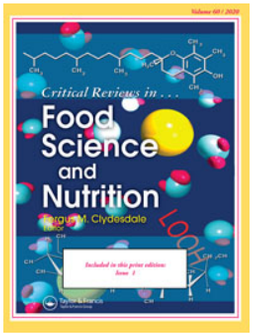

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REVIEW

Paper-based lateral flow strip assay for the detection of foodborne pathogens: principles, applications, technological challenges and opportunities

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ABSTRACT

As a representative colorimetic biosnesor, paper-based LFSA have emerged as a promising and robust tool that can easily and instansly detect the presence of target biological components in food sample. Recently, LFSAs have gained a considerable attention as an alternative method for rapid diagnosis of foodborne pathogens to the conventional culture-based assays such as plate counting and PCR. One major drawback of the current LFSAs for the detection of pathogenic bacteria is the low sensitivity, limiting its practical applications in POCT. Not like many other protein-based biomarkers that are present in nM or pM range, the number of pathogenic bacteria that cause disease can be as low as few CFU/ml. Here, we review current advances in LFSAs for the detection of pathogenic bacteria in terms of chromatic agents and analyte types. Furthermore, recent approaches for signal enhancement and modifications of the LFSA architecture for multiplex detection of pathogenic bacteria are included in this review, together with the advantages and limitations of each techniques. Finally, the technological challenges and future prospect of LFSA-based POCT for the detection of pathogenic bacteria are discussed.

KEYWORDS

Lateral flow strip assay; foodborne pathogen; detection; biosensors; signal amplification; multiplex assay; point-of-care testing

1. Introduction

Pathogenic microorganisms in food and agricultural products are one of the most serious threats to human health, which could cause various diseases and even deaths. Early diagnosis of pathogenic microorganisms in contaminated food and infected person is thus critical to ensure the safety of food and appropriate treatment. Conventional culture-based assays, a golden standard for the identification of pathogenic microorganisms, provides the most accurate results together with the subsequent biochemical analysis. But it requires lengthy and labor intensive culturing and identification process. Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) provides a high-throughput and multiplexing tools in microbial diagnosis. Especially, there has been meaningful progresses in PCR technology over the past decade with regard to the miniaturization of the device and quantitative analysis of the target microorganisms. However, wide use of those technologies in real fields, such as food processing facilities and cafeteria, are limited because they typically require bacterial enrichment or sample preparation process to remove background matrices of the sample that could inhibit the amplification reaction.

On the other hand, biosensor is a new generation detection system that utilizes the specificity of biological component integrated with optical, electrical and mechanical transducing system for monitoring the presence of a specific pathogen in food or patient. With the simple and rapid nature of the detection process, biosensor has been regarded as one of the most promising alternative to the conventional culture-based assay, PCR and ELISA for the diagnosis of pathogenic microorganisms. Biosensor is also suitable for point-of-care testing (POCT) system that is capable of the rapid screening of specific pathogens in places where sophisticated lab facility is not available. It allows immediate decision-making of a specific antibiotic therapy at the hospital bedside, which enhances patient survival as well as reducing unnecessary antibiotic uses (Vashist et al., 2015). The timely decision-making is also important in food handling facilities, which could prevent the spread of contaminated food to public. In addition to the rapid diagnostic decisions-making, this system could reduce potential analytical interference by minimizing complicated sample handling and transportation time of test specimen to the diagnosis facility. WHO defined that diagnostics for developing countries should fulfil the ASSURED: affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users (Quesada-González and Merkoçi, 2018). However, there are still many technological challenges that need to be resolved for the realization of POC diagnostic system in terms of satisfying the ASSURED.

Over the past two decades, lateral flow strip assay (LFSA) have become one of the most widely used POC diagnostic technology that fulfills the demand of ASSURED, thus holding a great promise to deliver POC diagnostic services to

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Table 1. Commerical lateral flow strip assay kits for the detection of foodborne pathogens.

Manufacturer	Target analytes	Source
DuPont™	*E. coli* O157; *Salmonella*; *Listeria*; *Campylobacter*	www.dupont.com
Biocontrol	*Salmonella*; *Listeria*; EHEC	www.biocontrolsys.com
Neogen	*E. coli* O157; *Salmonella*; *Listeria*	www.neogen.com
New Horizons Diagnostic	*E. coli* O157; *Salmonella*	www.nhdiag.com
Hygiena	*E. coli* O157; *Salmonella*; *Listeria*	www.hygiena.com
Singlepath	*E. coli* O157; *Listeria*; *Salmonella*; *Campylobacter; B. cereus*	www.singlepath.com
Oxoid Listeria Rapid Test	*Listeria*	www.oxoid.com
Ubio	*E. coli* O157; *Salmonella*; *Listeria*; Shigella; *V. cholera*; *V. parahaemolyticus*	www.ubio.in
Romer Labs	*E. coli* O157; *Salmonella*; *Listeria*	www.romerlabs.com

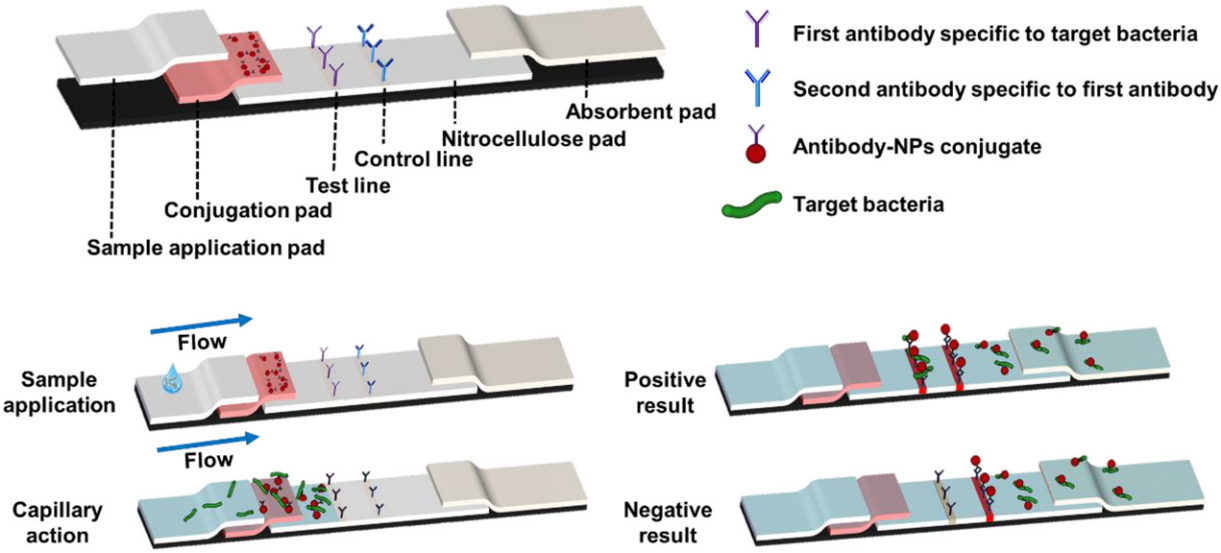

Figure 1. Schematic representation of LFSA for bacterial diagnosis. When a sample with target bacteria is applied on sample pad the antibodies labelled with chromatic agent in conjugation pad bind to the bacteria, which is subsequently travelling through the nitrocellulose pad by capillary action. The target bacteria captured on test line together with chromatic agent-conjugated antibody is responsible for the red signal in test line. The signal in control line is derived from the same antibody without target analyte.

resource-limited settings. For instance, the home pregnancy strip and glucose testing strip are the most successful and well-known product of LFSA, which have made a significant milestone in POC diagnostics. LFSA has also emerged as a promising and robust diagnostic tool that can instantly identify the presence of pathogenic microorganisms in food sample. The concept of bacteria-diagnostic LFSA was initially developed by Abdel-Hamid et al. (1999), who reported a flow-through amperometric immunofiltration assay system offering a rapid detection of *E. coli* O157:H7 with a dynamic range from 100 to 600 cells/ml. A range of paper-based LFSA for detecting foodborne pathogen have been commercialized and used in food industry. The commercialized products of LFSA that are applied to detect foodborne pathogens is summarized in Table 1. Although the accuracy of those commercial LFSAs is comparable to those of conventional methods, they typically require pre-enrichment of at least 24 h. The high limit of detection (LOD) of LFSA necessitated the need of lengthy bacterial enrichment process and limited its on-site applications. Therefore, there have been enormous efforts to develop LFSA with enhanced sensitivity that can fulfill the required criteria without enrichment step on-site. In this review, we discuss the current advances in LFSAs for bacterial diagnosis, together with the advantages and limitations of each techniques. Current developmental efforts towards enhancing the sensitivity of LFSA as well as the realization of multiplex diagnosis of pathogenic bacteria are discussed.

1.1. Methodology of LFSA

LFSA biosensor is normally manufactured in strip type and utilizes capillary force to transport the analyte through a series of capillary pad, including sample pad, conjugation pad, detection pad, and absorbent pad (Fig. 1). Once a liquid sample containing the target analyte of interest is applied to the sample pad, the sample solution is driven by capillary force to the conjugation pad where capture probe conjugated with colored or fluorescent label is located. In conjugation pad, the target analyte forms complex with antibody labeled with chromatic or fluorescent tag through a specific interaction between the target analyte and the antibody. The solution containing labelled analyte keeps moving by capillary force toward absorbent pad located at the other end of the strip via detection zone and control zone. The target analyte complexed with labeled antibody binds to the immobilized antibody in test zone (or detection zone) whereas the labeled antibody without analyte binds to the antibody immobilized in control zone (Fig. 1). The captured antibodies with and without target analyte in test zone and control zone, respectively, were identified by the colored or fluorescent label conjugated to the antibody.

1.2. Chromatic agents and fluorescent nanoparticles

There are variety of LFSA biosensors depending on the types of colored or fluorescent nanoparticles (NPs) whose sizes are usually 15-800 nm. As NPs play a significant role as a reporter in determining the sensitivity of LFSA, the selection of NPs should be taken into account. For example, it should be size-tunable, easy-to-synthesize, highly stable over a long period, and cost-efficient. The surface of NPs is typically modified with specific functional groups, such as carboxyl, amine, and hydroxyl groups, allowing the subsequent conjugation to a variety of bio-receptors including antibodies, aptamers, oligonucleotide, and so on. In past twenty years, colored NPs, such as gold nanoparticles (AuNPs) and magnetic nanoparticles (MNPs) have emerged as an excellent signal generator in LFSA. Amongst them, colloidal AuNPs is still the most widely used in LFSA biosensor as a reporter offering a signal of intense red color capable of detecting by naked eye or color reader (Cho et al., 2015; Cho and Irudayaraj, 2013b; Li et al., 2011; Shen et al., 2013b). The typical method of AuNPs synthesis is reduction of $HAuCl_4$ by sodium citrate at boiling temperature. The size of AuNPs can be tuned by changing the molar ratio of Au^{3+} to sodium citrate (McFarland et al., 2004). To reach the full potential of LFSA sensing, however, there remain many challenges that should be addressed to maximize the colorimetric contrast of AuNPs. Recently, Zhan et al. (2017) reported that the size of AuNPs played a predominant role in the sensitivity of LFSA, where the AuNPs ranging from 30 nm to 100 nm in diameter presented the best analytical performance in LFSA (Zhan et al., 2017).

MNPs are another widely used NPs that are either black or brown in color. Due to the paramagnetic nature, MNPs are mainly used for target enrichment through selective separation and concentration of target components from a large volume of heterogeneous matrices, which significantly improves the detection limit of the sensing system (Chen et al., 2015b; Wu et al., 2015). The selectivity of the MNPs toward target components is typically derived from the immobilized ligands on the surface of MNPs, such as antibody, and the captured targets along with MNPs are readily separated from the aqueous sample by external magnetic field. MNPs have also been utilized as a signal generator in LFSA due to their colorimetric properties (Alhogail et al., 2016; Liu et al., 2015; Shi et al., 2015; Suaifan et al., 2017a, b; Yan et al., 2014). There are several types of magnetic nanoparticles depending on the oxidation number of the iron oxide, mainly Fe_3O_4 (magnetite) and γ- Fe_2O_3 (maghemite). The most conventional method for the synthesis of Fe_3O_4 and γ- Fe_2O_3 NPs is by co-precipitation through mixing ferric and ferrous ions in a ratio of 1:2 at room temperature or at elevated temperature under alkali condition (Luo et al., 2018a; Luo et al., 2018b). The size and shape of magnetic nanoparticles can readily be tuned by the types of added salt (e.g. chlorides, sulfates, perchlorates, etc.).

In addition, up-converting phosphors (UCPs) are submicron-sized particles composed of rare earth elements embedded in a crystal. They possess unique optical properties that emit light in visible range upon absorbtion of a light in IR photons (980 nm) through anti-stokes shift. The optical properties of these phosphors are mainly dependent on the material of UCPs, which makes this material suitable for multiplex detection. Thus, UCPs have been employed as a reporter agent in LFSA since 2000 (Corstjens et al., 2001; Hampl et al., 2001; Niedbala et al., 2001). In particular, a number of studies reported UCP-based LFSA for the detection of foodborne pathogens over the past decades (Hao et al., 2017; Hong et al., 2010; Qu et al., 2009; Yan et al., 2006; Zhang et al., 2014; Zhang et al., 2015b; Zhao et al., 2016; Zhou et al., 2014). These studies also demonstrated that UCP-based LFSA exhibited considerably lower detection limit comparing to other types of chromatic nanoparicles-based LFSA. In addition, quantum dots (QDs), fluorescent nanoparticles (FNPs) with a diameter ranging from 2 to 6 nm, are semiconductor nanocrystals that have attracted a great deal of attention with its high chemical stability, high photo-stability, and excellent photoluminescence properties. Cadmium has been most widely used material for the synthesis of QDs due to its excellent optical and electrochemical propertis. However, its application in biological area is rather restricted due to its toxicity. Carbon-based QDs are a new class of nanomaterial with a diameter below 10 nm, which has attracted attentions as a cadmium-free QDs. Owing to its excellent photoluminescence property, carbon-based QD provides potential for a range of diagnostic applications including DNA, protein, and even whole cells diagnosis (Chai et al., 2015; Loo et al., 2016; Morales-Narváez et al., 2015). Recently, the application of QD-based LFSA has increased as an alternative to AuNP-based LFSA (Bruno, 2014; Chen et al., 2014; Morales-Narváez et al., 2015). Table 2 lists representative studies on paper-based LFSAs for bacterial detection.

2. Nucleic acid-based LFSA for bacterial detection

2.1. AuNPs-based NALFSA

NALFSA offers a facile means of bacterial detection combining the basic strategy of lateral flow assay, ELISA and nucleic acid hybridization. For this, an oligonucleotide that is capable of probing the presence of target nucleic acid is typically labelled with chromatic NPs, and then used as a specific detection probe to capture the target nucleic acids by hybridization. Recently, a number of NALFSA biosensors have been developed for bacterial diagnosis (Ang et al., 2012; Blažková et al., 2009; Liu et al., 2013; Rastogi et al., 2012; Roskos et al., 2013; Shukla et al., 2011; Yeung et al., 2014; Zhang et al., 2017). In particular, Pohlmann et al. (2014) designed a RNA based LFSA for the detection of *E. coli* in combination with a simple cell lysis strategy capable of collecting the 16S rRNA from live cells. The fragmented 16S rRNA was reacted with three other components, oligodeoxynucleotide-AuNPs (40 nm) conjugates, helper oligodeoxynucleotide, and biotinylated capture oligodeoxynucleotide, to form a four-components complex through Watson-Crick base pairing. In the presence of target 16S rRNA, the complex is captured by the immobilized neutravidin in test zone and visualized by the chromatic AuNPs. In

Table 2. Summary of studies on paper-based LFSAs for the detection of pathogenic bacteria.

Probe	Analytes	Receptor	Sample	Target bacteria	Assay time	LOD	Refs
AuNPs	Whole cell	Antibody	raw beef	*E. coli* O157:H7	10 min	1.8×10^5 CFU/ml	(Jung et al., 2005)
AuNPs + IMPs	Whole cell	Antibody	meat products, fish	*L. monocytogenes*	15 hours	1×10^2 CFU/10 g	(Shim et al., 2008)
AuNPs + HRP-TMB	Whole cell	Antibody	buffer	*S. typhimurium*	16 min	9.2×10^3 CFU/ml	(Park et al., 2010)
AuNPs + IMPs	Whole cell	Antibody	water, milk, beef	*E. coli* O157:H7	<1 hour	1×10^3 CFU/ml	(Qi et al., 2011)
AuNPs	Whole cell	Antibody	milk	*S. typhimurium*	30 min	10^2 cells	(Pandey et al., 2012)
AuNPs	Whole cell	Antibody	sea food	*V. cholerae* O139	20 min	1×10^4 CFU/ml	(Pengsuk et al., 2013)
AuNPs	Whole cell	Antibody	meat products vegetables	*S. typhimurium*	18 hours	2.3×10^3 CFU/ml	(Yonekita et al., 2013)
AuNPs	Whole cell	Antibody	buffer	*S. typhimurium; S. enteritidis;*	15 min	1×10^4 CFU/ml 1×10^6 CFU/ml	(Moongkarndi et al., 2011)
AuNPs	Whole cell	Antibody	buffer	*P. aeruginosa; S. aureus;*	10 min	500-5000 CFU/ml	(Li et al., 2011)
AuNPs	Whole cell	Antibody	human serum	*S. typhi*	15 min	1.14×10^5 CFU/ml	(Preechakasedkit et al., 2012)
AuNPs + IMPs	Whole cell	DNA	buffer	*S. enteritidis*	NA	1×10^1 CFU/ml	(Fang et al., 2014)
AuNPs + IMPs	Whole cell	DNA	buffer	*E. coli* O157:H7	NA	1×10^1 CFU/ml	(Wu et al., 2015)
AuNPs	Whole cell	Antibody	buffer	*E. coli* O157:H7	10 min	1×10^2 CFU/ml	(Cui et al., 2015)
AuNPs	Whole cell	Antibody	water	*S. typhi*	10 min	1×10^4 CFU/ml	(Singh et al., 2015)
AuNPs + $HAuCl_4$	Whole cell	Antibody	milk	*E. coli* O157:H7	20 min	5×10^3 CFU/ml	(Wang et al., 2015)
Dual AuNPs	Whole cell	Antibody	Buffer milk	*E. coli* O157:H7	15 min	1.14×10^3 CFU/ml 1.14×10^4 CFU/ml	(Chen et al., 2015a)
AuNPs	Whole cell	Antibody	buffer	*E. coli* O157:H7 *S. aureus*	NA	1×10^6 CFU/ml	(Park et al., 2016)
AuNPs	Whole cell	Antibody	buffer	*E. coli* O157:H7	15 min	1×10^3 CFU/ml	(Zhang et al., 2015a)
AuNPs + HRP-TMB	Whole cell	Antibody	beef	*E. coli* O157:H7	15 min	1×10^2 CFU/ml	(Cho et al., 2015)
Pt-AuNPs + TMB	Whole cell	Antibody	buffer	*E. coli* O157:H7	10-20 min	10^2 cells/ml	(Jiang et al., 2016)
Fe_3O_4/Au core/shell	Whole cell	Antibody	milk	*S. choleraesuis*	22 hours	5×10^5 CFU/ml	(Xia et al., 2016)
AuNPs	Whole cell	Antibody	bread, milk, jelly	*E. coli* O157:H7; *S. boydii;*	10 min	1×10^6 CFU/ml	(Song et al., 2016a)
AuNPs	Whole cell	Antibody	milk	*L. monocytogenes*	13 hours	3.7×10^6 CFU/ml	(Wang et al., 2017)
AuNPs	Whole cell	CBD	buffer	*B. cereus*	20 min	1×10^4 CFU/ml	(Kong et al., 2017)
AuNPs	Whole cell	Antibody	lettuce	*E. coli* O157:H7 *S. typhimurium*	20 min	1.87×10^4 CFU/ml	(Shin et al., 2017)
AuNPs + $HAuCl_4$	Whole cell	Antibody	milk	*S. enteritidis*	6 hours	1×10^4 CFU/ml	(Bu et al., 2018)
AuNPs	Nucleic acid	DNA	water, milk, blood, spinach	*E. coli* *S. aureus*	1 hour	10-1000 CFU/ml	(Choi et al., 2016)
AuNPs	Nucleic acid	DNA	pork	*S. aureus*	48 hours	2×10^2 CFU/g	(Zhang et al., 2017)
AuNPs	Nucleic acid	DNA	milk, juice, egg, wastewater	*S. typhimurium*	1 hour	1×10^3 CFU/ml	(Tang et al., 2017)
AuNPs/Ag core/shell	Nucleic acid	DNA	milk, breast, beef, chicken	*L. monocytogenes* *S. epidermidis*	30 min	2×10^1 CFU/ml	(Liu et al., 2017)
AuNPs + $HAuCl_4$	Nucleic acid	DNA	buffer	*E. coli* O157:H7	NA	0.4 nM	(Rastogi et al., 2012)
AuNPs	Nucleic acid	DNA	buffer	*E. coli*	25 min	5×10^4 CFU/ml	(Pohlmann et al., 2014)
AuNPs + Silver	Nucleic acid	DNA	buffer	*Salmonella.*	40 min	10^4 cells/ml	(Liu et al., 2013)
AuNPs	Nucleic acid	DNA	fecaluria	*S. typhimurium*	30 min	5×10^8 CFU/ml	(Yeung et al., 2014)
AuNPs	Nucleic acid	DNA	food samples	*E. coli* O157:H7	18 hours	1×10^6 CFU/ml	(Suria et al., 2015)
CNPs	Nucleic acid	DNA	fruit juice buffer	*E. coli*	1 hour	1-5 ng/ml	(Posthuma-Trumpie et al., 2012)
CNPs	Nucleic acid	DNA	buffer	*E. coli*	70 min	6.7×10^4 CFU/ml	(Noguera et al., 2011)
CNPs	Nucleic acid	DNA	milk	*Listeria spp.; L. monocytogenes;*	28 hours	10^5 cells	(Blažková et al., 2009)
AuNPs + IMPs	Nucleic acid	DNA	buffer	*E. coli* *S. enterica*	NA	0.59-0.75 pg/μl	(Aissa et al., 2017)
AuNPs	Nucleic acid	DNA	buffer	*S. typhimurium* *V. parahaemolyticus*	80 min	50 CFU	(Park et al., 2017)
IMPs	Whole cell	Antibody	food samples	*L. monocytogenes*	25 min	1×10^4 CFU/ml	(Shi et al., 2015)
IMPs	Whole cell	Antibody	shrimp clam	*V. parahaemolyticus*	NA	1×10^5 CFU/ml	(Yan et al., 2014)
IMPs	Whole cell	peptide	lettuce, milk, meat, sausage	*E. coli* O157:H7	30 sec	30-300 CFU/ml	(Suaifan et al., 2017a)
IMPs	Whole cell	Antibody	dairy products	*B. anthracis*	40 min	5×10^5 CFU/ml	(Fisher et al., 2009)
IMPs + HRP-TMB	Whole cell	Antibody	buffer milk	*L. monocytogenes*	< 1 hour	1×10^2 CFU/ml	(Cho and Irudayaraj, 2013b)
IMPs	Whole cell	Antibody	sea food	*V. parahaemolyticus*	4 hours	1.58×10^2 CFU/ml	(Liu et al., 2015)
IMPs + FNs	Whole cell	Antibody	milk	*E. coli* O157:H7	5 hours	1×10^2 CFU/ml	(Huang et al., 2016)
UCPs	Whole cell	Antibody	buffer	*E. coli* O157:H7	10 min	1×10^2 CFU/ml	(Niedbala et al., 2001)
UCPs	Whole cell	Antibody	279 food samples	10 epidemic foodborne pathogens	NA	1×10^4 to 1×10^5 CFU/ml	(Zhao et al., 2016)
UCPs	Whole cell	Antibody	buffer	*Y. pestis* *B. pseudomallei*	NA	1×10^3 CFU/test	(Liang et al., 2017)
QDs + IMPs	Nucleic acid	DNA	raw meat milk	*S. aureus*	2 hours	3×10^0 CFU/ml 3×10^1 CFU/ml	(Chen et al., 2014)
QDs	Whole cell	Antibody	buffer milk	*E. coli*	NA	1×10^1 CFU/ml (buffer) 1×10^2 CFU/ml (milk)	(Morales-Narváez et al., 2015)
QDs	Whole cell	DNA	buffer	*E. coli*	15 min	300-600 cells	(Bruno, 2014)
QDs	Whole cell	Antibody	buffer	*V. cholera*	10 min	1×10^3 CFU/ml	(Gharaat et al., 2017)
EuNPs	Whole cell	Antibody	milk	*E. coli* O157:H7	30 min	1×10^2 CFU/ml	(Xing et al., 2018)
FITC	Whole cell	Antibody	bread, milk, jelly	*E. coli* O157:H7	10 hours	1×10^0 CFU/ml	(Song et al., 2016b)

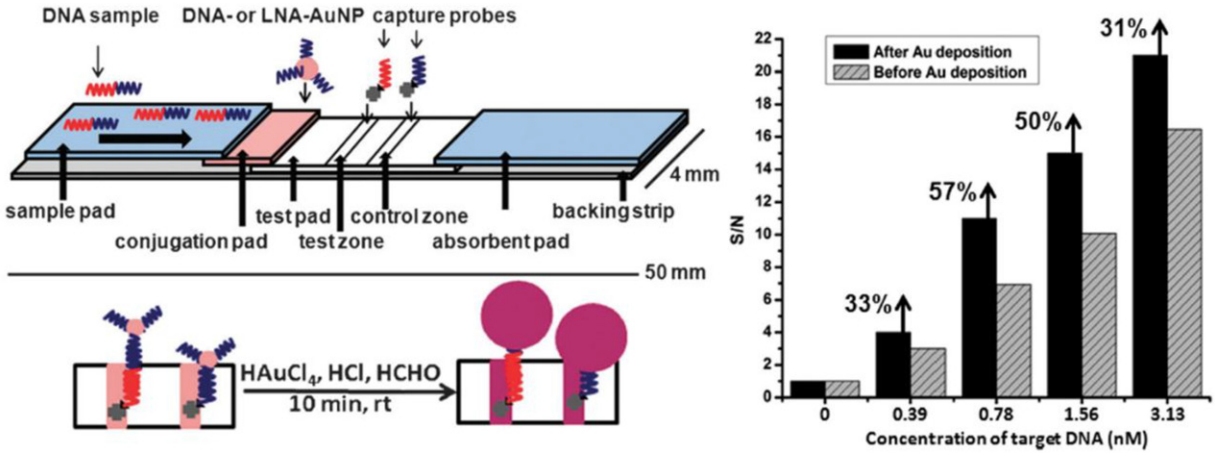

Figure 2. Nucleic acid-based LFSA for the detection of *E. coli* O157:H7 with signal amplification by growing the size of primary AuNPs (Rastogi et al., 2012).

this assay, a 16S rRNA corresponding to 5×10^4 CFU/ml *E. coli* was successfully detected by naked eyes. Even though, AuNPs confer a strong chromatic signal on LFSA, its use is limited to the target analytes that are present in large quantity. In order to enhance the detection limit of AuNP-based LFSA, there have been many efforts to amplify the intensity of chromatic signals from AuNPs. Rastogi et al. (2012) developed a NALFSA for detection of *E. coli* O157:H7 by using the oligodeoxynucleotide-AuNPs (15 nm) conjugate as capture probes (Fig. 2). The detection limit of this NALFSA was enhanced from 1 nM to 0.4 nM of target DNA by introducing $HAuCl_4$-HCl-HCHO mixture to the reaction, which enlarged the diameter of AuNPs through gold deposition onto the primary AuNPs, thereby improving the intensity of optical signal. On the other hand, Shen et al. (2013b) employed larger secondary AuNPs (30 nm) that could couple to the primary AuNPs (16 nm) through the hybridization of two complementary oligonucleotides (DNA 1 and DNA 2) immobilized on each AuNPs for enhancing the color intensity of test line. By introducing the secondary AuNPs, this dual AuNPs method increased the LOD down 0.25 nM which is 30-fold higher than the conventional methods.

2.2. PCR-integrated NALFSA

As the most powerful means of amplifying the number of target DNA in short period of time by far, PCR is commonly employed to enhance the detection limit for NALFSA (Blažková et al., 2009; Chen et al., 2014; Noguera et al., 2011; Terao et al., 2015). For example, Noguera et al. (2011) and Terao et al. (2015) combined PCR and NALFSA for the detection of the genes encoding virulence factors of Shiga toxin-producing *E. coli*. Noguera et al. (2011) performed 30 cycles of PCR (30 min) to amplify the number of target DNA that was subsequently detected by NALFSA with LOD of 10^4–10^5 CFU/ml. Forty five cycles of PCR before NALFSA lowed the detection limit down to 20 CFU/ml (Terao et al., 2015). However, the low detection limit achieved by combining conventional PCR together with NALFSA does not seem quite attractive since real-time PCR itself is already powerful enough to quantify the number of target bacteria down to 10 CFU/ml. To maximize the advantage of NALFSA while simplifying the bulky PCR process, Park et al. (2017) developed an integrated rotary microfluidic system for the detection of foodborne pathogen. The disc-type system contains a series of components that can carry out DNA extraction, loop mediated isothermal amplification (LAMP), and colorimetric lateral flow strip-based detection in a sequential manner (Fig. 3A). Once cell lysate was introduced into the rotary microdevice through the sample inlet (Fig. 3B), the genomic DNA in cell lysate was adsorbed onto the surface of glass microbeads in the presence of chaotropic salt (Fig. 3C). The DNA was eluted from the glass microbeads and transported to the LAMP chamber where amplification of the specific gene was taking place. The amplicons were then loaded onto the lateral flow strips for the final detection of target microorganisms. This rotary microfluidic system was successful in multiplex detection of *S. Typhimurium* and *V. parahaemolyticus* in water or milk sample with a limit of detection of 50 CFU in 80 min.

2.3. QDs-based NALFSA

QDs are nanoscale semiconductor materials whose unique optical properties make them attractive fluorophores in a variety of biological applications. QDs are superior to conventional organic dyes in terms of brightness, narrow emission spectra, tunable emission peaks and long fluorescence lifetime, which are ideal as labeling materials for optical imaging and biosensors. Chen et al. (2014) demonstrated a QDs-based NALFSA for the detection of *Staphylococcus aureus* in food sample. In their assay, *S. aureus* DNA obtained by boiling treatment were concentrated by using silica-coated magnetic NPs, followed by PCR-based amplification using digoxigenin/biotin-labeled primers. The digoxigenin/biotin-labeled target gene was sandwiched between streptavidin coated QDs and anti-dioxigenin antibodies that were immobilized in test line whereas the QDs without target DNA were captured in control line by streptavidin-biotin interaction. The QDs captured in both test line and control line were visualized by UV. This system could detect *S. aureus* in milk powder and meat samples with LOD as low as $3 \times 10^{\circ}$ CFU/mL and 3×10^{1} CFU/g, respectively, within 2 h.

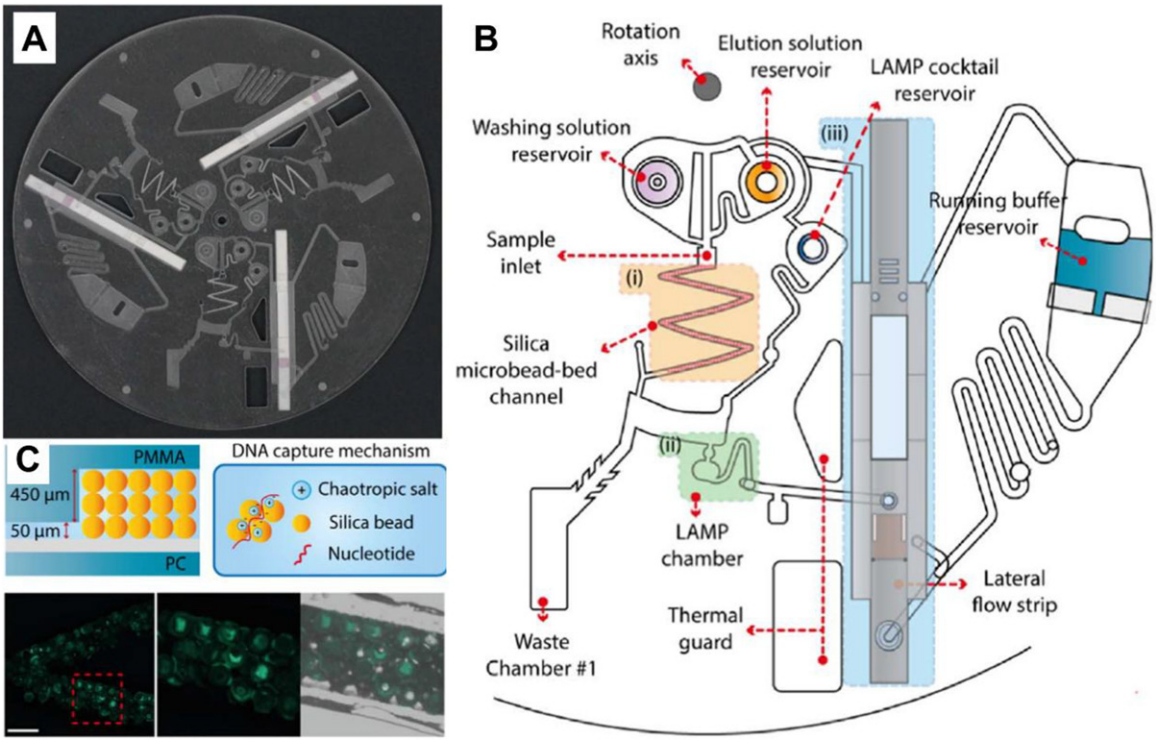

Figure 3. Integrated rotary microfluidic system for NALFSA-based detection of *S. Typhimurium* and *V. parahaemolyticus*. (A) Integrated rotary disc. (B) The diagnistic component in rotary microdevice for DNA extraction, amplification and lateral flow strip detection. (C) Schematics showing the DNA extraction unit. Fluorescence-labeled DNA captured on the surface of glass microbeads was visualized by fluorescence microscopy (Park et al., 2017).

3. Whole cell-based LFSA for bacterial detection and signal amplification

Recently, WCLFSA has emerged as a promising tool capable of diagnosing foodborne diseases through direct visualization of labeled target bacteria concentrated on test zone of membrane. Comparing to NALFSA biosensor, WCLFSA could detect the target bacteria without any pretreatment step such as cell lysis and nucleic acid amplification that typically require 1-2 h. Over the past two decades, a variety of WCLFSA biosensors were developed in combination with a range of different types of NPs as a chromatic agent. So far, AuNPs are still the most popular and widely used chromatic NPs in LFSA system. However, there are two major hurdles that need to be resolved for the detection of whole microorganism using LFSA. Fitst, the size of microorganism is around 1 micron which is far bigger than conventional protein-based biomarkers such as hormons, toxins and antibodies. Therefore, a clever selection of membrane with optimum porosity in combination with appropriate surface modification to facilitate the migration of micron-sized microorganisms through the cellulose membrane is necessary. Second, the number of microorganisms that need to be monitored for the sake of food safety is typically under 10^3 CFU/ml or even lower for some cases. But the intensity of colors derived from the complexation of microrganisms and chromatic agent is not strong enouth for the sample containing pathogenic bacteria lower than 10^4 CFU/ml (Jung et al., 2005; Moongkarndi et al., 2011; Pengsuk et al., 2013; Yonekita et al., 2013). For example, the LOD of AuNPs-based WCLFSA developed by Pengsuk et al. (2013) and Preechakasedkit et al. (2012) was in the range of $10^4 \sim 10^5$ CFU/ml for *Vibrio cholerae* O139 in seafood and *Salmonella Typhi* in human serum, respectively. Given that pathogenic bacteria can grow rapidly to the level that causes food poisoning by temperature abuse, the detection limit of any diagnosis system including WCLFSA should at least be as low as 10^3 CFU/ml. Therefore, a great deal of efforts have been placed on improving the sensitivity of WCLFSA by elaborately tailoring the chromatic agents or by employing signal amplification strategies using appropriate enzymes. A representative chromatic agents together with additional signal enhancing strategies to improve the detection power of WCLFSA were described in following section.

3.1. AuNPs-based WCLFSA and signal enhancement

Recently, Zhang et al. (2015a) and Cui et al. (2015) evaluated the effect of surface morphology and sizes of AuNPs on the sensitivity of LFSA for bacterial diagnosis. In an effort to enhance the chromatic signal of AuNP by modulating the surface morphology, Zhang et al. (2015a) synthesized flowerlike and popcornlike AuNP with average diameter of 40 nm by reprecipitation of Au on the surface of AuNP seed (20 nm). Due to the enhancement in localized electromagnetic field from the tipped structure of AuNPs, the flowerlike AuNPs exhibited higher optical intensity comparing to the spherical AuNPs of the same size. They highlighted that the molar ratio between Au seeds and $AuCl_4^-$ is an important factor influencing the morphology of AuNPs. The flowerlike AuNPs exhibited 100-fold increase in the sensitivity of WCLFSA with LOD of 10^3 CFU/ml for the detection of *E. coli* O157:H7, comparing to that of popcornlike and

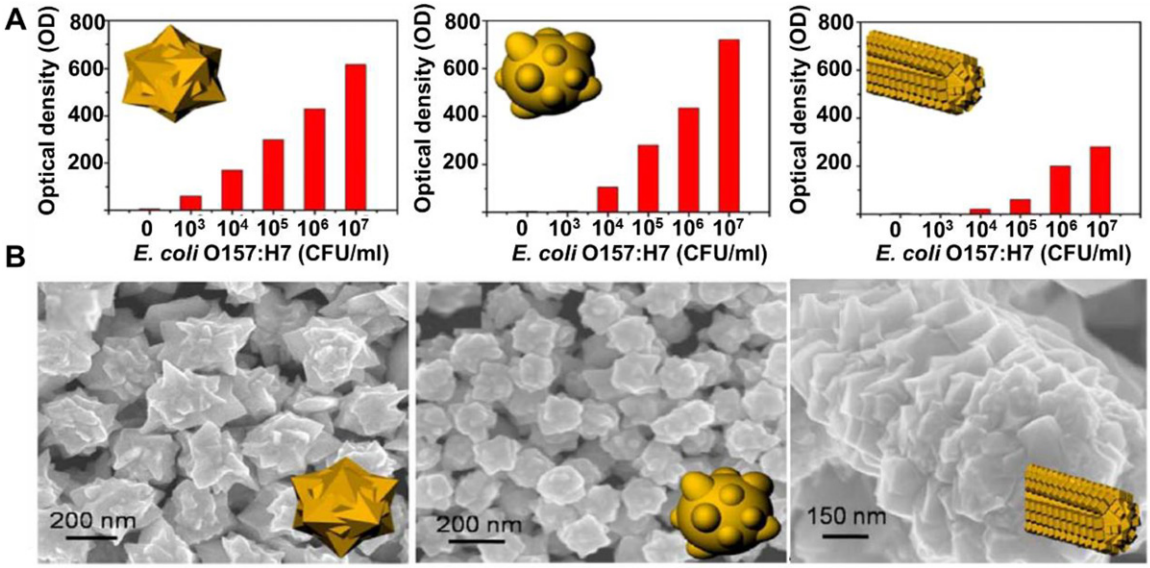

Figure 4. WCLFSA for the detection of *E. coli* O157:H7 using AuNP probes with varying sizes and shapes. (A) The morphological effect of of AuNPs on the detection limit of LFSA. (B) SEM image of AuNPs with different surface morphologies (Zhang et al., 2015a).

spherical AuNPs (Fig. 4). Their works demonstrated the importance of surface morphology of AuNPs in sensitivity of LFSA. On the other hand, AuNPs with a diameter from 20 to 54 were investigated in order to evaluate the size effect of the AuNPs on the sensitivity of WCLFSA (Cui et al., 2015). From their study, the AuNPs with diameter of 35 nm conferred the greatest sensitivity on LFSA for the detection of *E. coli* O157:H7. In addition, Chen et al. (2015a) reported a signal enhancement by coupling AuNPs with different diameters. In their work, AuNPs with a diameter from 18 nm to 80 nm were used to evaluate the efficacy of the each combination in bacterial detection. The first AuNP was designed to capture target bacteria, *E. coli* O157:H7, by antigen-antibody binding, followed by immobilization on the test zone of nitrocellulose membrane through capillary flow. The first AuNP was then decorated with a secondary AuNPs which resulted in a significant enhancement of the color intensity, thereby improving the sensitivity of WCLFSA. They reported that the use of the dual AuNPs that combined 28 nm and 45 nm of AuNPs resulted in 100-fold improvement in detection sensititvity of this immunoassay comparing to single AuNPs-based one. This dual AuNPs-based WCLFSA successfully detected *E. coli* O157:H7 as low as 1.14×10^3 CFU/ml.

Wang et al. (2015) have also demonstrated a signal enhancement in WCLFSA by enlarging the primary AuNPs that were bound to target bacteria on nitrocellulose membrane by reprecipitation method. The target bacteria and bound AuNPs to the surface of bacteria were captured on the test zone of nitrocellulose membrane by capillary flow and antigen antibody interaction. By reacting with $HAuCl_4$ and $NH_2OH{\cdot}HCl$, the size of the primary AuNPs on the membrane increased from 30 nm to 120 nm via reprecipitation of Au^0 on the surface of primary AuNPs, which intensified the color of AuNPs from red to dark purple. They demonstrated that 5×10^3 CFU/ml of *E. coli* O157:H7 was successfully detected by 5 min signal enhancement, in which the LOD was enhance 8-fold comparing to that without the enhancement. In addition, there have also been an effort to develop the alternatives of antibodies for the recognition and binding to the target bacteria. Kong et al. (2017) employed CBD from phage as a recognition element that is specific to *B. cereus*. They demonstrate that CBD-conjugated AuNPs yielded a stronger detection signal when comparing to that of AuNPs conjugated with the commercial antibody. Using this engineered CBD, the strip sensor achieved high specificity and sensitivity to detect *B. cereus* as low as 1×10^4 CFU/mL within 20 min.

3.2. FNPs-based WCLFSA

FNPs, such as QDs and UCPs, are also increasingly considered as an alternative to AuNPs due to their unique photoluminescence properties. These properties could improve the detection sensitivity of LFSA by increasing the signal-to-noise ratio of FNPs, and also suitable for multiple assays by simultaneous use of multiple FNPs with varying emissions spectra. The surface of these particles is generally coated with silica or polymers in order to provide a long-term colloidal stability in solution (Panagiotopoulou et al., 2016; Que et al., 2017; Sun et al., 2016). Recently, it has been reported that LFSA integrated with these two FNPs exhibited better sensitivity in bacterial detection comparing to conventional AuNPs-based LFSAs (Bruno, 2014; Chen et al., 2014; Hao et al., 2017; Niedbala et al., 2001; Zhao et al., 2016). For example, Zhao et al. (2016) developed a UCPs-based WCLFSA biosensor, in which UCPs (NaYF4:Yb3+, Er3+) with excitation and emission spectrum of 980 nm and 541.5 nm, respectively, and of approximately 50 nm in diameter were employed to detect *Vibrio cholerae*. Upon pre-incubation, they successfully detected *V. cholerae* O1 and O139 with LOD of 1×10^1 CFU/ml. A similar approach was also reported by Hao et al. (2017), who developed a 10-channel UCPs-based WCLFSA for multiplex detection of 10

foodborne pathogens with LOD of 10^4 to 10^5 CFU/ml within 20 min. This UCPs-based WCLFSA exhibited high tolerance to 279 real food samples, and the assay results were highly consistent with culture-based methods. When selecting or designing a nanoparticle probes, the size should be taken into account since bigger probes would produce lower signals due to the decrease in the number of probes binding to target bacteria. In this regard, QD probes may present better results with its small size (5–20 nm), comparing to UCP probes with its typical diameter of 25-200 nm (Liang et al., 2017). Fluorescent carbon nanoparticles whose diameter is below 20 nm have been of great deal of interests to researchers due to their excellent photoluminescence properties (Bruno, 2014; Hu et al., 2017; Morales-Narváez et al., 2015). With all these advantages, QDs-based LFSA may offer higher specificity and sensitivity in bacterial detection. On the other hand, the requirement of the portable detector equipped with light source and detector to read the signal is one drawback of QDs-based LFSA. However, this problem can be resolved by coupling this system with smartphone whose optical and image analysis functions could be utilized for the quantitative detection of target bacteria.

3.3. Enhancement of detection limit through IMS

Food is highly complex matrices composed of polysaccharides, protein, fat and many other ingredients in varying physicochemical forms, which makes it difficult to isolate target pathogenic bacteria from the complicated food matrices. The components in food matrices also severely interfere with the most detection reactions, thus lowering the sensitivity of sensing systems including WCLFSA. Therefore, effective isolation or separation of target bacteria from the food matrices, typically in large volume, is critical to enhancing the detection power of any sensing systems.

Immunomagnetic separation (IMS) is one of the most effective strategies capable of separating and concentrating the bacteria or viruses of interest from samples including food, water and medical specimen. The detection limit of WCLFSA can be significantly improved by employing these techniques in advance to applying the sample to the detection system (Alhogail et al., 2016; Liu et al., 2015; Shi et al., 2015; Suaifan et al., 2017a, b). For example, Qi et al. (2011) improved the detection sensitivity of WCLFSA system for *E. coli* O157:H7 down to 10^3 CFU/ml by employing IMS technique. They stated that the increased detection sensitivity by 100-fold was resulted from the preconcentration process by IMS. However, one drawback of this system is that the bacteria bound to the immunomagnetic particles (IMPs) during IMS step should be eluted before applying to WCLFSA. Otherwise, the large IMP-bacteria complex would not migrate through the nitrocellulose test strip. To resolve this problem, Liu et al. (2015) employed a small IMP (~140 nm) for both IMS and colorimetric detection as a chromatic agent. The target bacteria captured by the IMP were separated by magnet and directly applied on WCLFSA, and the target bacteria immobilized on test line were visualized by naked eyes by the brown IMP that complexed with the target bacteria. The detection limit of this system was rather poor, but by performing pre-incubation for 3 h, they were able to detect *Vibrio parahaemolyticus* in shrimp sample with a detection limit of 1.58×10^2 CFU/ml. There has been an effort to enhance the chromatic characteristics of the IMPs by coating gold layer on the surface of IMPs in core shell structure (Xia et al., 2016). The bifunctional nanobeads can be utilized as an IMP as well as chromatic agent. The gold surface made the bio-conjugation easy, and also enhanced the dispersibility of the colloid in aqueous solution. They utilized this bifunctional nanobeads for WCLFSA and were able to detect *Salmonella choleraesuis* with a LOD of 5×10^5 CFU/ml. The sensitivity of WCLFSA was further improved by employing magnetometer that quantifies the amount of IMPs immobilized to the target bacteria on test line (Shi et al., 2015). By establishing the correlation between the amplitude of magnetic signal from immunocomplex and the number of target bacteria associated with the IMP, they were able to detect *L. monocytogenes* with LOD of 10^4 CFU/ml.

3.4. Signal amplification using HRP

HRP is an enzyme that can convert chromogenic substrates, such as TMB and DAB, into colored products by catalyzing the redox reaction. HRP has been widely used in various research fields, such as ELISA and immunohistochemistry, to detect a trace amount of the specific target analytes such as proteins and cells. Recently, HRP has also been used for the signal amplification in WCLFSA to improve the sensitivity in bacterial detections (Cho et al., 2015; Park et al., 2010; Ren et al., 2016). In the work of Cho et al. (2015), AuNPs coupled with antibody and HRP were used to label *E. coli* O157:H7, followed by sandwich-detection in WCLFSA. To amplify the intensity of signal, TMB was introduced to the capturing pad by cross-flow from the substrate supply pad placed next to the capturing pad (Fig. 5). Enzymatic amplification of the color intensity enabled the detection of *E. coli* O157:H7 by naked eyes as low as 1×10^3 CFU/ml. The detection limit of WCLFSA was further improved by combining the enzymatic amplification with IMPs (Cho and Irudayaraj, 2013a). The IMPs were functionalized with HRP-antibody through EDC/NHS (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide) chemistry for the detection of *L. monocytogenes*. The target bacteria were first concentrated and separated from the raw sample using HRP-antibody-IMPs complex via a magnetic field. Upon application of the sample to the strip, the captured target bacteria on HRP-antibody-IMPs were collected on test line by the immobilized antibody that is specific to *L. monocytogenes* on strip membrane. The HRP conjugated to the IMPs together with captured bacteria catalyzed the oxidation of TMB, leading to a rapid color development. Their HRP-based LFSA system exhibited a successful chromatographic analysis with LOD of 10^2 CFU/ml regardless of sample type within 2 h. It is also important to note that the HRP and its chromatic substrates is stable in dry state on the membrane and they are fully functional after rehydration.

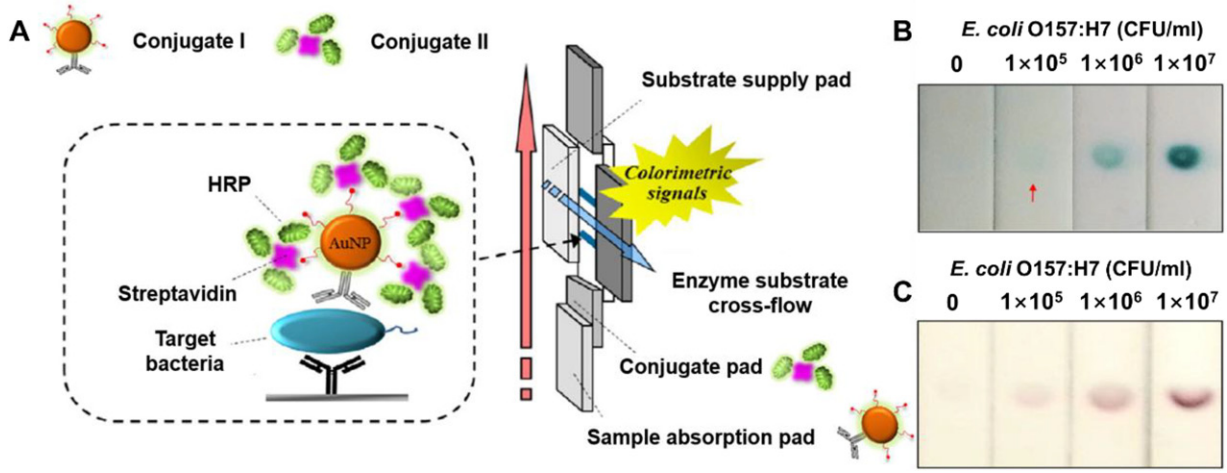

Figure 5. WCLFSA for the detection of *E. coli* using HRP-conjugated AuNPs. (A) Conceptual illustration of HRP-mediated signal enhancement and the layout of analytical elements for bacterial detection (B) detection strip after HRP-mediated signal enhacement. (C) detection strip without signal enhacement. The detection limit was improved by three-order of magnitude through HRP-mediated signal enhancement (Cho et al., 2015).

Ramachandran et al. (2014) suggested a strategy for long-term dry storage of antibody-HRP conjugates as well as its chromogenic substrate DAB. In their storage study, the antibody-conjugated HRP was mixed with 0.01 M Fe^{2+}-EDTA, while the DAB was suspended in water containing 2 mg/ml of 4% trehalose. The antibody-HRP conjugate and the DAB retained the enzyme activity and chromogenic functionality, respectively, after storage under vacuum condition at 22 °C and 45 °C for over 5 months.

4. Multiplex detection of pathogenic bacteria through integration of digital reader with LFSA

4.1. Multiplex detection of pathogenic bacteria

In addition to improving the sensitivity of LFSA, development of LFSA system capable of multiple detection is another challenging task that should be resolved for the realization of true POCT. In an effort to achieve this, Carter and Cary (2007) developed a lateral flow microarray (LFM) biosensor in which the capture probes were immobilized on test zone in array form (5×5) for the detection of target genes of *Bacillus anthracis* through hybridization-mediated capture. Their LFM system could also offer a means of semi-quantitative assay by employing five reference spots that react with known amount of detection probes. The limitation of this system is the requirement of lengthy sample preparation step to amplify target genes using nucleic acid sequence-based amplification before LFM analysis. However, the time required for pre-enrichment of target gene is getting shorter and shorter thanks to the advancement in nucleic acid-based amplification strategies, which would elevate the practical value of the LFM system in near future. The LFSA system coupled with array of capture probes would also provide a useful means for multiplex detection of major pathogenic bacteria. Song et al. (2016a) developed a multiplex LFSA by abovementioned concept to simultaneously detect two different pathogenic bacteria, *Shigella boydii* and *E. coli* O157:H7, with a detection limit of 10^6 CFU/ml for both pathogens (Fig. 6A). The detection limit of the system could be improved by two orders of magnitude (10^4 CFU/ml) after 8 h pre-incubation of the bacteria. In addition, a disc-shape plate equipped with 10 lateral flow strips in radial form was developed for multiple diagnosis of *Yersinia pestis* infection by Hong et al. (2010). As the sample-adding window located at the center of disc cartridge is connected to 10 strip-holding channels, a drop of sample solution applied to the window flows simultaneously to 10 strip sensors, which makes multiplex detection of 10 analytes possible (Fig. 6B). Nine intrinsic proteins of *Y. pestis* were employed as capture probes and immobilized on test zone of each strip, and the presence of corresponding antibodies in patient serum was successfully analyzed. The number of strips in disc cartridge would be equal to the degree of detection spectra, especially in multiplex assay, meaning that higher degree of multiplex assay could be achieved by integrating as many strips as possible. However, there exist many factors that could affect the effectiveness or accuracy of the multiplex LFSA assay, which would include the sample volume, flow rate, size of strip, flow distribution of sample solution to every strip and so on. Li et al. (2011) attempted to optimize LFSA strip in order to obtain the best results for multiple assay of target bacteria. In their work, the fan-shape LFSA system that assembled 3 strips with an average angle of 120 degrees was found to exhibit best performance (Fig. 6C). On the other hand, there has been a number of efforts to design multiple detection system in one paper form instead of attaching multiple strip sensors in one cartridge. In this regards, the use of wax could be an ideal strategy to create the multichannel LFSA due to its excellent hydrophobic properties (Renault et al., 2014). Its potential in the multichannel LFSA have been proposed by Li et al. (2011) and (Park et al., 2016). A sophisticated channel structures can be generated by printing hydrophobic wax materials to the paper or membrane, so that the flow of sample liquid can easily be guided as needed. This strategy could provide a powerful means to design a paper based multiple detection system in small size. Multiplex detection system could also take advantage of various chromogenic agents that could label different target analytes with different colors

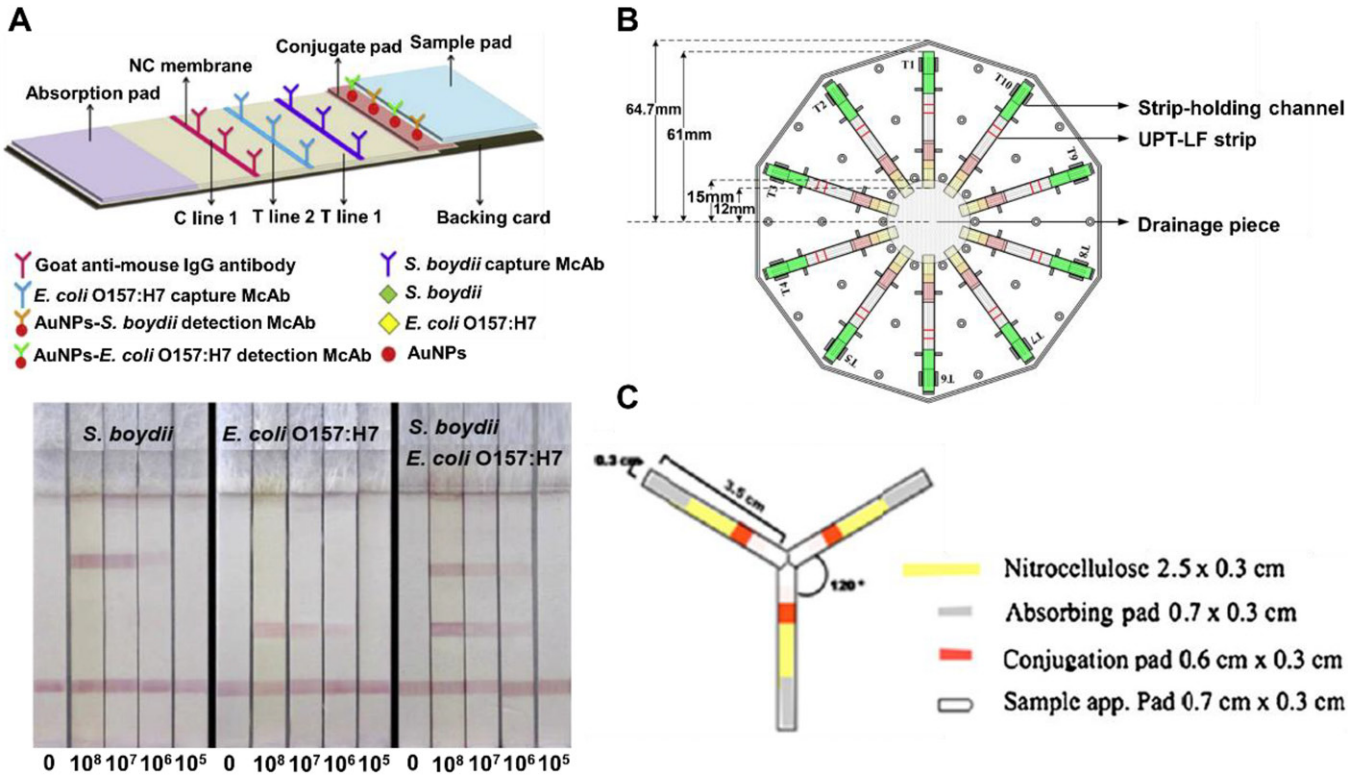

Figure 6. Multichannel LFSA for simultaneous detection of multple bacteria. (A) The layout of analytical components on strip membrane and detection strips showing simultaneous detection of two different bacteria, *S. boydii* and *E. coli* O157:H7 (Song et al., 2016). (B) 10 strips-multichannel LFSA with nine intrinsic proteins of *Y. pestis* for the diagnosis of *Y. pestis* infection using human serum (Hong et al., 2010). (C) 3 channel-WCLFSA for multiple detection of three different bacteria (Li et al., 2011).

or optical spectra. Shen et al. (2013a) and Zhao et al. (2016) utilized FNPs, such as UCPs and QDs with different diameter, and successfully demonstrated their ability for multiple assay due to their size-dependent photoluminescence properties.

4.2. Integration of digital reader with LFSA

Nowadays, many parts of currently produced smartphone, such as LED, powerful CPU, optical filters and high-resolution camera have become a promising tool to read and translate the colorimetric, chemiluminometric, or fluorometric signals produced from the sensing system. It has been demonstrated that LFSA combined with smartphone exhibited increased detection sensitivity using its user-friendly apps capable of reading fluorescent intensity of NP probes (Mudanyali et al., 2012; Shafiee et al., 2015; Zhu et al., 2012). To detect *E. coli*, Shafiee et al. (2015) created a customized imaging analysis application capable of analyzing the difference in red and blue pixel values using a customized MATLAB code (Fig. 7A). There were two sample application spots on cellulose paper, which were control zone and bacterial sample zone for reference AuNPs solution and bacterial sample with AuNPs, respectively. Well dispersed AuNPs solution exhibited bright red color, but the color turned to blue when target bacteria were present in sample because of the aggregation of AuNPs together with target bacteria. The antibodies conjugated on the surface of AuNPs was responsible for the aggregation with target bacteria, and the target bacteria were determined by the type of antibodies. The difference in color between control zone and sample zone represented the presence of target bacteria in sample, which can be analyzed by using the APPs installed in smartphones such as iPhone, Samsung Galaxy and HTC Vivid. The lateral flow detection system integrated with smartphone successfully detected target bacteria with LOD of 8 CFU/ml. Zhu et al. (2012) also reported a QD based sandwich immunoassay for specific detection of *E. coli* O157:H7 in liquid samples using a cell phone (Fig. 7B). The surface of glass capillary array was functionalized with anti-*E. coli* O157:H7 antibody to capture *E. coli* O157:H7 that was labeled with QDs conjugated with the same antibody. The LED in cell phone was used to excite the labelled QD followed by imaging the emission from the QD through filter lens and camera in cell phone. Their system exhibited an outstanding sensitivity to target bacteria, *E. coli* O157:H7, with a detection limit of ~5 to 10 CFU/ml in both PBS and fat-free milk. Along with the fast development of various functionality in smart phone, fluorescent NP-based (e.g. UCPs or QDs) LFSA could readily be applicable in POCT with a high sensitivity and specificity.

As wireless internet has spread over the world, real time monitoring of the status of food from farm to table can be realized by IoT combined with smartphone to prevent the introduction of contaminated food materials into the food supply chain. However, there remain many technical challenges that need to be overcome when the smartphone is to be implemented in biosensing applications. Seo et al. (2016) reported a sensing system with IoT for monitoring food

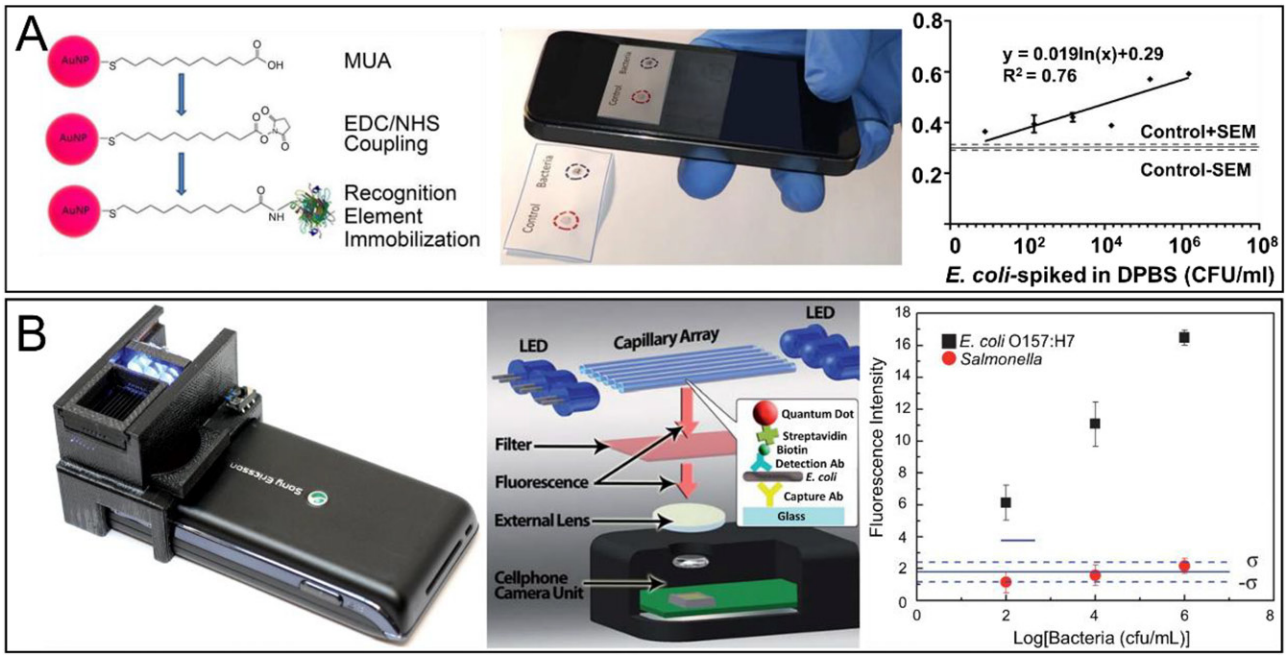

Figure 7. Paper-based immunoassay integrated with smartphone. (A) Cellulose paper-based immunoassay for the detection of *E. coli* by using image process functions of smartphone (Shafiee et al., 2015). (B) Immunodetection of *E. coli* O157:H7 using antibody functionalized glass cappilaries coupled with smartphone (Zhu et al., 2012).

contamination. The pocket-sized CMOS (complementary metal–oxide–semiconductor) image sensors coupled with a Wi-Fi module was used for identifying *Vibrio* species in real food samples with a LOD of 1.4×10^4 CFU/ml. The results of analysis could instantly be transmitted to a certified institution by using a smartphone app. Google once ran a modular smartphone project that any hardware modules, such as cameras, speakers, processors, displays and batteries, can be integrated into a common smartphone frame. The modular smartphone that can be upgraded or replaced with different modules any time would empower the LFSA based sensing system. The LFSA system developed in modular form would greatly expand the spectrum of target analytes that can be analyzed by the common smartphone base and could bring about the realization of real POCT system in near future.

5. Conclusions and future perspectives

LFSAs have been regarded as a promising tool that is capable of replacing the conventional methods for the detection of target analytes. However, there are several drawbacks with respect to the low sensitivity, low compatibility with complex food sample, and difficulties to build in multiple assay form, limiting their practical application in food industry. For example, conventional AuNPs-based LFSAs suffered from low sensitivity in bacterial diagnosis with a typical LOD of over 10^5 CFU/m. However, as shown in Table 2, the sensitivity of LFSA for bacterial diagnosis is improved through various signal amplification strategies including pre-concentration, enzymatic color enhancement, modification of size and shape of AuNPs, and utilization of other groups of chromatic agents (e.g. dye-loaded ILPs, (e.g. MNPs, UCPs, QDs, etc.) with outstanding color, magnetic or fluorescent properties. In addition, portable optical reader that can be realized by the optic and imaging parts of smart phone and appropriate software program could successfully be integrated with LFSA to enhance the analytical performance of bacteria-diagnostic LFSA, which would generate far greater sensitivity than conventional system. On the other hand, wax-printing methods provided an effective means to construct LFSA with multi-channel detection units, which allow simultaneous detection of multiple target bacteria. Combination of multiple optical reporters (e.g. UCPs and QDs) with different spectral characteristics could also provide means for multiple detection. Although current LFSA is facing a number of challenges that need to be resolved, it is still the most promising tools for future POCT system with its indispensable nature, which is simple, portable, user-friendly and cost-effective. For the realization of practical LFSA for bacterial detection, the detection limit should ideally go down to a single cell level since certain pathogenic bacteria could cause illness with few cells. The long-term stability of antibodies conjugated with various chromogenic agents in dry form should also be ensured for commercialization of LFSA biosensors. It is also important to develop a simple and effective sample preparation unit, which is fully compatible with the complicated food matrix, particularly solid food. In an age that we experience a fast-technological evolution, portable personal electronic devices, like smartphone or new google glasses, are expected to provide a powerful means to advance the performance of LFSA in near future.

Abbreviations

AuNPs	gold nanoparticles
CBD	cell wall binding domains
DAB	3,3'-Diaminobenzidine
ELISA	enzyme-linked immunosorbent assay

FNPs	fluorescent nanoparticless
HRP	horseradish peroxidase
IMNPs	immuno-magnetic nanoparticles
IMS	immunomagnetic separation
LAMP	loop mediated isothermal amplification
LFM	lateral flow microarray
LFSA	lateral flow strip assay
LOD	limit of detection
MB	methylene blue
MNPs	magnetic nanoparticles
NALFSA	nucleic acid-based lateral flow strip assay
NPs	nanoparticles
PCR	polymerase chain reaction
POCT	point of care testing
QDs	quantum dots
TMB	3, 3′, 5, 5′,-tetramethylbenzidine
UCPs	up-converting phosphors
WCLFSA	whole cell-based lateral flow strip assay

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Conflict of interest:

The authors declare that they have no conflict of interest.

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