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REVIEW

Biosensors, modern technology for the detection of cancer-associated bacteria

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Abstract Cancer is undoubtedly one of the major human challenges worldwide. A number of pathogenic bacteria are deemed to be potentially associated with the disease. Accordingly, accurate and specific identification of cancer-associated bacteria can play an important role in cancer control and prevention. A variety of conventional methods such as culture, serology, and molecular-based methods as well as PCR and real-time PCR have been adopted to identify bacteria. However, supply costs, machinery fees, training expenses, consuming time, and the need for advanced equipment are the main problems with the old methods. As a result, advanced and modern techniques are being developed to overcome the disadvantages of conventional methods. Biosensor technology is one of the innovative methods that has been the focus of researchers due to its numerous advantages. The main purpose of this study is to provide an overview of the latest developed biosensors for recognizing the paramount cancer-associated bacteria.

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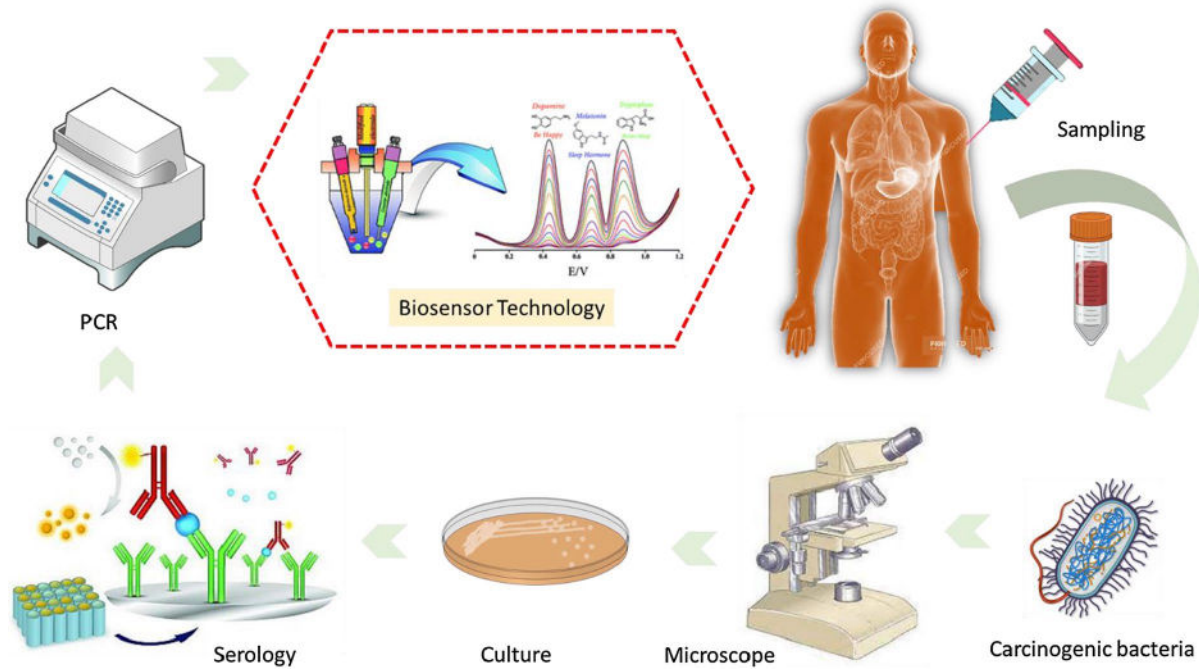
Graphical abstract



Keywords Cancer-associated bacteria · Biosensors · Nanomaterial · Food control

Introduction

The connection between cancer and bacteria was first reported in 1890 by a Scottish pathologist (Russell 1890). Years later, in 1926, Thomas Glover described that a specific bacterium could be isolated from human and animal neoplasmic tissues (Al-Hilu and Al-Shujairi 2020; Khan and Shrivastava 2010). Nowadays, the carcinogenicity of some bacteria is so well known that their accurate diagnosis and treatment is deemed to play a key role in cancer control and prevention. *Salmonella typhi*, *Listeria monocytogenes*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Mycoplasma*, and *Heamophilus influenza* are the most common pathogens associated with different types of cancer in humans (Caygill et al. 1994; Rogers 2011). Bacteria may contribute to the progress of cancer through metabolites, inflammation, stimulation of DNA damage by toxins, and/or manipulation of host cell signaling pathways throughout their infection cycle (Chumduri et al. 2016). From ancient times to the present day, several methods have been employed to identify bacteria. Culture and serology are known as the oldest diagnostic methods in bacteriology and they still have wide applicability today. The uncultivable aspect of some bacteria as well as false-positive and false-negative results are important disadvantages of such conventional methods (Bonner 2017). After the invention of PCR by Kary Mullis and the development of molecular-based methods, the problems associated with older methods were largely overcome, although supply costs, machinery fees, training expenses, and the need for advanced equipment challenged the use of these methods (Crosby 2016). In recent years, various methods have been developed to overcome the shortcomings in bacterial diagnostic methods. Biosensors as nanomaterial-based methods have significantly drawn the attention of researchers among these methods (Ashrafi et al. 2019). Simple and low-cost structure and high sensitivity and

specificity are the most important merits of biosensors that can make their development hugely influential in medical and laboratory sciences (Mobed et al. 2020a). The main focus of the present study is to review and introduce the latest biosensors developed in order to detect cancer-associated bacteria. The advantages and disadvantages of the old methods and the challenges associated with the expansion of biosensors are also discussed in this paper.

Cancer-associated bacteria and mechanism of action

Bacterial infectious diseases have traditionally not been considered the leading cause of cancer. However, recently, bacteria have been implicated in cancer through two mechanisms: the production of carcinogenic bacterial metabolites and the induction of chronic inflammation. In the following, some important cancer-related bacteria have been introduced and discussed. Mutagenic bacterial metabolites are also said to increase the risk of cancer. This model is best represented in colon cancer. Bile acid metabolites increase colon cell proliferation (Mosele et al. 2015). Exogenous compounds such as rutin can be metabolized to mutagens by the resident gut flora (Song and Chan 2019; Johnson et al. 1994). In addition, *bacteroides* species can produce fecapentaene, a powerful in vitro mutagen at relatively high concentrations (Mosele et al. 2015). However, in vivo data on human carcinogenesis by bacterial metabolites are unpredictable. Local bacterial infections can also affect nonnodular lymphoma, but the mechanism has not been identified (Johnson et al. 1994). Gastric lymphoma and small bowel immune-proliferative disorders are most strongly associated with the underlying bacterial infection. Bacterial infections can be treated with antibiotics, so identifying the bacterial cause of malignant tumors can have important implications for cancer prevention (Mosele et al. 2015).

Salmonella species are non-spore-forming, motile, and rod-shaped gram-negative bacteria of the *Enterobacteriaceae* family. *Salmonella* species are intracellular pathogens that commonly invade the gastrointestinal tract and cause salmonellosis (Chaudhuri et al. 2018; Meza n.d.). Patients diagnosed with severe salmonellosis face significantly higher risk of emerging cancer in some parts of the colon (Mughini-Gras et al. 2018). *Mycoplasma* is one of the smallest living organisms that can be isolated from environment and cultured in a special medium (Loo et al. 1991). Mycoplasmas spread extensively at mammalian cell membranes of numerous types. Mycoplasma is a restricted pathogenic organism considered to be related to many diseases such as prostate cancer (Rogers 2011; Loo et al. 1991; Cassell and Cole 1981). *Helicobacter pylori* is one of the gastric pathogens that has been identified in large populations worldwide. Infection with *H. pylori* causes chronic inflammation and considerably raises the risk of emergent gastric ulcer disease as well as gastric or duodenal cancer (Moss 2017; Cheung et al. 2018). *Listeria monocytogenes* is a ubiquitous, gram-positive bacterium and an intracellular pathogen acting as a causative organism in numerous outbreaks of foodborne diseases (Watson 2019). *Listeria* bacteremia and meningoencephalitis are the most common demonstrations of Listeriosis (LT) in patients with cancer (Rivero et al. 2003). *Mycobacterium tuberculosis* (MTb) is a fastidious bacterium and a human pathogen with huge global impact. *M. tuberculosis* can play an active role

Table 1 The most important cancer-related bacteria

Bacteria	Cancer	Detection methods and their limitations	References
Salmonella typhi	Melanoma, head, and neck or esophageal adenocarcinoma	Methods: Culture, serology, PCR, real-time PCR Limitations: Routine methods are difficult to perform, time consuming, requires advanced tools, requires professional personnel, and are costly despite acceptable sensitivity and specificity	Heimann and Rosenberg (2003); Miller et al. (2011); Cohen et al. (1996)
Haemophilus influenza	Lung		Zhu and Fang (2017)
Mycoplasma	Prostate, cervical		Miyake et al. (2019)
Helicobacter pylori	Gastrointestinal		Wen et al. (2017)
Listeria monocytogenes	Pleural mesothelioma		Hassan et al. (2019)
Mycobacterium tuberculosis	Lung		Çakar and Çiledağ (2018)

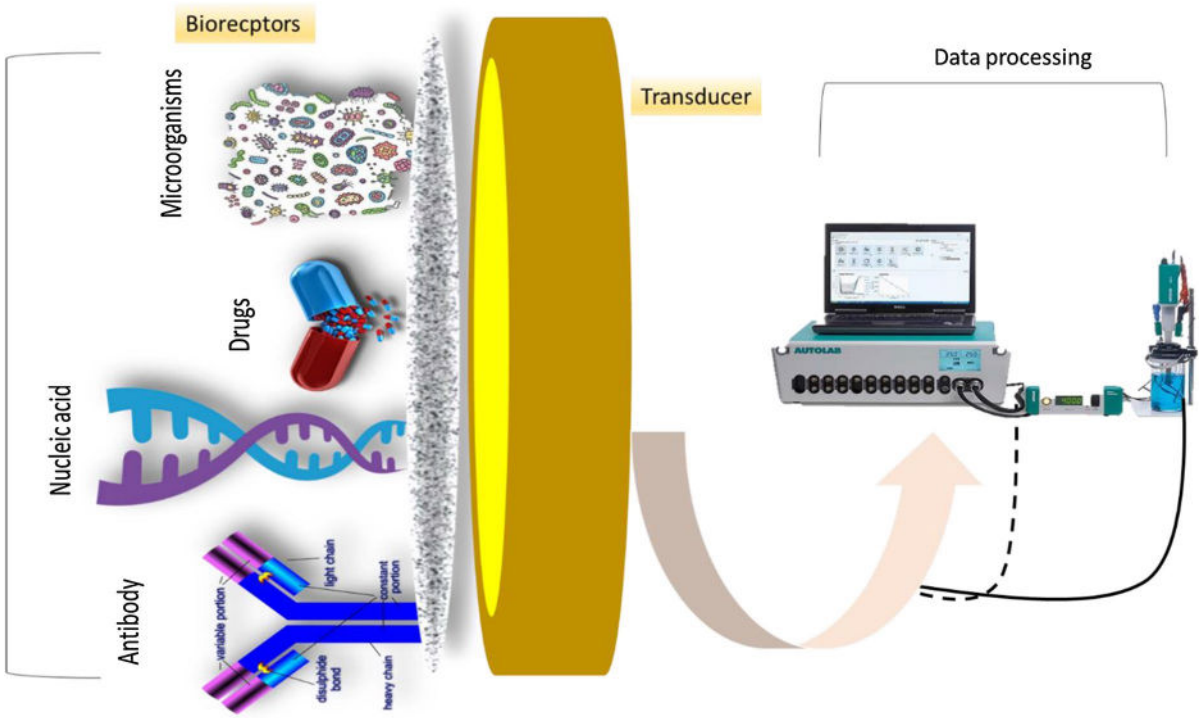


Fig. 1 Schematics of the structure of a biosensor (Mobed et al. 2020b)

in intracellular signaling and lung cancer (Molina-Romero et al. 2020) (Table 1).

Biosensors

In recent years, various methods have been developed to overcome the disadvantages of bacterial diagnostic methods. Biosensors as nanomaterial-based methods have been one of the most attractive options among these methods. Biosensors are strategies categorized as microsystem tools incorporating a bio-receptor on the biological side and a transducer on the physical side (Martins et al. 2019). In summary, when a target molecule interacts with the biological recognition element, the interaction produces a quantifiable signal that can be converted into data by the integrated transducer (Martins et al. 2019; Mobed et al. 2020b). The structure of a biosensor is schematically illustrated in Fig. 1.

Rapid, specific, and low-cost diagnosis is a major challenge in medical sciences including diagnostic, pharmaceutical, and drug delivery fields (Yao et al. 2014). Clinical observations and laboratory tests such as biochemical methods, ELISA, western blotting, imaging, and microscopic observations are among the most important and oldest medical diagnostic methods (Parsons et al. 2011). The invention of the polymerase chain reaction (PCR) by Karry Mollis in 1980 revolutionized diagnostic methods. The development of PCR-based methods largely resolved the problems faced by the traditional methods (Kaltenboeck and Wang 2005). For instance, the molecular-based methods such as real-time PCR in most cases exhibited good sensitivity and specificity.

The need for expensive and advanced equipment as well as experienced and professional personnel is also another fundamental challenge in the development of molecular based methods (Gabaldón 2019). Advances in nanobiotnology have led to the emergence of modern and innovative diagnostic methods. Biosensors are one of the most efficient nanomaterials-based detection methods that have experienced dramatic developments in the recent two decades (Yao et al. 2014). The greatest among such developments has been the detection of biomarkers associated

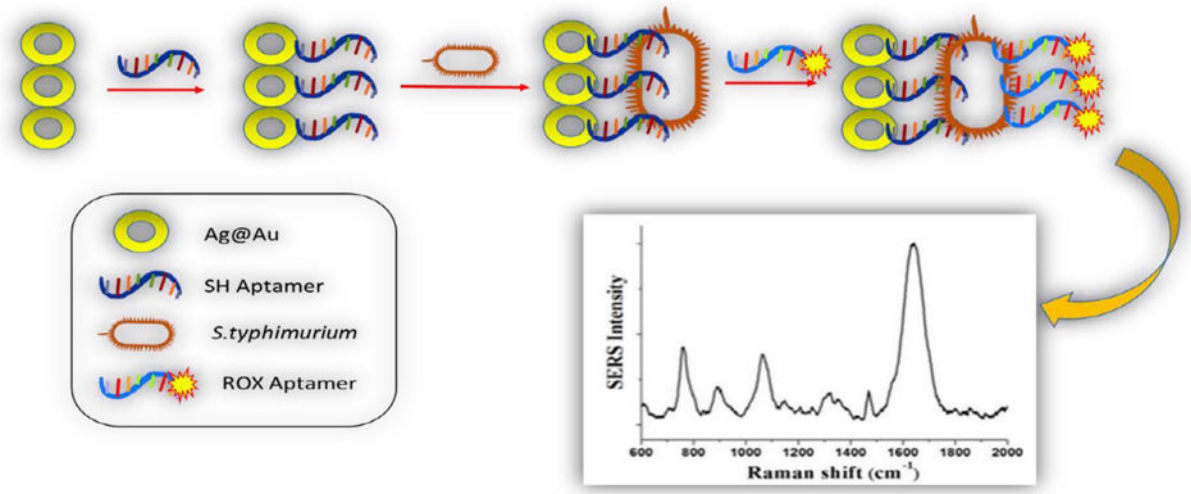


Fig. 2 Schematics of the SERS based aptasensor for the detection of *Salmonella typhi*, Reproduced from Ref. (Duan et al. 2016a)

with a variety of diseases, including cancer and infections. In this regard, the development of bacterial biosensors has been the subject of many studies so that to date, several biosensors have been developed in relation to almost all bacteria (Mahmoudpour et al. 2019). As a result, there are many research studies and reviews in this field. In this trend, the main purpose of the present study is to highlight and bridge a clear gap in the field of carcinogenic bacteria biosensors. According to studies, to date, only a very small number of biosensors have been specifically developed in connection with carcinogenic bacteria, while this group of pathogens is the main challenge in medical bacteriology. It may be claimed that the current review will be the only distinct study on carcinogenic bacteria biosensors. Also, in this study, the challenges arising from the existing gap and how to cover it will be deliberated and discussed.

Developed biosensors for carcinogenic bacteria detection and diagnosis

Surface-Enhanced Raman Spectroscopy (SERS) is deemed one of the most selective, reliable, and sensitive systems for non-invasive molecular analysis through the amplification of electromagnetic fields (Demirel et al. 2018). SERS-based aptasensor was designed for the identification of *Salmonella typhi*

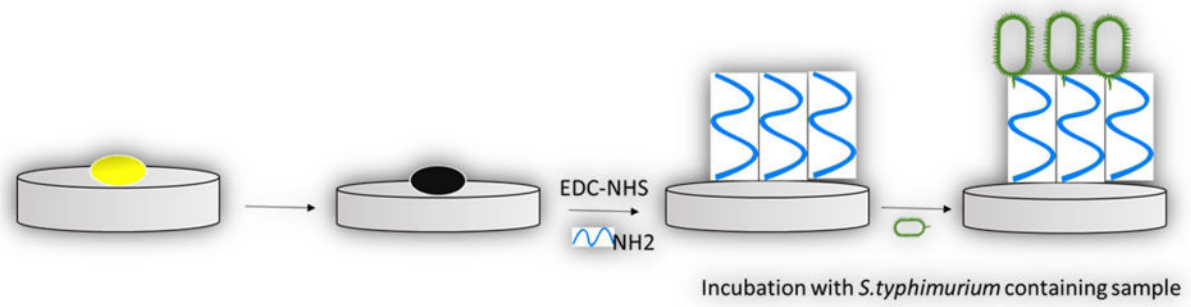


Fig. 3 Schematics of the label-free impedimetric biosensor for the detection of *Salmonella typhi*, Reproduced from Ref. (Sheikhzadeh et al. 2016)

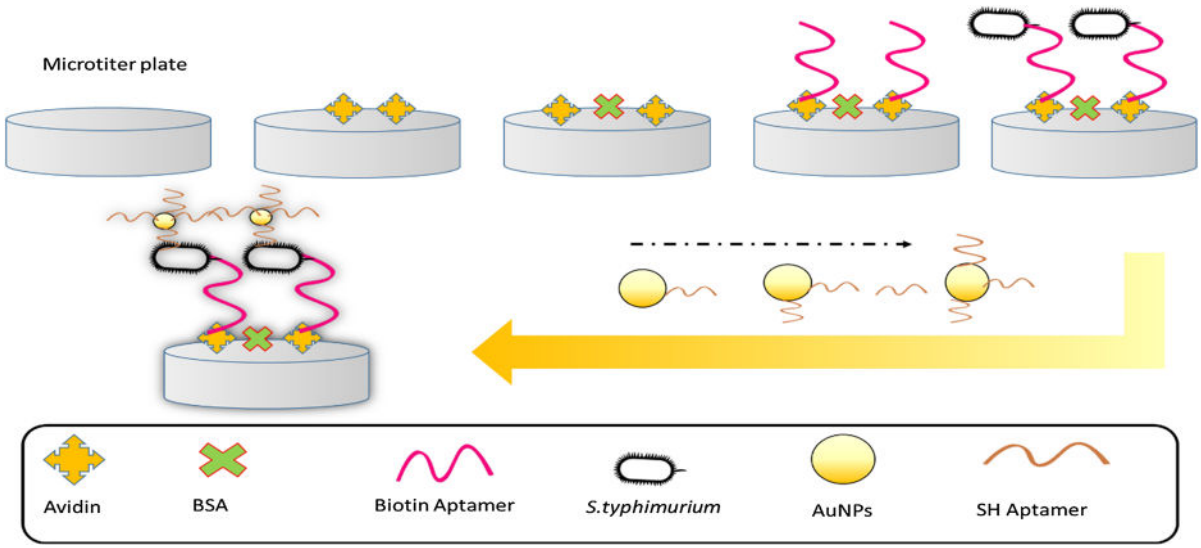


Fig. 4 Schematics of the aptasensor based biosensor for the detection of *Salmonella typhi*, Reproduced from Ref. (Yuan et al. 2014)

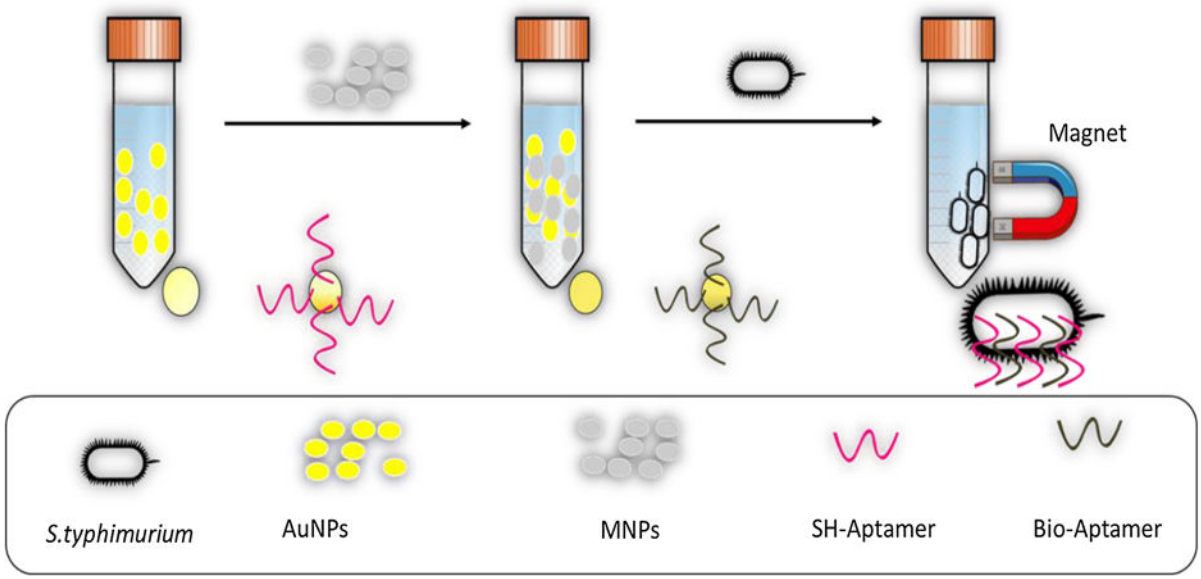


Fig. 5 Schematics of the colorimetric based aptasensor for the detection of *S. typhi*, Reproduced from Ref. (Duan et al. 2016b)

(Duan et al. 2016a). The developed system (Fig. 2) showed acceptable sensitivity and rapid operation in the detection of *Salmonella typhi* in food industries (Duan et al. 2016a).

Amongst biosensors, the label-free ones designed for the direct detection of the analyte have several advantages that seemingly will make them the most favorable strategy in the future (Malvano et al. 2020). Label-free impedimetric biosensors for the detection of *S. typhimurium* have proven successful. Pyrrole-co-3-carboxyl-pyrrole, due to its special electrical and chemical properties, has been employed for sensitive identification (Fig. 3) and it has shown applicability to food and conceivably other environmental samples (Sheikhzadeh et al. 2016).

Optical biosensors have several advantages over old analytical methods as they allow real-time, direct, and label-free detection of several chemical and biological substances. Their advantages consist of small size, cost effectiveness, and high sensitivity and specificity (Damborský et al. 2016). An optical-based recognition technique has been developed for rapid and specific detection of *S. typhimurium* based on aptamer. The system (Fig. 4) showed good sensitivity and specificity in optimal conditions and proved usable for different samples (Yuan et al. 2014).

Colorimetry is a remarkable procedure used for routine clinical and food sample analysis (Mondal et al. 2018). The colorimetric based method was established for rapid and simple detection of *Salmonella typhi.* The designed system (Fig. 5), along with a cost-effective structure, had worthy sensitivity and specificity (Duan et al. 2016b).

Nucleic-acid aptamers have engrossed researchers and found extensive use in a range of areas. They provide excellent modeling of practical molecules determined in vitro (Song et al. 2008). Aptamer-based fluorometric platform was invented for sensitive detection of the *S. typhi.* Conjugated Quantum Dots (QDs) with a specific DNA aptamer were used for optimal determination of the *S. typhi* (Ren et al. 2019). An electrochemical immunosensor was created for *S. typhimurium* recognition based on antigen–antibody complex formation. Monoclonal anti-*S. typhimurium* antibody was employed for sensitive and simple detection of *S. typhi* and it overcame problems associated with food health and safety (Fig. 6) (Salam and Tothill 2009).

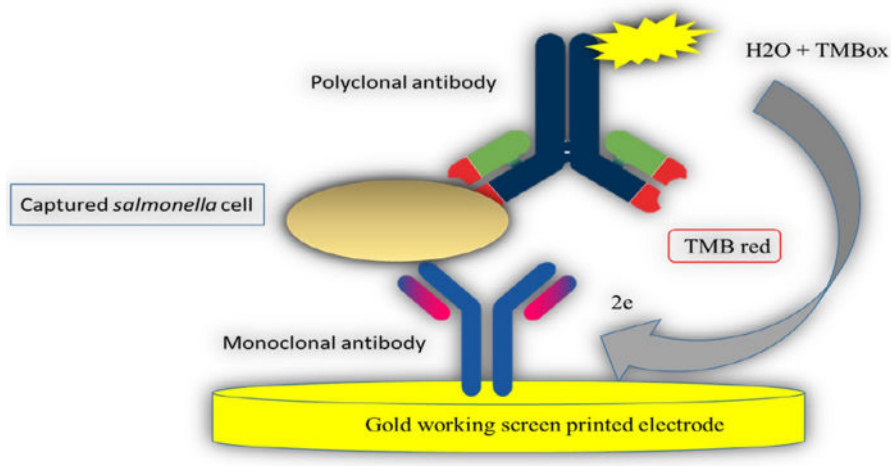


Fig. 6 Schematics of the electrochemical biosensor for the detection of *S. typhi*, Reproduced from Ref. (Salam and Tothill 2009)

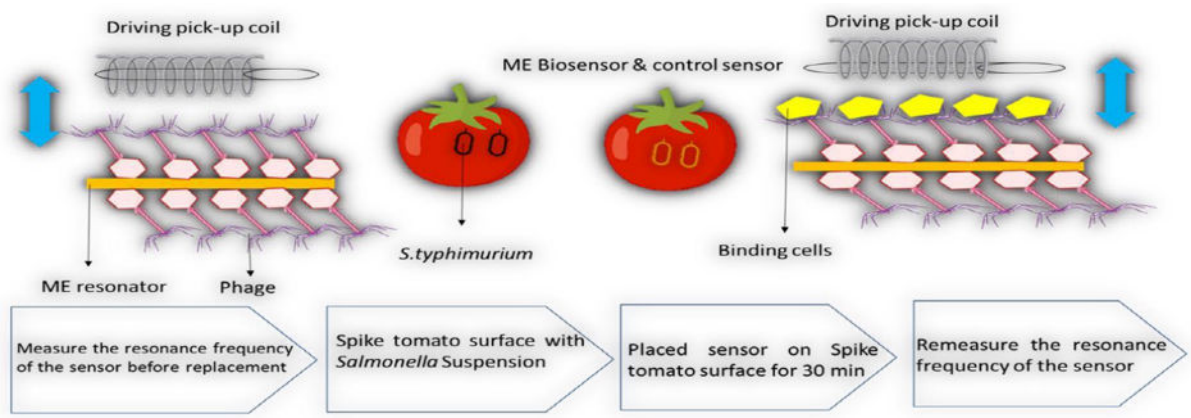


Fig. 7 Schematics of the phage-based biosensor for the detection of *S. typhi*, Reproduced from Ref. (Li et al. 2010)

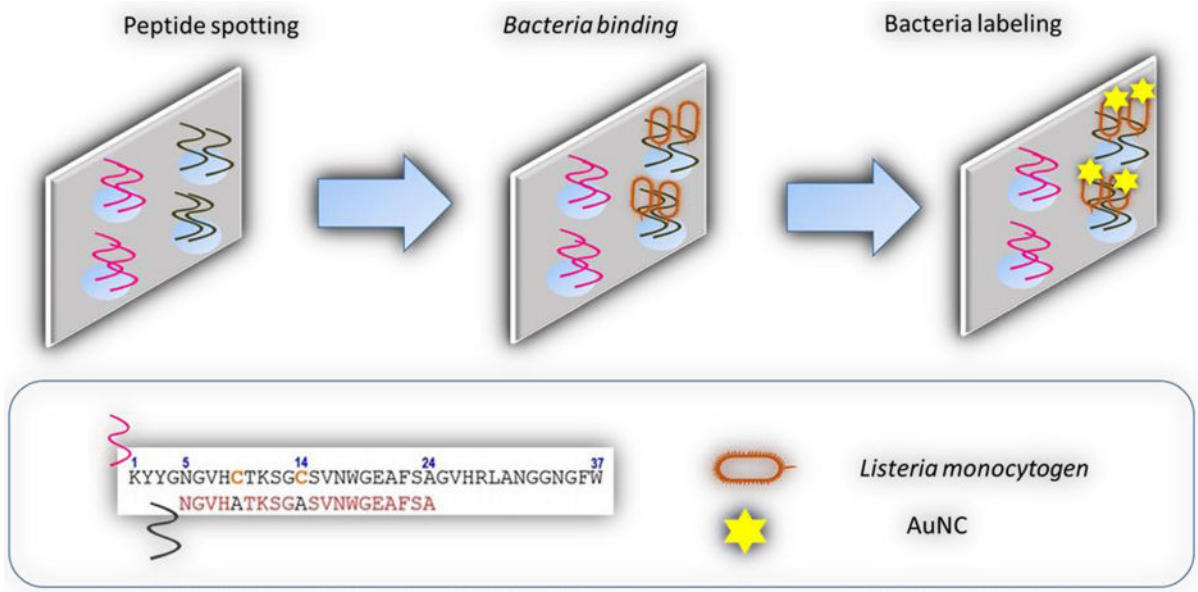


Fig. 8 Schematics of the peptide-based biosensor for the detection of *L. monocytogenes* Reproduced from Ref. (Hossein-Nejad-Ariani et al. 2018)

Bacteriophage-based biosensors have applicability to the direct analysis of pathogens in various media such as milk, fresh food, and water (Lakshmanan et al. 2007). The phage-based biosensor as a novel technology was developed for the direct detection of *S. typhi* in fresh food production. Filamentous E2 phage was employed for sensitive and specific determination of *S. typhi* without any pretreatment (Fig. 7) (Li et al. 2010).

A novel immunosensor is a type of biosensor that incorporates a biological recognition mechanism with a transducer and produces a quantifiable signal in response to alterations in the concentration of a given biomolecule (Mobed et al. 2019a, 2020c). An antibody–aptamer functionalized fiber optic sensing platform was developed for specific detection of *L. monocytogenes* in food products. The system exhibited acceptable sensitivity and range linearity in application to food industries (Ohk et al. 2010). A cost-effective biosensor was fabricated for rapid and sensitive detection of the *L. monocytogenes*. The immunosensor showed suitable LOD and commercial potential (Davis et al. 2013). Cell-based biosensor equipment based on the bioelectric recognition assay (BERA) was designed for robust detection of the *L. monocytogenes*. The developed biosensor identified *L. monocytogenes* without any cross-reaction, which is usual in conventional methods (Hadjilouka et al. 2020). A simple, inexpensive, and portable peptide-based biosensor was developed for the determination of the *L. monocytogenes.* The system (Fig. 8) showed acceptable sensitivity and it was applicable to food and pharmaceutical products (Hossein-Nejad-Ariani et al. 2018).

DNA biosensors based on nucleic acid have been established with the aim of simple, rapid, and low-price testing of infectious diseases, genetic observations, and the detection of interactions as well as DNA damage (Mobed et al. 2019b, 2019c). An electrochemical DNA biosensor was developed for the specific detection of the *L. monocytogenes.* The fabricated method was able to detect the PCR sample of *L. monocytogenes* hly gene sequence effectively (Fig. 9) (Niu et al. 2017).

Lateral Flow Biosensors (LFBs) have been used as commercial tools for simple, inexpensive, and rapid tests in real-time screening of drugs and infectious diseases. Lateral Flow Strip Biosensors (LFSBs) are the widely used type, in which the conjugate pad, sample pad, absorption pad, and nitrocellulose membrane are layered on a common sheet of plastic adhesive backing (Huang et al. 2019). An innovative

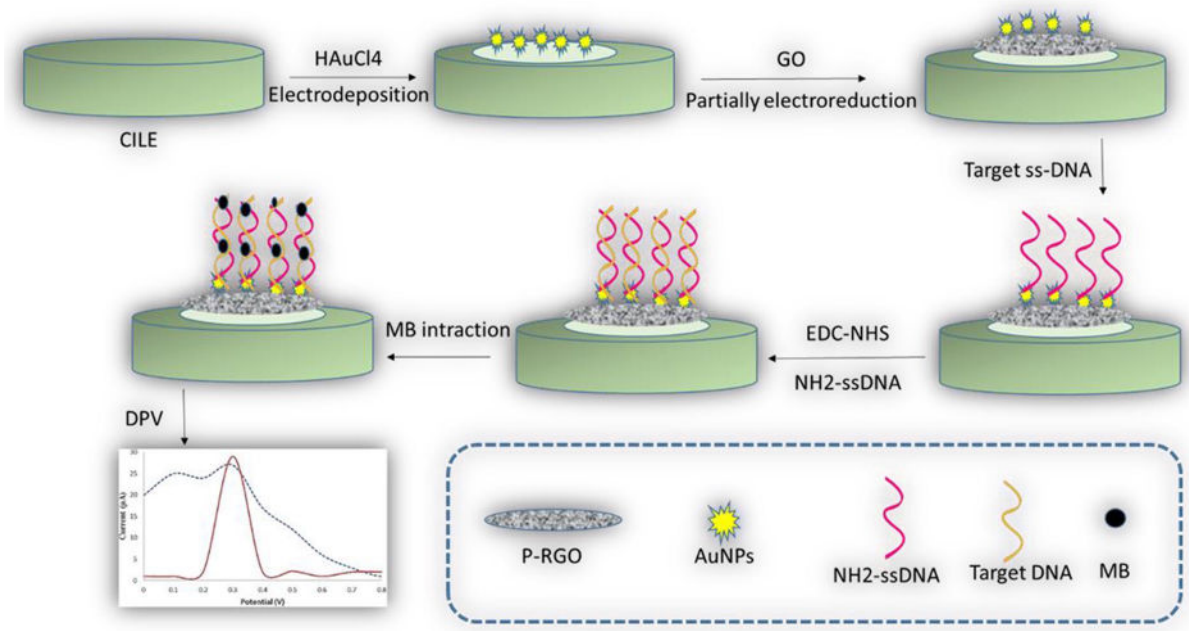


Fig. 9 Schematics of the peptide-based biosensor for the detection of *L. monocytogenes*, Reproduced from Ref. (Niu et al. 2017)

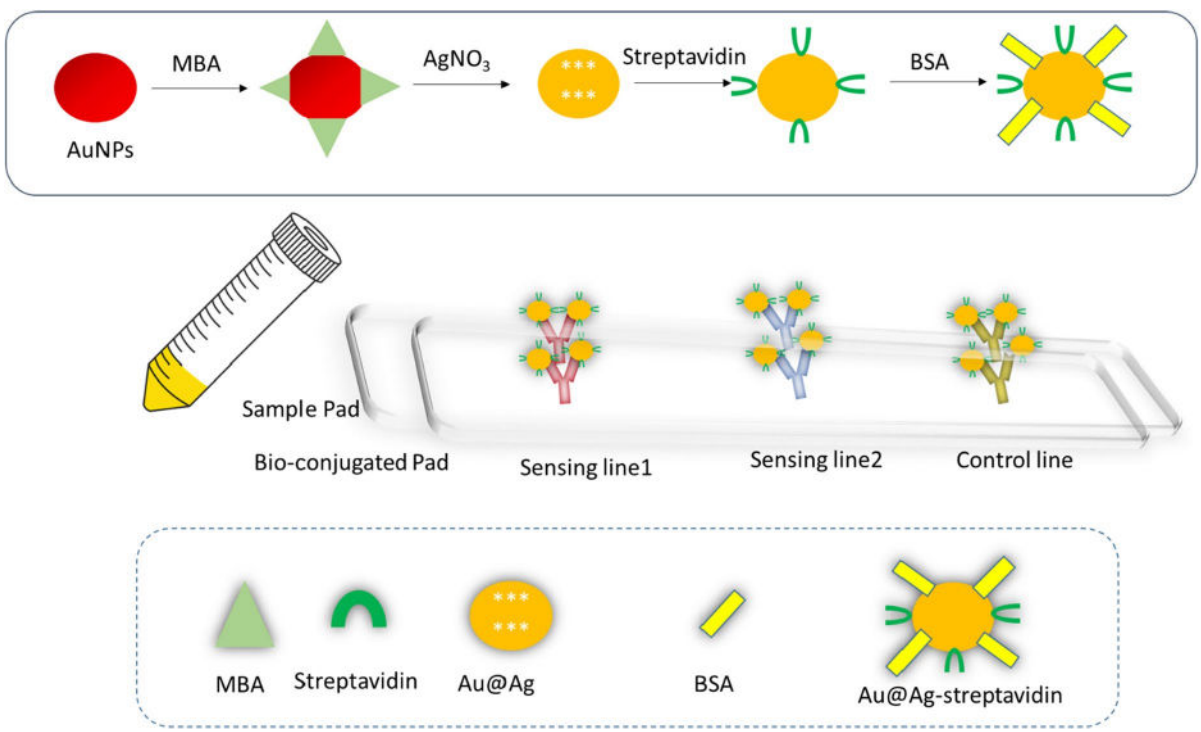


Fig. 10 Schematics of the SERS-based LF biosensor for the detection of *L. monocytogenes*, Reproduced from Ref. (Liu et al. 2017)

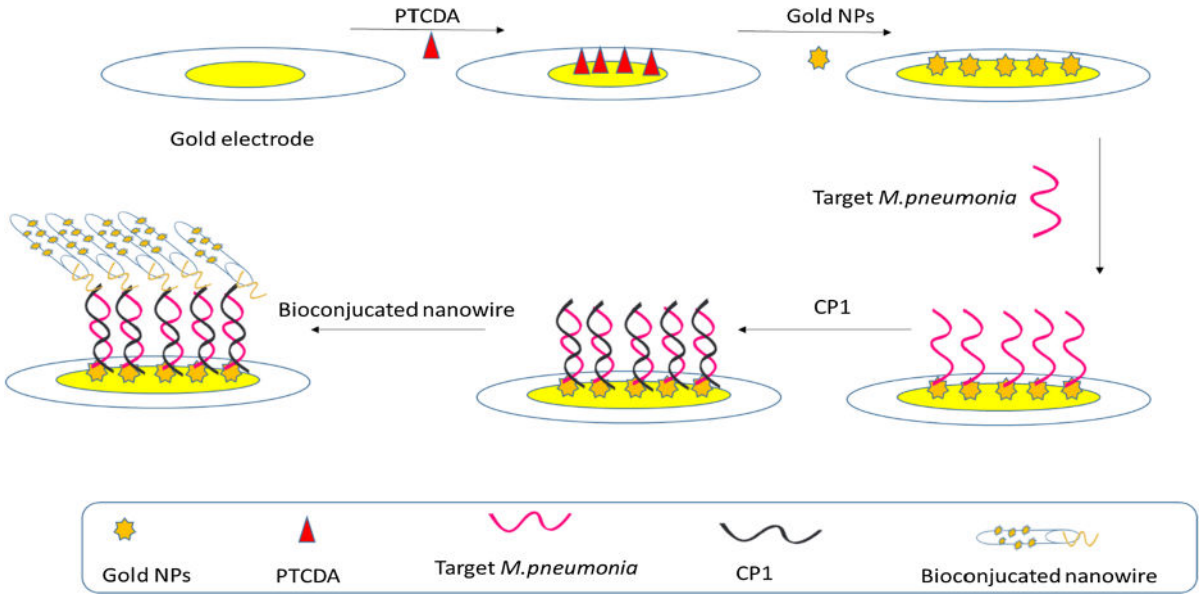


Fig. 11 Schematics of the SERS-Based LF biosensor for the detection of *Mycoplasma pneumonia*, Reproduced from Ref. (Liu et al. 2016)

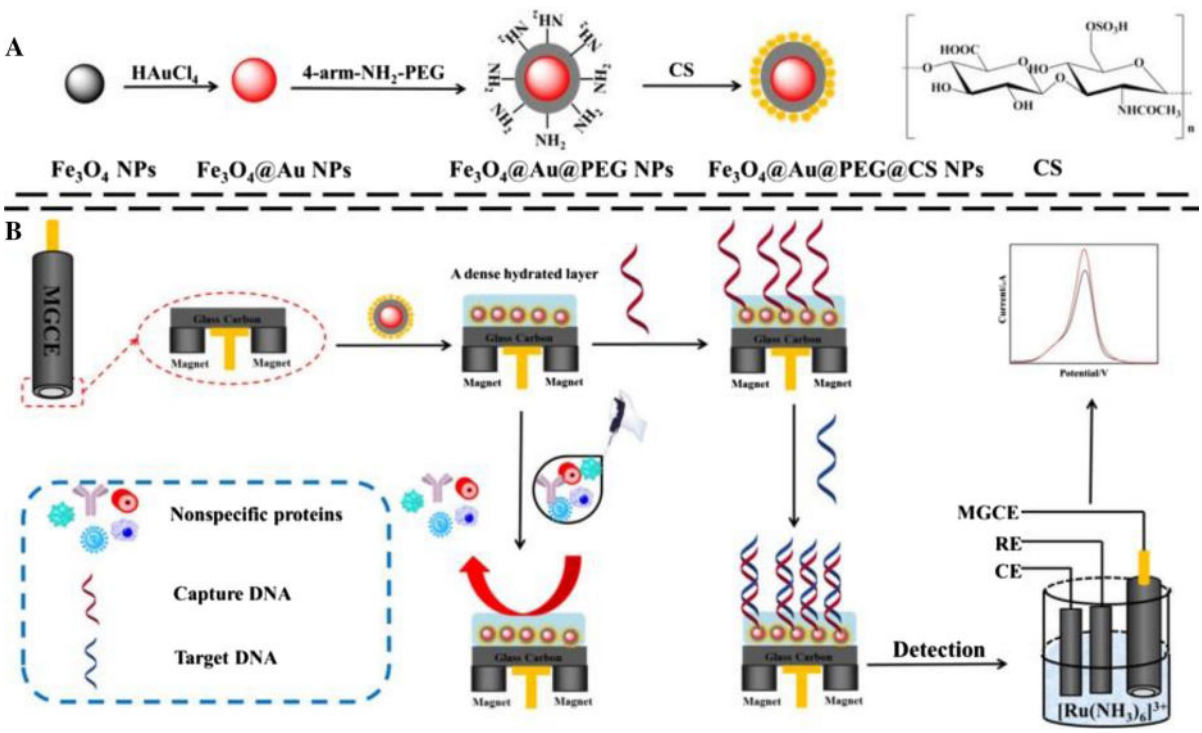


Fig. 12 Schematics of the SERS-Based LF biosensor for the detection of *mycoplasma ovipneumoniae* (Zhao et al. 2020)

Surface-Enhanced Raman Scattering (SERS)-based Lateral Flow (LF) strip biosensor incorporating Recombinase Polymerase Amplification (RPA) was developed for real-time detection of *L. monocytogenes* and *Salmonella enterica*. Wide range linearity, suitable sensitivity, and fast operation were reported with real food samples (Fig. 10) (Liu et al. 2017).

An ultrasensitive peptide-based multiplexed electrochemical biosensor was developed for the identification of the *L. monocytogenes.* Some advantages such as high selectivity, fast working, and simple structure were reported for this system (Eissa and Zourob 2020). An optical biosensor using immunomagnetic separation was fabricated for rapid and sensitive recognition of *L. monocytogenes.* The established system showed low cost and ultra-sensitivity as well as applicability to the control of foodborne diseases (Chen et al. 2018a).

An important DNA-based biosensor was assembled for the determination of the *Mycoplasma pneumonia* DNA. The developed system (Fig. 11) was low-cost and had high sensitivity and specificity compared to the molecular methods (Liu et al. 2016).

An innovative DNA-based biosensor was designed for the rapid and sensitive detection of *mycoplasma ovipneumoniae.* Proper selectivity and high stability were the features of the designed system, which could easily replace the routine methods (Fig. 12) (Zhao et al. 2020).

A nanoparticle-based Lateral Flow Biosensor (LFB) incorporating Multiple-Cross-Displacement Amplification (MCDA) assay was used for the rapid and selective determination of *M. pneumonia.* The designed biosensor, besides simple and cost-effective structure, had high sensitivity and selectivity and hence, was a good alternative to the routine methods (Wang et al. 2019a). Loop-mediated isothermal amplification (LAMP) combined with a nanoparticle-based was utilized for the selective identification of *M. pneumonia.* The developed LAMP-LFB platform showed high accuracy and sensitivity in the detection of the *M. pneumonia* in clinical samples (Wang et al. 2019b).

A DNA-based electrochemical biosensor was established for the ultra-sensitive detection of *H. influenza*. The created genosensor could selectively differentiate the complementary sequence from target samples with other similar sequences (Mobed et al. 2019b). An original immunosensor has been offered recently for selective determination of *H. influenza* (Fig. 13). It was able to easily distinguish the target sequence from similar sequences without cross-reaction.

An electrochemical DNA-based biosensor was successfully designed for the detection of *Mycobacterium tuberculosis*. Wide linear range and acceptable LOD were achieved besides simple and low-cost construction (Torati et al. 2016). For rapid screening of *Mycobacterium tuberculosis* complex (MTBC), a portable Surface Plasmon Resonance (SPR)-based biosensor has been developed recently. This system (Fig. 16) showed acceptable sensitivity and selectivity and it was applicable to patient

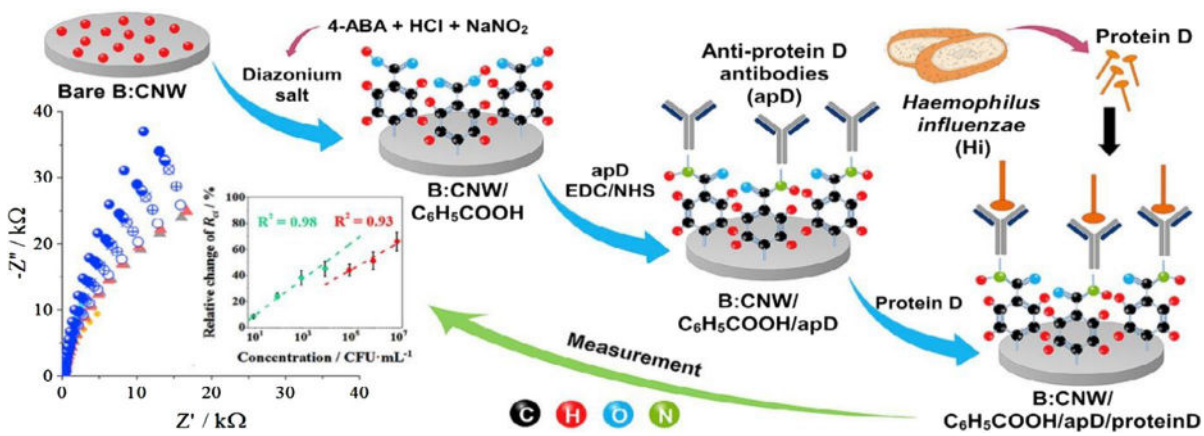


Fig. 13 Schematics of the impedimetric biosensor for the detection of *H. influenza* (Brodowski et al. 2021)

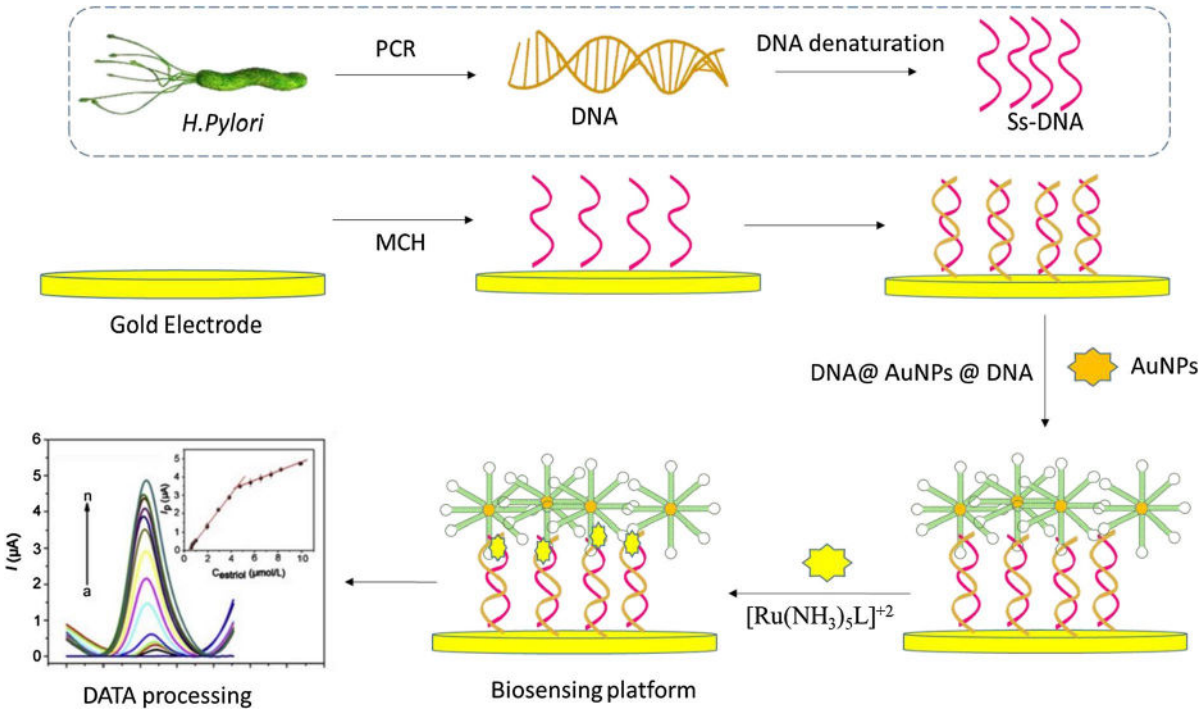


Fig. 14 Schematics of the DNA electrochemical biosensor for the detection of *H. pylori*, Reproduced from Ref. (Chen et al. 2018b)

sputum samples (Prabowo et al. 2018). Loop-mediated isothermal amplification (LAMP) coupled with a chromatographic Lateral-Flow Dipstick (LFD) was fabricated for the detection of the IS6110 gene of *M. tuberculosis.* The LAMP-LFD platform demonstrated suitable sensitivity and selectivity with rapid working and it was usable for clinical and medical samples (Kaewphinit et al. 2012). A Peptide Nucleic Acid (PNA) biosensor based on nanomaterials was prepared for the identification of *M. Tuberculosis*. The prepared system exhibited good sensitivity and selectivity and it was applicable to *M. Tuberculosis* screeninig (Mat Zaid et al. 2017).

A nanohybrid-based BabA immunosensor was developed for rapid and sensitive detection of *H. pylori* (Gupta et al. 2020). An electrochemical DNA biosensor was prepared for the recognition of *H. pylori.* The arranged platform (Fig. 14) showed promising aspects and it was applicable to dental plaque samples as a noninvasive diagnostic tool (Chen et al. 2018b).

An electrochemical biosensor was fabricated successfully for the determination of *H. pylori*. The produced system presented high repeatability and reproducibility and was usable for the determination of *H. pylori* in feces (Peng et al. 2017). An enzyme-free electrochemical sandwich DNA assay coupled with Hybridization Chain Reaction (HCR) was invented for the detection of *H. pylori.* Due to its high selectivity, this system was able to distinguish similar sequences from each other (Lv et al. 2019) (Table 2).

Research trends, gaps, and future prospects

Quantification of cancer-associated bacteria, is very important for tasks in many areas of microbiology and medicine (Hazan et al. 2012). Traditionally, bacterial viability is determined by the number of colonies (called colony forming units or CFUs) that grow from a known volume on a solid growth medium after a period of incubation. This procedure is necessarily labor intensive and involves a significant delay of 1–5 days (Hazan et al. 2012). In addition, this method only considers cells that can be cultured under experimental conditions. Therefore, it is not possible to indicate the number of dead or

Table 2 Developed biosensors for carcinogenic bacteria detection and diagnosis

Bacteria	Platform	In used	Linear range	LOD	References
S. typhi	SERS	Food	15–1.5 × 10^6 CFU/mL	15 CFU/mL	Duan et al. (2016a)
S. typhi	Impedimetric biosensor	Food and environment	10^2–10^8 CFU/mL	100 CFU/mL	Sheikhzadeh et al. (2016)
S. typhi	Aptasensor	Different samples	10–10^6 CFU/mL	7 CFU/mL	Yuan et al. (2014)
S. typhi	Colorimetric-Aptasensor	Food and milk	25–10^5 CFU/mL	10 CFU/mL	Duan et al. (2016b)
S. typhi	Aptamer-based fluorometric	Spiked food samples	10–10^{10} CFU/mL	1 CFU/mL	Ren et al. (2019)
S. typhi	Electrochemical immunosensor	Food	5 × 103 cells/mL	20 cells/mL	Salam and Tothill (2009)
S. typhi	Phage-based magnetoelastic biosensors	Food	5 × 10^1 to 5 × 10^8 CFU/mL	5 × 10^2 CFU/mL	Li et al. (2010)
L.monocytogenes	Fibre-optic aptamer-based biosensor	Food	10^3 CFU/mL	10^2 CFU 25 g^{-1}	Ohk et al. (2010)
L. monocytogenes	Immunosensor	Food	5–1 log CFU/mL	2 log CFU/mL	Davis et al. (2013)
L.monocytogenes	BERA	Food	_	10^2 CFU/mL	Hadjilouka et al. (2020)
L. monocytogenes	Immunosensor	Food	_	2 × 10^5 CFU/mL	Hossein-Nejad-Ariani et al. (2018)
L. monocytogenes	Electrochemical immunosensor	_	1.0 × 10^{-13}–1.0 × 10^{-6} mol/L	3.17 × 10 − 14 mol/L	Niu et al. (2017)
L. monocytogenes	SERS-based LF	Food	1.9 × 10^0 to 1.9 × 10^6 CFU/mL	1.9 × 101 CFU/mL o	Liu et al. (2017)
L. monocytogenes	Peptide-based multiplexed electrochemical biosensor	Food	10–10^8 CFU/mL	9 CFU/mL	Eissa and Zourob (2020)
L. monocytogenes	Optical immunosensor	Food	20–50 M	1.0 × 10^2 CFU/mL	Chen et al. (2018a)
M. pneumonia	DNA based biosensors	Clinical samples	0.1 pM–20 nM	0.03 pM	Liu et al. (2016)
M. ovipneumoniae	DNA based biosensors	Real biological samples	1017–1012 M	3.3 M	Zhao et al. (2020)
M. pneumonia	LFB	Culture and clinical samples	_	_	Wang et al. (2019a)
M. pneumonia	LAMP-LFB	Clinical samples	_	600 fg of DNA templates	Wang et al. (2019b)
H. influenza	DNA-based biosensors	Spike	1 µM–1 ZM	1 ZM	Mobed et al. (2019b)
H. influenza	Impedimetric biosensor	Clinical samples	8.39 × 10^1–8.39 × 10^3 CFU/mL	5.20 × 10^2 CFU/mL	Brodowski et al. (2021)
M. Tuberculosis	DNA-based biosensors	Sputum samples	0.01–100 ng/µL	0.05 ng/µL	Torati et al. (2016)
M. Tuberculosis	SPR	Sputum samples	_	63 pg/mL	Prabowo et al. (2018)
M. Tuberculosis	LAMP-LFD	Clinical samples	_	_	Kaewphinit et al. (2012)
M. Tuberculosis	DNA based biosensors	Clinical sample	1 × 10^{-11} to 1 × 10^{-7}	8.948 × 10^{-13} M	Mat Zaid et al. (2017)

Table 2 (continued)

Bacteria	Platform	In used	Linear range	LOD	References
H. pylori	Electrochemical immunosensor	_	0.2–20 ng/mL	0.2 ng/mL	Gupta et al. (2020)
H. pylori	DNA-based biosensors	Dental plaque samples	_	12 fM dsDNA	Chen et al. (2018b)
H. pylori	DNA-based biosensors	Excrement	0.3 nM–0.24 µM	0.15 nM	Peng et al. (2017)
H. pylori	Enzyme-free electrochemical sandwich DNA assay	Physiological samples	1–100 fM	0.68 aM	Lv et al. (2019)

SERS surface-enhanced Raman Spectroscopy, *BERA* bio-electric recognition assay, *LFB* lateral flow biosensor, *LAMP* loop-mediated isothermal amplification, *SPR* surface plasmon resonance

viable but nonculturable (VBNC) cells that maintain metabolism and cell activity under stress. In addition to detecting live bacteria, counting and distinguishing dead bacteria is valuable or necessary in many applications (Ou et al. 2019). By using the fluorescent dye SYTO9 and propidium iodide (PI), which have different staining's for live and dead bacteria, efficient detection of live and dead bacteria that does not depend on culture can be achieved. In other words, live cells have intact membranes and are impermeable to dyes such as PI, which only leaks into cells with compromised membranes (Ou et al. 2019). Fluorescence detection is most commonly achieved by microscopy, which allows direct examination of individual cells. However, due to the limited number of cells that can be detected at the same time, analysis of large samples can be time consuming (Ou et al. 2019).

Biosensors that integrate genetically programmed live cells into hostile and synthetic environments (devices, matrices, etc.) provide powerful tools for scientific research and enable new technological applications. However, maintaining the viability and function of biological components exposed to a variety of chemical, physiological, or mechanical conditions in a particular application remains a challenge (Zhao et al. 2021). Electrochemical biosensors can be easily integrated into smaller wearable devices. Biometrics provide reliability and excellent analytical performance, but have drawbacks such as high cost, short lifespan, and low stability. Using a series of genetic engineering approaches to overcome these limitations to generate more stable biometric elements is the main focus of current research. The development of structured materials with tuned properties for effective and selective immobilization of biometric elements is required for each individual system. The point-of-care detection of small molecules such as bacteria has been successfully demonstrated. However, detection of large molecules such as proteins and nucleic acids has problems such as stains on electrodes and non-specific adsorption of biomolecules. Solving these problems allows for a wider range of applications of electrochemical methods. The analysis of large biomolecules requires a low detection limit, but the detection limit can be increased by using nanomaterials such as nanoporous gold, graphene, and carbon nanotubes. Some advantages and disadvantages of biosensors summarized in Table 3.

In summary, it can be concluded that a variety of methods have been developed to detect cancer-related bacteria, from observational and microscopic methods to nanomaterial-based methods including molecular and biosensors (Fig. 15).

While conventional methods, especially molecular methods (PCR), have many advantages, the development of nanomaterial-based methods, including biosensors, has been more popular among researchers due to their unique advantages.

Table 3 Important advantages and disadvantages of biosensors

Advantages	Disadvantages	References
High-sensitivity, real-time measurement Excellent reproducibility, wide linearity, acceptable LOD, fast detection, portable, no need for advanced tools, no need for professionals, user friendly, easy operation, and easy interpretation of results	Low stability; low selectivity, Sensitive for environment temperature and PH, need for sample pretreatment,	Mukundan et al. (2009); Li et al. (2021); Plekhanova and Reshetilov (2019)

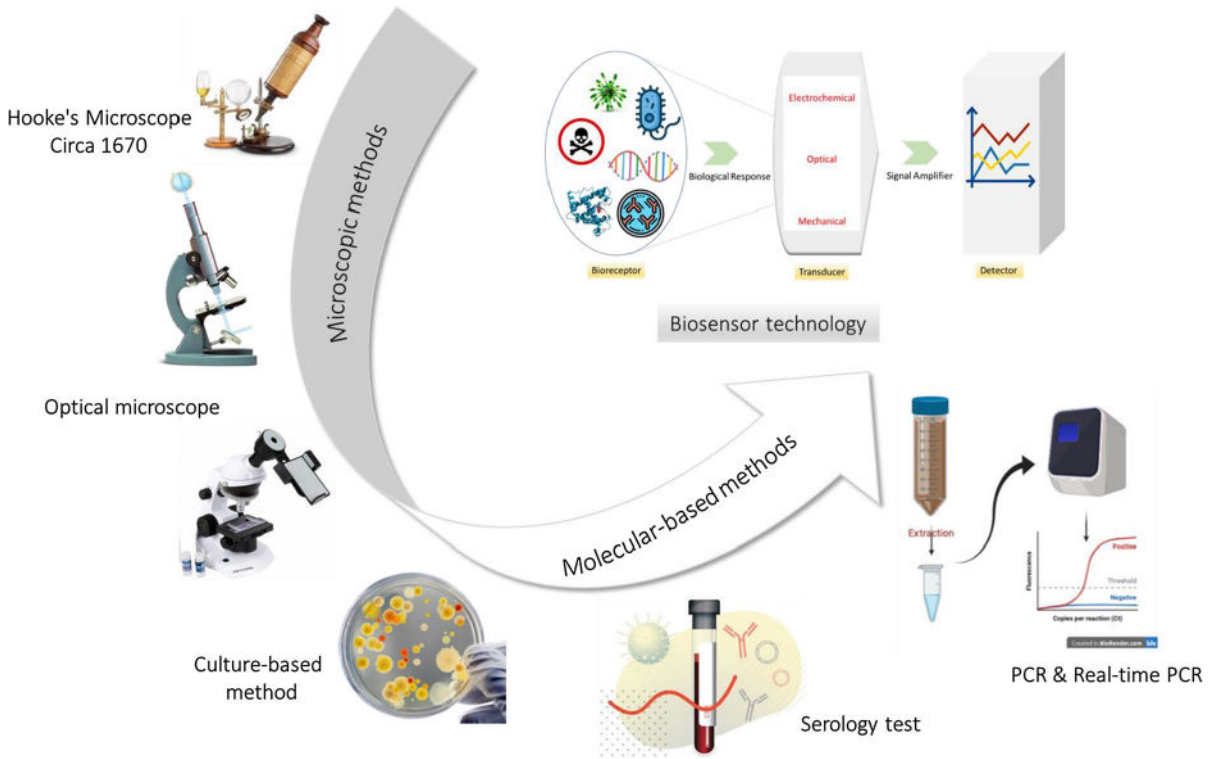


Fig. 15 Advances in detection of carcinogenic bacteria from observational and microscopic methods to nanomaterial-based methods including molecular and biosensors

Conclusion

Carcinogenic bacteria diagnosis is undoubtedly one of the main challenges in not only bacteriology but also the medical sciences. Various methods such as microscopic observation, culture, and molecular-based approach as well as PCR and real-time PCR have been employed in the determination of carcinogenic bacteria. Despite their acceptable sensitivity and specificity, the conventional methods are expensive, difficult to perform, and time-consuming and require advanced tools and professional people. Nanomaterial-based methods as a novel strategy have extensively been developed to overcome the limitations and problems of the conventional methods. Among them, biosensors have considerably drawn the attention of researchers due to their advantages including high sensitivity, rapid operation, cost effectiveness, and simple construction. The results of this and related studies show that the development of biosensors can have a significant impact on improving the diagnostic methods for carcinogenic bacteria and accelerate the therapeutic process for infected people. In other words, biosensors can be a reliable alternative to old methods in the detection of carcinogenic bacteria. Undoubtedly, extensive research is needed to reach an ideal point. For example, in the case of some carcinogenic bacteria such as *Streptococcus bovis* and *Chlamydia pneumophila*, a suitable biosensor has not been developed to date.

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Declarations

Conflict of interest There is no conflict of interest.

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