



Recent progress in nanomaterial-based electrochemical biosensors for pathogenic bacteria

Ramin Pourakbari^{1,2,3} · Nasrin Shadjou⁴ · Hadi Yousefi⁵ · Ibrahim Isildak⁶ · Mehdi Yousefi^{1,3} · Mohammad-Reza Rashidi⁷ · Balal Khalilzadeh^{1,8}

Received: 22 May 2019 / Accepted: 18 October 2019 / Published online: 21 November 2019
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Abstract

This review (with 118 refs.) discusses the progress made in electroanalytical methods based on the use of organic and inorganic nanomaterials for the determination of bacteria, specifically of *E. coli*, *Salmonella*, *Staphylococcus*, *Mycobacterium*, *Listeria* and *Klebsiella* species. We also discuss advantages and limitations of electrochemical methods. Strategies based on the use of aptamers, DNA and antibodies are covered. Following an introduction into electrochemical biosensing, a first large section covers methods for pathogen detection using metal nanoparticles, with subsections on silver nanoparticles, gold nanoparticles, magnetic nanoparticles and carbon-based nanomaterials. A second large section covers methods based on the use of organic nanocomposites, graphene and its derivatives. Other nanoparticles are treated in a final section. Several tables are presented that give an overview on the wealth of methods and materials. A concluding section summarizes the current status, addresses challenges, and gives an outlook on potential future trends.

Keywords Bioassay · Metal nanoparticles · Carbon allotropes · Graphene · Carbon nanotubes · Nanocomposite · Biotechnology · Polymeric nanoparticles

Introduction

Bacterial infections are an important drivers of mortality in animals and human beings but also their secondary infections have deep effect on disease severity and human death. Pathogens have to be detected in both living species and in food and feed [1, 2], and electrochemical methods have had a strong impact in recent years when developing new methods for detection and quantitation of pathogens. Figure 1a gives an overview on the most important classes of pathogens.

Figure 1b compares the various analytical techniques used for bacteria recognition according to the number of publications. The most popular methods are the polymerase chain reaction (PCR) [3], and culture colony counting methods [4], respectively. Culture and colony counting methods are time consuming than PCR methods. Recently, new PCR technology namely real-time-PCR enable obtaining outcomes in a few hours. As limitation of these techniques, any pollution of the sample would owing to misleading outcomes [5]. It is important to mention that, some sequence data is required for designing PCR primers. Thus, PCR method is able to analyze the pathogens, in which, the gene sequence of them is access able. Also primers maybe

✉ Balal Khalilzadeh
khalilzadehb@tbzmed.ac.ir; balalkhalilzadeh@gmail.com

- ¹ Stem Cell Research Center (SCRC), Tabriz University of Medical Sciences, Tabriz 51664-14766, Iran
- ² Student's Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
- ³ Department of Immunology, Tabriz University of Medical Sciences, Tabriz, Iran
- ⁴ Department of Nano-chemistry, Nanotechnology Research Center, Urmia University, Urmia 57154, Iran
- ⁵ Department of Basic Medical Sciences, Khoy University of Medical Sciences, Khoy, Iran
- ⁶ Department of Bioengineering, Faculty of Chemistry-Metallurgy, Yildiz Technical University, 34220 Istanbul, Turkey
- ⁷ Research Center for Pharmaceutical Nanotechnology (RCPN), Tabriz University of Medical Sciences, Tabriz, Iran
- ⁸ Biosensors and Bioelectronics Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

non-specifically attach to sequences, accordingly not totally identical to target DNA [6]. Traditional pathogen diagnosis tests are considered sensitive enough. However, they are often costly, time-consuming and the need for a large sample size. Consequently, new approaches are needed for overcome the limitation of the traditional methods [7]. Biosensor technology showed reliable results at a very short time and are low cost. That why they have already attracted a lot of interest. However, a lot of changes have to made biosensors can by a real alternative to clinical diagnostic methods [8]. Biosensors are analytical devices, which were applied for detection of biological and chemicals. Biosensors are consist of different section like; analyte, bioreceptor, transducer and signal amplifier (Fig. 2). Recently, application of biosensors was highly increased in clinical detections. For example, pathogens, toxins and tumor markers were widely analyzed by nanomaterial based biosensors. Biosensors presented some advantages like; fast response time, cost effective, free from interfering agents, and real time monitoring. Finally the mentioned features make the biosensor as powerful tool for clinical diagnosis and they have high ability to in vivo application at future laboratory tests [9]. During the designing of biosensors, some critical points can consider. For example; acceptable sensitivity, ability to detect the target analyte in the presence of unprocessed samples (without any extraction and separation), the stability, noninvasive for in vivo applications, users ecofriendly and lastly it has ability to miniaturization [10]. The most analytical challenges in the quantification and characterization process of pathogenic bacteria are time consuming and lack of the sensitivity of the common methods. For overcoming the mentioned challenges, application of the fast response time and also sensitive methods like biosensors (especially electrochemical ones) is highly recommended.

Electrochemical biosensors

Electrochemical biosensors for their simplicity and sensitivity are highly considered by the biomedical and environmental research

programs [11, 12]. Based on the determination strategies, electrochemical biosensors are categorized in two main groups; the labeled and label free methods. Commonly, in labeled methods, an electrochemical reporter was used during construction of the biosensors. For example (ferrocene, methylene blue) [13], enzymes (horseradish peroxidase, glucose oxidase) [14], some metal complexes (ruthenium, osmium) [15], and some metal nanoparticles (gold, silver, palladium, and platinum) [16]. The label free method mostly based on the decrease in the conductivity of working electrode. Importantly, the labeled methods is named as “on” method, while the label free methods is called “off” method [17]. The label free methods have some advantages like quick construction process, cost effective and more importantly, this method is its fast response time. However, its sensitivity is poor. In different circumstances, the top feature of the labeled method is its sensitivity. Interestingly, the labeled method mostly based on the sandwich like biosensors, in other work, the target analyte was captured by two biological receptors, like sandwich making. Also, the selectivity is increased in the labeled methods [18]. Mostly four electrochemical methods (Voltammetry/ amperometry, Potentiometry, Impedance and Conductometry) are involved in biosensor designing. [19]. An interesting review on the application of nanomaterials for detection of drug resistant *Staphylococcus aureus* and related problems in hospitals was reported, in which, the most electrochemical and optical methods were comprehensively discussed [20].

Bacteria pathogen detection based on the use of nanomaterials

Materials, which their size in 1 to 100 nm are called nanomaterials. They have different properties, shapes and sizes. Because of their high surface area, they categorized as advanced materials, too [21]. Some nanomaterial with high conductivity are mostly used in biosensor constructions [22, 23]. nanomaterials classified in four groups like; zero dimension (0D), one dimension (1D), two dimension (2D) and three

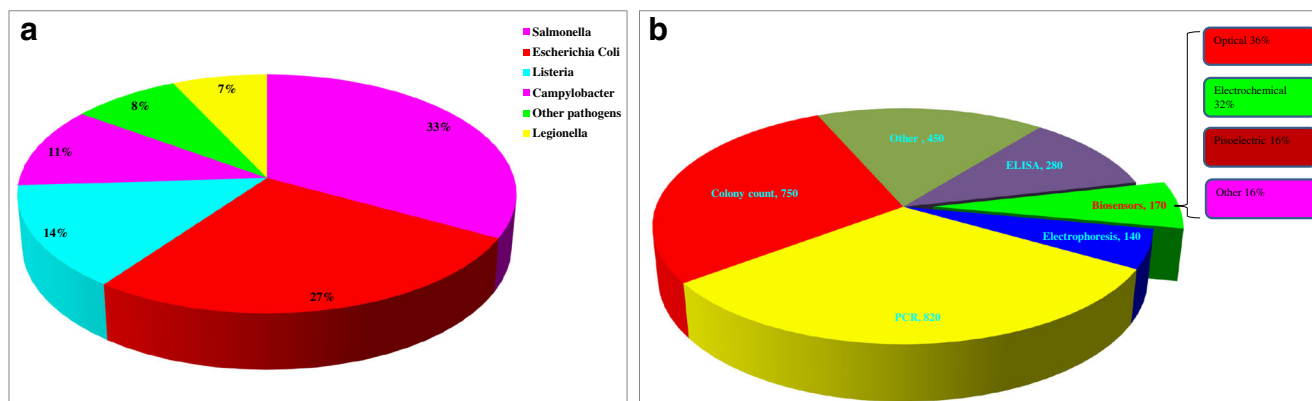


Fig. 1 a An overview on common pathogenic bacteria. b Commonly used techniques for detection of pathogenic bacteria

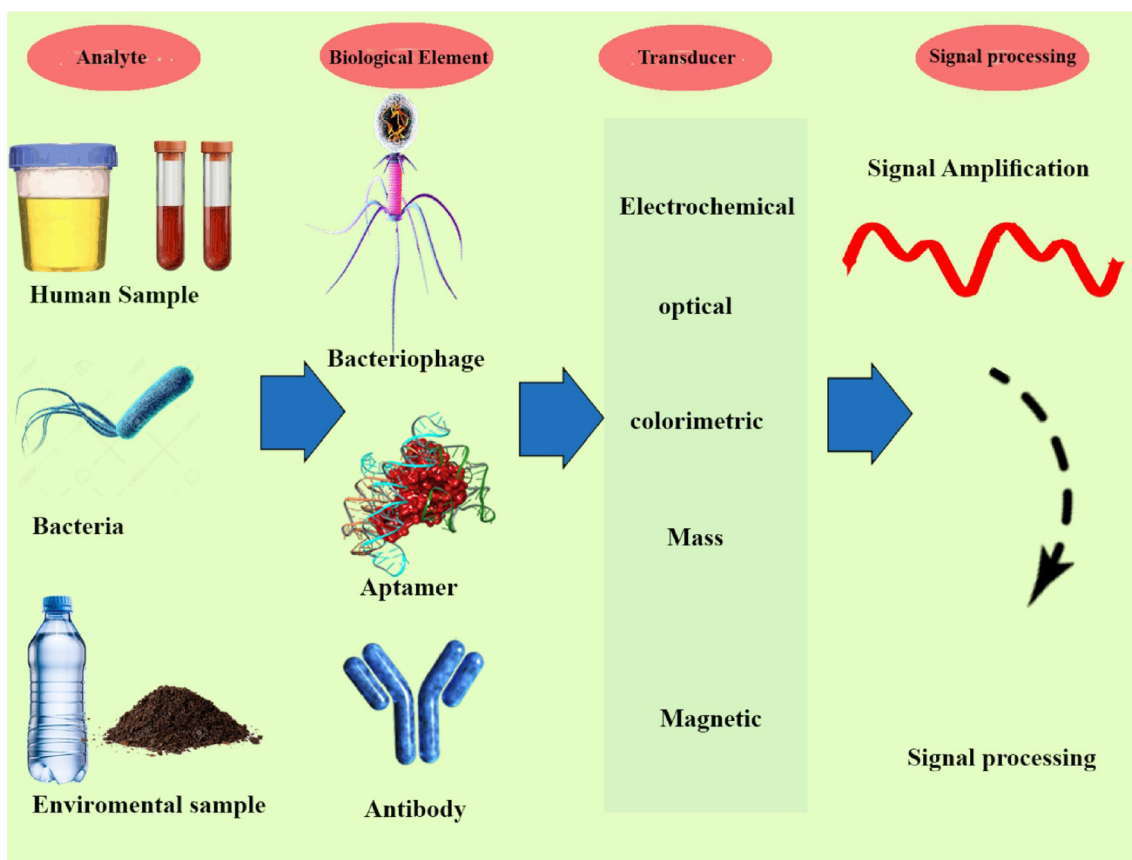


Fig. 2 common features of biosensors were applied for detection of pathogenic bacteria

dimension (3D) [24]. In 0Ds nanomaterials all of the height, width and length are smaller than 100 nm, like; quantum dots (QDs). In 1Ds nanomaterials, both of the height, width and length are smaller than 100 nm, like; nanowires [25], nanotube [26], nanorods [27]. The 2Ds group, one dimension is lower than 100 nm, like; ribbon [28], plates and sheets [29], and triangles [30]. In 3Ds nanomaterial, all of the height, width and length are bigger than 100 nm, like; stars [31], corns [32], dumbbells [33], flowers [34], boxes [35], cubes [36]. Among the above discussed types of nanomaterials, only some of them have been used in biosensors designing.

Mostly nanomaterials are classified into both organic) generally include carbon nanoparticles (and inorganic (such as metal nanoparticles and semiconductors) categories [37]. Inorganic nanoparticles have some top features like; simply produced, high surface-to-volume ratio, controlled bioreceptor orientation, and better optical and electrical features in comparison with other materials [38]. According to the discussed advantages of the inorganic nanoparticles, they play crucial role in the progress of sensitive electrochemical sensors and spectrophotometric measurements [39].

In following subsections, we discussed about types of organic and inorganic nanomaterials used in electrochemical biosensing of infection bacteria.

Metal nanoparticles

Silver nanoparticles (AgNPs)

Silver nanoparticles have unique electrical, optical and physicochemical properties. Which highly attracted the opinions of the researchers in biomedical applications fields such as pharmaceutical and therapeutics [40], biosensors, biocatalysts, bioelectronics [41, 42]. In addition, AgNPs are applied as substrates for Surface-Enhanced Raman Scattering (SERS) [43], surface plasmon resonance (SPR) [44], and also in localized Surface Plasmon Resonance (LSRP) [45]. AgNPs have another benefits like; no need sophisticated tools and a minimum amount of substance for the synthesis, also electrochemical redox reactions of AgNPs were occur at lower potentials and importantly, it gives a specific and sharp voltammetric peak [46].

On the other hand, AgNPs have “particle-specific” effects as known antimicrobial activity of released silver ions (Ag^+). Therefore, the ability of AgNPs toxicity for bacteria and other microorganism might be regulated by modifying Ag^+ release [47].

Recently, these NPs are highly use in the biosensing of infectious bacteria. Staphylococcus as a gram positive

bacteria was detected by a nanomaterial based electrochemical method. Interestingly, the removal and also its deactivation were performed by the designed approach. The quantification process was done by using EIS technique. In this EIS technique, the fluorine doped tin oxide (FTO) was applied as working electrode and modified by 3D zinc oxide nanorods, silver nanoparticles and vancomycin (Van) as bacteria capture element. For this propose, a galvanic process was used for electrochemical in situ electrosynthesis of ZnO nanorods on the FTO platform. Then, after multiple washing and drying steps, the AgNPs were grew on the nanorods by a wet reduction method (immersing in silver solution and in a weak acid, respectively). Following the mercaptoacetic acid (MPA) was covalently immobilized on the attached AgNPs. Then, the carboxylic groups of MPA were activated by 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide/N-hydroxysuccinimide (EDC/NHS) and finally the Van was attached on the modified electrode. The *S. aureus* concentration was quantified by the reverse ratio between the electron transfer resistances (RCT) and the concentration of *S. aureus*. The DL of the constructed bioassay was recorded as 1×10^3 cfu/mL. The biosensor was effectively examined in the presence of *E. coli*. The precision of the constructed system was checked and the RSD for 6 repetitive measurements was gained as about 8%. [48].

As a result, AgNPs are used as an electrode modification platform, to increase the selectivity and sensitivity. Also, based on antibacterial property of AgNPs, it seems that these nanoparticles can be used not only in construction of biosensing platforms but also as an antibacterial agent. According to Table 1, it's obvious that, minor research on the application of AgNPs for detection of pathogenic bacteria detection were done. Therefore, because of their multiple actions in the biosensing of bacteria, it's suggested that, researchers focused in this field of study, which is important for health care.

Gold nanoparticles (AuNPs)

Nowadays, an interesting and popular group of inorganic nanoparticles are AuNPs and they have comprehensive application in biomedical analysis and therapy like; prognostic, photodynamic, probes and drug delivery [49]. AuNPs have unique features, such as excellent optoelectronic properties, changing the size and shape via variation in the chemical environment, synthesis temperature and high biocompatibility [50]. AuNPs were applied in the construction of biosensors. Because of the excellent conductivity and stability [51].

A study was performed for measuring *E. coli* O157:H7 bacteria in water and minced meat samples by Hussein et al. In this report, stock solution mixing with anti-*E. coli*-magnetic beads conjugate (MBs-pECAb) as serve as capture probe under slow stirring, added casein sodium salt 5% (for avoiding

unspecific absorption) and then kept overnight in freezer. The blocked MBs-pECAb were incubated with different concentrations heat killed *E. coli* O157:H7, and after that MBs-pECAb/EC complex was magnetically separated and washed with buffer. AuNPs conjugated with secondary antibodies (AuNPs-sECAb) and add into solution, then magnetic separation and washing steps was carried out under the same conditions of the previous incubation, therefore ready for to analyzed. The results of this work showed that, LOD were 457 and 309 CFU/mL for minced meat and water respectively, in a logarithmic range from 10^2 to 10^5 cfu/mL⁻¹ (56).

For complete of our discussion, Table 1 summarizes the AgNPs and AuNPs which were used for signal amplification agent or bacteria capture agent during detection of some bacteria.

Consequently, the electrocatalytic activity and also electron transfer ability of the designed biosensors were highly enhanced and correspondingly, the sensitivity of the designed biosensors will be significantly improved. In addition, AuNPs have biocompatible property and they can be used as biosensing agent in in-vivo conditions. In other word, based on non-toxicity along with suitable physico-electrical of AuNPs. The biosensors constructed based on these Nobel metal nanoparticles can be implant in the human body and use for the on line monitoring of pathogenic infects bacteria. So, bio-conjugated of Nobel metal based biosensors can apply in wearable biosensors too. Based on the summarized results in Table 1, approximately, all of the researches were focused on the immunoassay of pathogenic bacteria and one research work (86) was related to genosensing of *mycobacterium sp.* On the other hand, no research was found on the aptamer or peptide based biosensing of pathogenic bacteria. So, we need to enlarge our research toward this area. Importantly, the Nobel metal nanoparticles based biosensors, because of the mentioned suitable features, are more applicable for in vivo analysis and online monitoring of pathogenic bacteria.

Magnetic nanoparticles (MNPs)

MNPs are usually made of iron oxide (Fe₃O₄) and it is synthesized from Fe (II and III) salts [52]. Their small sizes and suitable for surface modification caused to be a more applicable material in the cell separation and enrichment systems like MACS [53]. Biologically and chemically modified MNPs were widely used in the construction of biosensors as signal amplification agents for dense loading of electrochemical reporters (for example; streptavidin coated magnetic beads) [54], gold nanolayer coated magnetic beads [55]. Importantly, some of the physical, chemical and stability properties of them should be improved before their use in biosensors [56]. Unmodified MNPs or bare types have a few active groups on their surfaces and tend to aggregation. Moreover,

Table 1 The metal nanoparticles used for electrochemical detection of bacteria

Analyte	Modifications on electrode	Labeling	LODs (cfu/ml)	Detection Method	Reference
EcoliO157:H7	SPCE	MBs-1st Ab AuNPs-2nd Ab	148	Amperometry	[82]
EcoliO157:H7	Quartz crystal Au + Ab	Label free	10	EIS	[83]
EcoliO157:H7	AuNPs+ FeDC+Abs	HRP-2nd Ab	6	Voltammetry	[84]
<i>E. coli</i> O157:H7	AuNPs+ streptavidin Abs	Biotin-1st Ab	150	EIS	[85]
Salmonella spp	AuNPs+ ethylenediamine +Ab	Label free	100	EIS	[86]
Salmonella	probe	Detection probe conjugate with AuNPs	6	SWV	[87]
<i>Staphylococcus aureus</i>	ZnO + AgNPs+vancomycin	Label free	330	EIS	[48]
Mycobacterium sp	AuNPs+DNA	ALP-1st DNA AuNPs-2nd DNA	1.25 ng/ml	EIS	[88]
<i>Escherichia coli</i> O157:H7	Silver solution	AuNPs	500	EIS	[89]
<i>Escherichia coli</i> O157:H7	ITO glass electrode	AuNPs-PANI@Ab1	330 cells/mL	DPV	[90]
<i>E. coli</i>	SPCE+AuNPs	Digoxigenin-labeled DNA	4	CV	[91]

SPCE Screen-printed carbon electrodes, MBs Magnetic beads, AuNPs Gold nanoparticles, Ab Antibody, FeDC Ferrocenedicarboxylic acid, HRP Horseradish peroxidase, ZnO zinc oxide, ITO indium-tin-oxide, PANI polyaniline

quickly oxidized and soluble in acidic media leading to poor stability of them [57, 58]. A series of bio-conjugation strategies including physical and covalent are quickly bonded with these nanoparticles. Therefore, MNPs becomes excellent option for localized drug delivery in some malignancies [59]. Accordingly MNPs wide applied in biomedical research area such as magnetic resonance (MR) imaging [60], and in particular isolation and purification of target molecules [61, 62].

Wang et al., offered an EIS biosensor for detect of *E. coli* O157: H7 in ground beef. In this work streptavidin coated on magnetic nanobeads, mixed with anti- *E. coli* O157:H7 and applied Bead/antibody. The nanobeads was poured into two separate tubes, A sample of *E. coli* was added to one tube, after mixing, the magnetically separated by magnetic. A linear range from 10^4 to 10^7 cells mL^{-1} of *E. coli* O157: H7 and detection limit, concentration of $10^{4.45}$ cfu $\cdot \text{mL}^{-1}$ (~1400 bacterial cells in the volume of 25 μL) was recorded less than 1 h [63].

In other study by Abbaspour et al., a novel magnetic biosensor was constructed for the detection of *Staphylococcus aureus*. Based on combination of trace amount of magnetic beads (Fe_3O_4) and capture ssDNA, which is improve the adsorption of the capture element on the working electrodes via electrostatic attraction. Therefore when the sandwich elements are both consists of ssDNA or aptamers are superior to the sandwich both elements consists of antibodies, because of aptamer have better stability when immobilized on nanomaterials and specify than antibody for detect target analyte. On other hand, the results of applying of aptamers and antibodies simultaneously, may be interesting in the future projects [46].

Table 2 categorized application of MNPs, in the bacteria detections. The analytical figures of merits were highlighted in this Table.

Consequently, MNPs have good biocompatibility, little toxicity and also quick separation process while utilizing an external magnetic field, and lead to decrease the background interference and also concentrate the target analyte. According to the Table 2, most of the research on the MNPs-based nanoparticles was used immunosensing strategy for the pathogenic bacteria detection. Also, one report was related to aptamer based biosensing of *staphylococcus* (46). The multiple properties of these nanoparticles will help us in the future applications like, detection of pathogenic bacteria in the peripheral blood, gastrointestinal system and especially for target and drug delivery in brain. It is important to point out that, MNPs because of their controlling and localizing with external magnet may be more useful in the diagnosis and therapeutic applications. Additionally, photodynamic therapy approaches may applicable by the MNPs for removing of the pathogenic bacteria sources.

Carbon based nanomaterials (CNMs)

CNMs have some desirable physico-chemical characteristics including wide active surface area, (lead to high dense loading of bioreceptor), high physical stability, excellent electrical conductivity and outstanding optical property [64]. These benefits have led to increasing application in biosensors configurations. In addition, CNMs, not only can be used as electrode modified, but also they can be applied for dense loading of the reporters in the sandwich like systems [65]. CNMs are categorized in different types for instance; Carbon nanotubes (CNTs), graphene nanoribbons (GNRs), carbon nanospheres (CNSs), carbon nanohorns (CNHs) [66],

Table 2 The MNPs applied for detection of bacteria using electrochemical methods

Analyte	Modifications on electrode	Labeling	LODs (cfu/ml)	Detection Method	Reference
Staphylococcus aureus	MBs + streptavidin+Aptamer	Biotin-1st Aptamer AgNps-2nd Aptamer	1	Voltammetry	[46]
<i>Salmonella enterica</i>	permanent magnet beneath+Abs	MBs-1st Ab AuNPS-2nd Ab	143	DPV	[92]
<i>E. coli</i> O157:H7	MBs + streptavidin+Abs	Biotin-1st Ab	7.4×10^4	EIS	[93]
<i>E. coli</i> O157:H7	permanent magnet beneath	MBs	1400	EIS	[63]
Salmonella	permanent magnet beneath+Abs	MBs-1st Ab HRP-2nd Ab	1.4	Amperometry	[94]

MBs Magnetic beads, AgNPs Silver nanoparticles, Ab Antibody, AuNPS Gold nanoparticles

Single walled CNTs (SWCNTs) and multi walled CNTs (MWCNTs). MWCNTs consist of several centralized tubes, while SWCNTs consist of only one carbon atomic layer. The diameter of the MWCNTs can be close to 100 nm, while the SWCNTs diameter is 0.4 to 3 nm. SWCNTs have a crucial advantage rather than MWCNTs, which can be combined in a variety of ways and produce and make a different form of CNTs [67].

A reliable impedimetric bioassay was constructed for detection of bacteria using phage approach. In this bioassay T2 phage was used for detection of *E. coli* B. The screen printed electrode (SPE) was used as working electrode and modified by CNT and bacteriophage as biorecognition element. In this construction, both electrostatic forces and covalent bonding were used for layer by layer assembling. In addition, polyethylene imine (PEI) was immobilized on the CNTs, and also the 1-pyrenebutanic acid succinimidyl ester (PBSE) was used for electrostatic and covalent bonding on the modified electrode. The immobilization of phage on the PBSE modified electrode was performed by chronoamperometry technique. After washing step, the final modified electrode was incubated by different concentrations of target bacteria for making of the calibration curve. After optimization of experimental factors, the DL and LDR were recorded as 50 CFU/mL and 1000 to 10 million CFU/mL, in turn. The specificity of the designed biosensor was successfully evaluated in the presence of *E. coli* K. Based on the recorded results; the designed bioassay is free from interfering agent. [68].

Chen et al., designed a platform to detect *Escherichia coli*O157:H7 bacteria, observed that, the carbon nanotubes can highly enhanced the loading efficacy of Ag nanoparticles indirectly and this phenomena may has critical role in the sensitivity of the designed bioassay. In addition, the composition of CNMs with other material such as poly acrylic acid (PAA)/ poly (diallyl dimethyl ammonium chloride) make biocompatible surface for immobilizing of bacteria capture element with the bioactivity for the robust affinity interaction with analyte [69].

The CNMs based electrochemical biosensors for the pathogenic bacteria recognition and quantification were summarized in Table 3.

Based on the excellent properties of carbon based materials, development of label free biosensing assays are so interesting for the detection of different infects bacteria. On the other hand, integration of metal nanoparticles in/on the structure of carbon based materials (GO and MWCNTs) led to more sensitivity in real samples, which, Table 4 confirms this idea. Consequently, because of great electrical conductivity of the CNMs, not only the sensitivity will be improved but also their application in the analysis of the pathogenic bacteria in human body fluids will be possible too.

Nanocomposites (NCs) and graphene and its derivatives

The NCs are composed of nanometer materials dispersed in 3D and 2D substrates. In this type of nanomaterials, based on the component of the NCs. some features like; optical, mechanical and catalytic properties will be improved and a new perspective in nanomaterials technology will be created [70]. The Nanocomposites classified into three categories such as, polymer matrix nanocomposites (PMNC), metal matrix nanocomposites (MMNC), ceramic matrix nanocomposites (CMNC) [71].

Today, two-dimensional nanomaterials (2D), such as graphene (GR), graphene oxide (GO), reduced graphene (RG) and reduce graphene oxide (RGO) have been produced. They have their own specific properties compared to other nanoparticles, graphene is made of 2D sheets with sp²-hybridization of carbon atoms bonded each other and made a tough honeycomb lattice [72]. The declared outstanding features of graphene has led to dramatic changes in development of biosensors and energy storage devices (batteries, fuel cell) [73]. Several ways for the synthesis of graphene have been reported, such as chemical and mechanical slicing of carbon nanotubes, mechanical exfoliation of graphite and chemical

Table 3 The use of carbon nanoparticles in electrochemical biosensors for bacteria detection

Analyte	modifications on electrode	Labeling	LODs (cfu/ml)	Detection Method	Reference
<i>E. coli</i> O157:H7	CNTs +Abs	Silica coated silver nanoparticles-2nd Ab	13	DPV	[69]
<i>E. coli</i> O157:H7, campylobacter and salmonella	MWCNT+Abs	Anti- <i>E. coli</i> -CdS, anti-campylobacter-PbS and anti-salmonella-CuS	<i>E. coli</i> 400 Salmonella 400 Campylobacter 800	SWV	[95]
<i>E. coli</i> B	MWCNT+ bacteriophage	Label free	50	EIS	[68]
<i>Mycobacterium tuberculosis</i>	SWCNTs/Aptamer/Au-IDE	Label free	100	EIS	[96]
staphylococcal enterotoxin B (SEB)	Abs	HRP + Si NPs + CNTs	10 pg/mL	DPV	[97]

CNTs Carbon nanotubes, Ab Antibody, MWCNT Multiwall carbon nanotube, CdS Cadmium sulfide, PbS Plumbum sulfide, CuS Copper sulfide, SWCNT Single walled carbon nanotubes, Si NPs Silicon nanoparticles, HRP Horseradish peroxidase

vapor deposition in situ graphenization of graphite by high voltage applying and etc. [74]. Because of the special properties of graphene; like as high electron transfer capability, flexible modification layer, good thermal conductivity, extraordinary mechanical strength and wide active surface area, this nanomaterial is widely used in electrochemical sensors [75]. The main challenge of graphene-based biosensors for real sample analysis includes two issues. Firstly, the real sample like plasma and blood generally have positive and negative ions and also some small molecules, which causes non-specific signal and led to decrease in specificity. Secondly the majority of graphene-based immunosensors designed at a lab scale and are not proper for commercial manufacture, in other word, there is some scale up problems [76].

The *Escherichia coli* (*E. coli* O157) concentration as gram negative bacteria was determined via an electrochemical method by Guner et al., 2016. In this designing, a mixture of bio/nanocomposition of AuNPs, multiwall carbon nanotube (MWCNT), chitosan and polypyrrole was used for construction of bacteria biosensor. The pencil graphite electrode (PGE) was applied as working electrode, and it was modified by a constant ratio combination of chitosan, pyrrole, MWCNT and 1 % solution of HAuCl₄. After a drying step, the modified electrode was modified by glutaraldehyde as crosslinking agent. The amine groups of polypyrrole on the drop-cast nanocomposites were efficiently modified by glutaraldehyde. At this time the final modified electrode is arranged to capture and quantify the *E. coli* as target analyte. After optimizing the experimental parameters, the analytical figure of merits like DL and LDR of the designed immunosensor were recorded as 30 cfu/mL and 30 to 30 million cfu/mL, in turn. The between lab precision was studied and ten different immunosensors were constructed for 30 cfu/mL concentration of *E. coli* and the acceptable RSD was recorded as about 9%. Also, the stability as an important parameter was examined and after 1 month storage at 4 °C, the constructed immunosensor has approximately its 50% of initial efficiency. In addition, the specificity of the designed

immunosensor was evaluated in the presence of some gram negative bacteria interferences like another type of *E. coli* (O124), *Pseudomonas aeruginosa* (-), *Salmonella* Enteritidis (-), *Shigella* (-) and *Burkholderia cepacia* [77].

Pan and coworkers produced an electrochemical biosensor for quantification of *Klebsiella pneumoniae* carbapenemase (KPC) as model of Tuberculosis affecting bacteria. In this DNA based biosensor, the glassy carbon electrode (GCE) was used applied as working electrode and modified by different compounds. At first, the graphene was cast on the GCE and then, it was modified by AuNPs by electrodeposition approach via cyclic voltammetry technique. The AuNPs were used for enhancing the electrical conductivity of the modified electrode and also importantly for attachment of biological element on the modified electrode. Following, the thiol (-SH) functionalized ssDNA was immobilized on the AuNPs modified electrode via thiol-Au covalent bond. After that, the complementary sequences (the target DNA) were cast on the ssDNA modified electrode and incubate at the optimized time and temperature. After passing the optimization of experimental factors, the DL and LDR of the DNA based electrochemical biosensor were recorded as 20 pM and 1 pM to 10 μM, sequentially. Importantly, the ssDNA was specifically designed to capture of KPC. The selectivity of the constructed biosensor was evaluated in the presence of one and three base mismatched sequences and also with non-complementary sequence. The interference study results indicate that, the one and three base mismatches sequences reduce the complementary currents with 22% and 7%, respectively. In addition, the non-complementary sequence approximately has no effect on the gained current in comparison with the complementary sequence. The reproducibility of the designed DNA based biosensor was evaluated in the presence of 1 nM of target DNA. [78].

Also, Xiaowei et al., showed that graphene-based electrochemical sensors are sensitivity for the detection of *Staphylococcus aureus* gene. Because of the high electron transfer effect and by merging some conductive or

Table 4 Nanocomposite- and graphene-based biosensing used for bacteria detection by electrochemical method

Analyte	modifications on electrode	Labeling	LODs (cfu/ml)	Detection Method	Reference
EcoliO157:H7	Nanoporous alumina+ permanent magnet beneath+Abs	MBs	10	EIS	[98]
E. coli	Fe ₂ O ₃ @Au + permanent magnet beneath	MBs-1st DNA HRP-2nd DNA	5	Amperometry	[99]
E. coli	Au@Pt NPs + silk fiber+carbon fiber+Abs	Label free	0.09 mg/L	EIS	[100]
E. coliO157:H7	PPy/AuNPs/MWCNT/Chi+Abs	Label free	~30	Voltammetry	[77]
Salmonella	Au NPs + Chi+Abs	HRP-2nd Ab	5	EIS	[101]
E. coli	Au NPs-CNT-Abs	HRP-2nd Ab	Not mention	EIS	[102]
Salmonella typhimurium	AuNPs-MWCNT-Chi	Label free	500	EIS	[103]
Staphylococcus aureus	MWCNT-Chi-bismuth+DNA	Detector DNA probe conjugate with PbS NPs	1.23 ng/mL in beef sample	DPV	[104]
Salmonella typhimurium	Cds nanocrystal+ Fe@Au NPs + Ab	Label free	13	Voltammetry	[105]
E. coli	PtNPs	Label free	20	DPV	[106]
Mycobacterium tuberculosis	RGO-AuNPs	Au-PANI	Not mention	Voltammetry	[107]
<i>Klebsiella pneumoniae</i> Carbapenemase	Au-NPs/Gr + DNA	Label free	2×10^{-13} mol/L	Voltammetry	[78]
staphylococcus aureus	Co ₃ O ₄ + Gr + chitosan+DNA	Methylene blue+DNA probe	4.3×10^{-13} mol/L	DPV	[79]
<i>Listeria monocytogenes</i>	Gr + AuNPs+DNA	Methylene blue+DNA probe	2.9×10^{-13} mol/L	DPV	[108]
Salmonella	nanoporous alumina membrane+ GQD + Abs	amino-modified GQDs by glutaraldehyde-1st Ab	not mention	EIS	[109]
Staphylococcus aureus	RGO-Cu(II)/Au electrode	Label free	4.4	EIS	[110]
E. coli O157:H7	RGO-CyCu/Au electrode	Label free	3.8	EIS	[111]
Staphylococcus aureusnuc gene	Gr	ssDNA+ Methylene Blue (MB)	3.3×10^{-13} mol/L	DPV	[112]
Mycobacterium tuberculosis	MOF-rGO	Aptamer+ Platinum/gold core/shell (Pt@Au) nanoparticles	3.3×10^{-5} ng/mL	CV	[113]
Mycobacterium tuberculosis	MOF-AuNPs	Aptamer+HRP	10 fg/mL	DPV	[114]
Escherichia coliO157:H7	Au@Pt core/shell nanoparticle+Gr	Fe ₃ O ₄ @SiO ₂ -Ab ₁ , rGO-NR-Au@Pt-Ab ₂ -HRP	91	CV	[115]
Mycobacterium tuberculosis	GO@Fe ₃ O ₄ @Pt	Aptamer+HRP	0.34 fg/mL	CV	[116]

Ab Antibody, MBs Magnetic beads, HRP Horseradish peroxidase, AuNPs Gold nanoparticles, PPy Polypyrrole, MWCNT Multiwall carbon nanotube, Chi Chitosan, PbS Plumbum sulfide, CdS Cadmium sulfide, PtNPs Platinum nanoparticles, RGO Reduced graphene oxide, PANI Polyaniline, Gr Graphene, GQD Graphene quantum dot, MOF metal-organic framework

magnetic oxides like Co₃O₄ this favorable feature is enhanced significantly. The outcomes established that the synergetic effects of Co₃O₄ nanorods and GR can efficiently improve the surface concentrations of capture element on the electrode surface [79].

The NCs and graphene based electrochemical biosensors for detection and quantification of bacteria were summarized in Table 4.

Consequently, the presence of electrochemically reduced GR nanosheets on the electrode not only improves the

conductivity, but also offers a wide area for the deposition of nanomaterials or capture elements. By improving some features of graphene nanosheets for instance; electrical conductivity, improving its immobilization on the working electrodes, again its application in electrochemical sensors and biosensors will highly enhanced. Similar to previous subsection (2.3), application of magnetic nanoparticles, fibers, polymers, and quantum dots in the construction of labeled and label free bioassays of bacteria, led to more ultra-sensitivity of biosensors.

Table 5 The use of other nanoparticles in electrochemical based bacteria detection

Analyte	Modifications on electrode	Labeling	LODs (cfu/ml)	Detection Method	Reference
EcoliO157:H7	Nanoporous alumina + (Hyaluronic acid) + Ab	Label free	10	EIS	[81]
E. coli O157:H7 and Staphylococcus aureus	Nanoporous alumina	Label free	100	EIS	[117]

According to the Table 4, we hope these types of nanomaterials will be highlighted on the future research studies for the point of care (POC) analysis of pathogenic bacteria. Accordingly, by making nanocomposites, actually we merge the useful features of some components together. So, the stability, selectivity and sensitivity as desire properties of the bioassay methods will be improved.

Other nanoparticles

Other metallic nanoparticles such as platinum and alumina with high electrical conductivity were applied for detection and quantification of bacteria. These nanoparticles which were used for detection of bacteria may not have a higher sensitivity than other nanoparticles, but they are mostly applied because of environmental friendliness and low cost [80].

A homemade working electrode was applied in this bioassay. The nanoporous structure of alumina with highly distributed uniform pore size was functionalized with epoxy silan coupling agent. Then, the poly hyiorenin acid (HA) was attached on the modified electrode via ring opening reaction of epoxy group on the modified electrode. Following, the carboxylic groups of the HA on the modified electrode were activated by EDC/NHS for attachment of monoclonal antibody of E-coli on the modified electrode. Now, the constructed system is ready to capture and quantification of pathogenic bacteria. After passing all optimization factors, the DL and LDR were recorded as 10 cfu/mL and 10 to 100,000 cfu/mL, respectively. The specificity of the produced bioassay was successfully evaluated in the presence of other bacteria like *B. cereus*, *S. aureus* and *E. coli* DH5a [81].

Table 5 categorized application of other nanoparticles on the fastidious bacteria detection. The analytical figures of merits were highlighted in this Table.

Based on the summarized analytical data in Table 5, only label free EIS based approach was applied for the detection of pathogenic bacteria by the alumina based immunosensor. In addition, the application of sandwich type strategies for the improvement of sensitivity is highly required. Furthermore, application of biopolymers and none toxic nanoparticles for enhancing the sensitivity and approving the selectivity of the bioassays for detection of pathogenic bacteria are necessary in health systems. As a result, the total cost of the designed bioassays will be reduced (especially in noble metal free systems).

Conclusion

The conventional methods which were applied for the detection of pathogen bacteria are ELISA, culture plating, single/multiplex PCR and bioluminescence. These methods have various limitation like as more power and labor consumption, and also requires various devices such as spectrophotometers, incubators and specialist personnel for correctly pre/post experimental and specially they are time consuming. Recently, by applying the new generation of diagnostic tools, these problems have been resolved as far as possible. As a modern analytical device, the electrochemical biosensors were used for detection and quantification of bacteria (especially food pathogens) and toxins.

Electrochemical biosensors have some advantages, like as high sensitivity, specificity and low-priced compared to other diagnostic techniques, and more amenable to miniaturization compare other instrumental. These techniques have low detection limits, which can be done with a very small sample size. But there are also several weaknesses of biosensors; warmth sterilization is not feasible, because that might be denaturalization of biological substance. Because of initiative the molecule attributes, Stability of biological material (such as DNA, aptamer, and antibody, it can be degraded under environmental conditions (pH and temperature). Nanomaterials and their combination together may lead to synthesise of hybrid nanocomposite with favorable characteristics for site specific immobilization of bioreceptors on the modified electrodes. The sandwich like or label-dependent methods (dual specific detection elements) are able to detect bacteria with high specificity and sensitivity in clinical samples. By merging the advance nanoparticles such as graphene nanosheets and numerous nanomaterials include; metal, metal oxide, can provide novel efficient and applicable biosensors.

Future and perspective

In the near future, it is hoped that by making biosensors more sensitive and cost-effective than current laboratory techniques for detecting pathogenic bacteria, it would be possible to take a big step in medical diagnosis field. Also clinicians can overcome the restrictions of different related technologies and provide a complete response for monitoring patients over weeks or months.

Today, implantable or a subcutaneous sensors like as a radio-frequency ID chips, which may be monitor the patient's medical conditions include blood biochemical like as, heart rate, blood glucose and pressure. It is expected that, in the near future, smart contact devices will be packed by hundreds of biosensors and nanomaterials, and engineered to early detection of cancers or other malignancies.

Acknowledgements This work was supported by the Stem Cell Research Center (SCRC), Tabriz University of Medical Sciences, Tabriz, Iran. (Grant number: 60976).

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