Another disadvantage is that some study involves the addition of target bacteria into pretreated samples, such procedures are usually not followed in the practical application. Furthermore, some environmental factors need to be considered such as temperature, pH, or other components especially in food, which is a big challenge for the sensitivity and selectivity of a developed sensor. Therefore, several efforts should be taken to overcome the aforementioned problems in the following aspects: 1) exploration of more stable nanoparticles, which is the most important part of biosensors; 2) exploration of novel methods for pretreatments of real samples, recently, the microfluidic platform has emerged as a promising method for in-situ detection, however, it is also limited to the high cost and universal to different detection condition. Thus, bringing out improvements or novelty in the pretreatment methods will be a trend in the upcoming future.

Disclosure statement

The authors declare that there is no conflict of interest regarding the publication of this study.

Abbreviation

E. coli *Escherichia coli*
B. thermosphacta
Brochothrix thermosphacta
M. luteus *Micrococcus luteus*
S. Enteritidis
Salmonella enterica subsp. enterica sv. Enteritidis
B. thuringiensis
Bacillus thuringiensis sv. israelensis
B. subtilis *Bacillus subtilis*
LGG *Lactobacillus rhamnosus GG*
S. typhimurium
Salmonella typhimurium
MRSA *methicillin-resistant Staphylococcus aureus*
S. aureus *Staphylococcus aureus*
Listeria *Listeria monocytogenes*
P. aeruginosa
Pseudomonas aeruginosa
E. coli O157:H7
Escherichia coli O157:H7
S. sonnei *Shigella sonnei*
C. sakazakii
Cronobacter sakazakii
S. flexneri *Shigella flexner*
V. parahaemolyticus
Vibrio parahaemolyticus
S. pneumoniae
Streptococcus pneumoniae
D. desulfuricans
Desulfovibrio desulfuricans
S. sciuri *Staphylococcus sciuri*
C. jejuni *Campylobacter jejuni*
E. faecalis *Enterococcus faecalis*
S. mutans *Streptococcus mutans*
S. pullorum
Salmonella pullorum
V. vulnificus
Vibrio vulnificus
K. pneumoniae
Klebsiella pneumoniae
Sh. flexneri *Shigella flexneri*
P. mirabilis *Proteus mirabilis*
X. campestris
Xanthomonas campestris
V. cholerae *Vibrio cholerae*
pVIII Pviii fusion

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