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Engineering nanomaterials-based biosensors for food safety detection

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ABSTRACT

Food safety always remains a grand global challenge to human health, especially in developing countries. To solve food safety pertained problems, numerous strategies have been developed to detect biological and chemical contaminants in food. Among these approaches, nanomaterials-based biosensors provide opportunity to realize rapid, sensitive, efficient and portable detection, overcoming the restrictions and limitations of traditional methods such as complicated sample pretreatment, long detection time, and relying on expensive instruments and well-trained personnel. In this review article, we provide a cross-disciplinary perspective to review the progress of nanomaterials-based biosensors for the detection of food contaminants. The review article is organized by the category of food contaminants including pathogens/toxins, heavy metals, pesticides, veterinary drugs and illegal additives. In each category of food contaminant, the biosensing strategies are summarized including optical, colorimetric, fluorescent, electrochemical, and immune- biosensors; the relevant analytes, nanomaterials and biosensors are analyzed comprehensively. Future perspectives and challenges are also discussed briefly. We envision that our review could bridge the gap between the fields of food science and nanotechnology, providing implications for the scientists or engineers in both areas to collaborate and promote the development of nanomaterials-based biosensors for food safety detection.

1. Introduction

The World Health Organization (WHO) expressly stated that safety food should be nontoxic and innocuous. Food safety is a multidisciplinary subject regarding food processing, preparation, and storage in ways that prevent foodborne illness. Food safety standards are now extensively adopted in the worldwide food industry, such as BRC, FSSC 22000, IFS, HACCP (Aung and Chang, 2014; Chassy et al., 2004). However, global food safety incidents still frequently occurred, leading to severe healthy, economic and even social problems (Carvalho, 2006; Henson and Caswell, 1999; Li et al., 2015; Pena-Rosas et al., 2012; Wilcock et al., 2004). For instance, beef products from America have been frequently banned to export to other countries due to outbreak of bovine spongiform encephalopathy (Jin and Kim, 2008). A banned chemical, clenbuterol, was found in pork to promote leanness in pigs (Prezelj et al., 2003). In 2008, an unforgettable scandal regarding food safety occurred in China: melamine has been detected in infant formula (milk powder), causing more than 290,000 infants suffered from severe healthy problems such as urinary tract stones (Chen, 2009; Wu et al., 2009). All these events alarm us the importance and urgency of guaranteeing food safety. Except for relevant policies and laws concerning food safety, detection of food contaminants has been attracting remarkable attention in last decade, which ensures the governments and customers to recognize whether the food is safe (Cocolin et al., 2011; Glynn et al., 2006).

A variety of well-developed technologies have been employed for food safety detection such as gas chromatography (GC), high performance liquid chromatography (HPLC), gas chromatography-mass spectrometer (GC-MS), liquid chromatography-mass spectrometer (LC-MS) and enzyme-linked immunosorbent assay (ELISA) (Malik et al., 2010; Patel, 2002; Pico et al., 2006; Rodriguez-Lazaro et al., 2007). Most of these methods have disadvantages such as complicated sample pretreatment and long detection time, especially relying on expensive instruments and well-trained personnel, which limit their applications in some scenarios such as in developing countries and areas with poor equipped facilities and specialists.

Nanotechnology, an emerging developing subject, provides opportunity to address these challenges pertaining to food safety detection. Nanotechnology refers to the science and technology of designing, building, manipulating and understanding materials and systems at

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nanoscale (size ranging from approximately 1 nm to 100 nm in general), which has demonstrated comprehensive impacts on a myriad of applications such as healthcare, environment and energy (Arico et al., 2005; Parak et al., 2015; Sahoo et al., 2007; Whitesides, 2005). In particular, nanotechnologies bring grand benefits to, and impose great impacts on food industries through the whole food chain, including production, processing, safety, packaging, transportation, storage and delivery (Kagan, 2016; Kalpana Sastry et al., 2013; Neethirajan and Jayas, 2011; Rossi et al., 2014; Sozer and Kokini, 2009). Regarding food safety in specific, nanotechnologies exhibit promising potential for detecting food contaminants, in which nanomaterials-based biosensors play important roles. Nanomaterials possess unique physiochemical properties in comparison with their bulk counterparts, providing valuable strategies for food safety detection (Gupta et al., 2016; Rai et al., 2009). Advances in nanomaterials have facilitated the developments of biosensing for food safety detection (Chen and Park, 2016; Sharma et al., 2015; Warriner et al., 2014). Biosensors, coupling biological components with physicochemical detectors, possess enormous benefits for the detection and analysis of food contaminants, because of the high sensitivity and specificity resulting from the precise recognition (Chaudhry et al., 2008; Lan et al., 2017; Rashidi and Khosravi-Darani, 2011). Compared to traditional chromatography methods, nanomaterials-based biosensors have some key advantages including more specific target recognition, improved selectivity and sensitivity, enhanced signal readout, and shorter analysis time (Lim and Kim, 2016; Yang et al., 2016).

We organize this review by the category of food contaminant sources, including pathogens/toxins, heavy metals, pesticides, veterinary drugs and illegal additives. In Fig. 1, we provide an overview of engineering nanomaterials-based biosensors for food safety detection. In this review, we do not intend to summarize all of the nanomaterials ever used in detection of food contaminants. Instead, we selectively focus on some lately important achievements. We further provide our perspectives on the future development.

2. Pathogens and toxins

Although advanced food-packaging technologies such as vacuum packaging and pasteurization treatment allowed food to be stored for a relatively long time, the emergences of foodborne pathogens infecting food have arisen inevitably, resulting in severe diseases of consumers, such as acute emesis and acute abdominalgia (Oliver et al., 2005). The most common foodborne pathogens are *Escherichia coli* (*E. coli*), *Salmonella* and *Listeria*. In last decades, events of foodborne pathogen infection occasionally occurred worldwide (Crim et al., 2014). These events gave rise alarm that preventive action should be taken before consuming, such as detecting pathogens in food. On the other hand, in many cases of foodborne pathogen infection, toxins produced by pathogens were subsequently released into food.

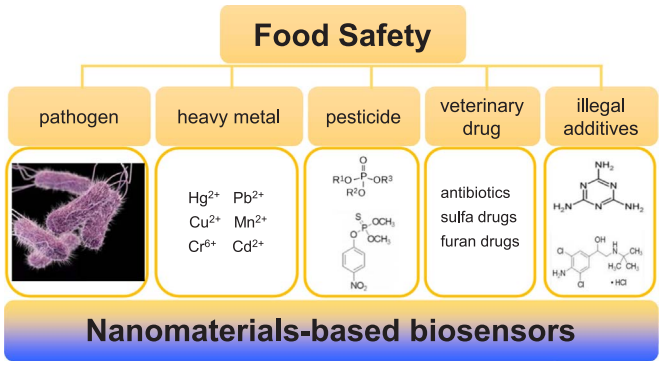

Fig. 1. Overview of nanomaterials-based biosensors for food safety detection. This review is organized by the category of food contaminant sources including pathogens/toxins, heavy metals, pesticides, veterinary drugs and illegal additives.

A variety of methods have been proposed to detect and quantify pathogens and toxins in food. Meanwhile some challenges still existed, including low specificity, low sensitivity and long time for identification (Lazcka et al., 2007). Nanomaterials-based biosensors provide alternative strategy to address these challenges (Burris and Stewart, 2012). Nanoparticles (NPs), quantum dots (QDs), nanorods and carbon nanotubes (CNTs) based biosensors have been developed to realize the detection of foodborne pathogens and toxins (Cho et al., 2014; Kaittanis et al., 2010). Various pathogens and toxins have been effectively detected by nanomaterials-based biosensors with numerous biosensing strategies (Table 1).

Functional noble NPs have been widely applied in pathogen detection, realizing colorimetric sensing in specific. It is notable that NPs such as gold and silver possessed excellent plasmon absorption, thus enhancing signal of detection. The colorimetric sensing was realized by selecting appropriate organic ligands to modify NPs. Phillips et al. used poly(paraphenyleneethynylene) (PPE) conjugated gold nanoparticles (AuNPs) to achieve fast and efficient identification of pathogens (Fig. 2a) (Kaittanis et al., 2010; Phillips et al., 2008), in which the interaction between anionic PPE and cationic AuNPs quenched the fluorescence of PPE. Specific pathogens were associated with AuNPs, resulting in the disassociation between AuNPs and PPE. Consequently, fluorescence PPE was released into solution and the fluorescence of PPE was turned on, which exhibited enhanced fluorescence emission. Similarly, Cheng and coworkers demonstrated a fast detection (in 4 h) of *E.coli* by using glassy carbon electrode modified with platinum NPs (PtNPs), which had high surface area ratio, thus improving the detection sensitivity to *E.coli* due to the electro-catalytic ability of PtNPs (Cheng et al., 2008). Hosseini et al. developed a colorimetric and chemiluminescence method based on aptamers conjugated AuNPs to detect aflatoxin B1 (AFB1), in which aptamers acted as specific recognition ligand and AuNPs exhibited high absorption coefficient. The desorption of the AFB1 binding aptamer from the surface of AuNPs induced the aggregation of AuNPs, leading to the apparent color change of the solution (Hosseini et al., 2015).

In comparison with normal NPs, magnetic NPs (MNPs) possess special properties, allowing for rapid separation and enrichment of target analytes. Joo et al. (2012) utilized antibody conjugated MNPs to capture *Salmonella* from milk. Once an external magnetic field was applied, the superparamagnetic MNPs enabled selective separation of target bacteria. The enrichment effect of MNPs rendered this method with high sensitivity (100 cfu/mL) (Fig. 2b). Similarly, Cheng and coworkers employed bio-functionalized MNPs (BMNPs) to detect *E. coli* in pasteurized milk. BMNPs were fabricated by immobilizing a specific anti-*E.coli* antibody on the surface of amine-functionalized MNPs, which showed high capture efficiency to *E. coli* (Cheng et al., 2009). Ma and coworkers demonstrated a novel colorimetric biosensor for detection of *Salmonella typhimurium (S. typhimurium)* by coupling MNPs and AuNPs. The MNPs and AuNPs were combined respectively with capture DNA and probe DNA which were partially complementary to the sequences of the *S. typhimurium* target DNA, which were fabricated as the capture probes and signal probes. In the presence of *S. typhimurium* target DNA sequences, complementary base pairing of DNA induced the probes and target to form sandwich-like structures, thus AuNPs aggregated and the color changed from red to blue. The absorbance spectra of AuNPs red shifted as the intensity ratio of A700/A521 changed, and the intensity ratio of A700/A521 had a linear correlation with the amount of *S. typhimurium* target DNA, therefore realizing the quantification of *S. typhimurium* (Ma et al., 2017).

Gold nanorods had higher sensitivity to the local dielectric environment, and demonstrated distinct optical properties due to their specific shape (Jana et al., 2001). Wang and Irudayaraj constructed gold nanorod bioprobes by functionalizing the amino-terminated gold nanorods with antibodies. Two major species of foodborne bacteria (*E. coli* and *S. typhimurium*) were simultaneously detected in less than

Table 1
Biosensors for the detection of pathogens and toxins.

Analytes	Biosensors	Nanomaterials	Ref.
Bacteria	Fluorimetric	AuNPs	(Phillips et al., 2008)
E. coli	Electrochemical	PtNPs	(Cheng et al., 2008)
aflatoxin B1	Colorimetric and chemiluminescence	AuNPs	(Hosseini et al., 2015)
Salmonella	Optical	MNPs	(Joo et al., 2012)
E. coli	Bioluminescent	MNPs	(Cheng et al., 2009)
S. Typhimurium	Colorimetric	MNPs and AuNPs	(Ma et al., 2017)
E. coli and *S. Typhimurium*	Optical	Gold nanorods	(Wang et al., 2008)
E.coli	Colorimetric	Gold nanorods	(Singh et al., 2009)
Bacillus anthracis	Fluorimetric	QDs	(Ho et al., 2005)
Campylobacter jejuni	Fluorimetric	MNPs and QDs	(Bruno et al., 2009)
E.coli	Electrochemical	MWCNTs and AuNPs	(Guner et al., 2017)

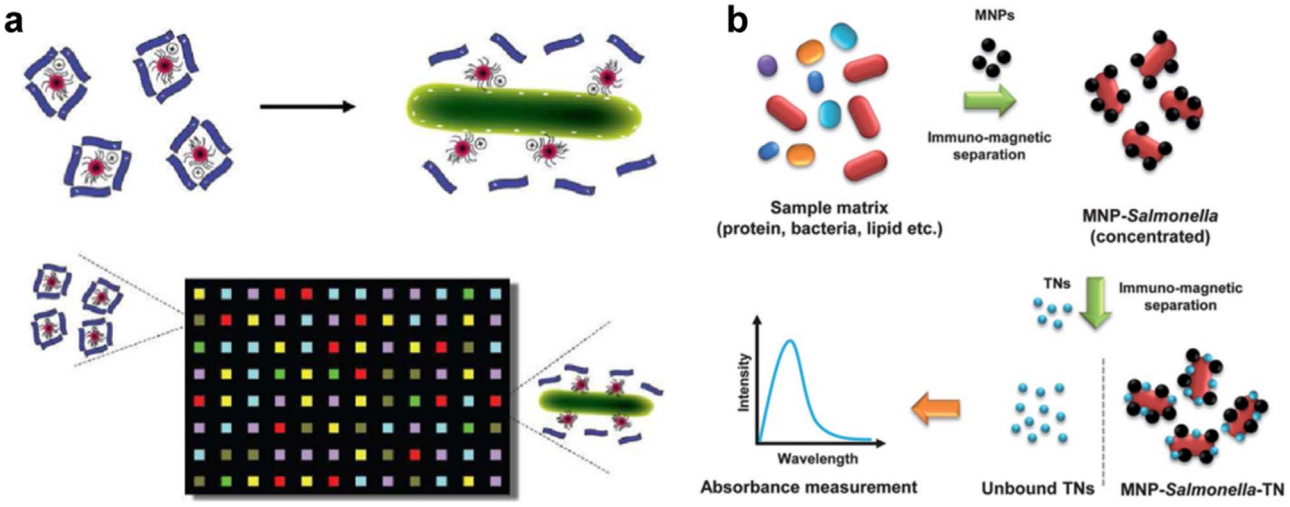

Fig. 2. Detection of pathogen bacteria. (a) AuNPs modified with anionic fluorescent polymers for detection of *E.coli* (Kaittanis et al., 2010; Phillips et al., 2008) and (b) MNPs for detection of *Salmonella* (Joo et al., 2012).

30 min (Wang and Irudayaraj, 2008). Singh et al. made use of two-photon Rayleigh scattering (TPRS) properties of gold nanorods for the detection of *E.coli*. The longitudinal absorption maximum shifted to longer wave length with an increase in the absorption intensity as the aspect ratio of gold nanorods increased. Due to the enhanced surface electric field stimulated by surface plasma, gold nanorods absorbed and scattered electromagnetic radiation. The unique optical property of gold nanorods led to advantages including no need of amplification or enrichment steps, high sensitivity (50 cfu/mL), and excellent discrimination against any other bacteria (Singh et al., 2009).

QDs were another special category of NPs, which contained elements from groups II-VI, III-V or IV-VI in periodic table, such as Cd, Zn, Se, Te, In, P or As. QDs have been widely used in biomedical fields due to their excellent optical properties (Gao et al., 2005; Klostranec and Chan, 2006; Smith and Nie, 2004). Numerous studies demonstrated the detection of foodborne pathogens by utilizing QDs as fluorophores. Ho et al. (2005) used a sandwiched nanoassembly to detect pathogenic strains of *Bacillus anthracis*, which was formed by two oligonucleotide functionalized QD nanoprobes and a target DNA. Since the size of the nanoassembly was smaller than the diffraction-limited resolution of an optical imaging system, the nanoassembly was imaged as multi-color due to the colocalization of both QD nanoprobes. Bruno and coworkers demonstrated that QD-aptamers conjugates could detect live and dead *Campylobacter jejuni* in buffer and various food systems without any washing steps (Bruno et al., 2009). Furthermore, QDs can be used for detecting multiple pathogens (Yang and Li, 2006).

In addition, CNTs have been used for signal amplification in pathogen detection (Chunglok et al., 2011; Ding et al., 2011). Guner et al. developed an electrochemical immunosensor for the detection of *E. coli* using a pencil graphite electrode which was modified with multiwalled CNT (MWCNT), chitosan, polypyrrole (PPy), and AuNPs. Anti-*E. coli* monoclonal antibody was immobilized on the hybrid bionanocomposite. The high surface area of MWCNT on the electrode enabled more space for the immobilization of antibodies. AuNPs enhanced the detection sensitivity by improving the electrochemical signal and adsorption capacity of antibody. The detection range was from 3×10^1 to 3×10^7 cfu/mL of *E. coli*. The hybrid biosensor offered high sensitive, specific, reliable manner for the bacteria quantification (Guner et al., 2017).

3. Heavy metals

Heavy metals, such as Hg^{2+}, Cd^{2+}, Pb^{2+}, pose huge threats to public health even when trace amount of these ions were present in food exceeding regulation level. Long-term ingestion of heavy metals contaminated food causes severe disease, such as neural disorder and cognitive deficits (Claudio et al., 2003; Hamilton et al., 1998; Sanchez-Camazano et al., 1998). Regarding the detection of heavy metal ions, numerous methods have been proposed, such as inductively coupled plasma mass spectroscopy (ICPMS) and atomic absorption/emission spectroscopy (AAS/AES). However, these traditional technologies require either bulky equipment or complicated pretreatment processes. Nanomaterials-based biosensors provide rapid, low-cost and label-free fashion to detect heavy metals (Table 2).

In particular, for example, colorimetric sensors of AuNPs for heavy metals are extremely attractive because they can be easily read out by naked eyes (Daniel and Astruc, 2004; Lin et al., 2011; Zhao et al., 2008). By taking advantages of the specific affinity between thymine

Table 2
Biosensors for the detection of heavy metals.

Analytes	Biosensors	Nanomaterials	Ref.
Hg^{2+}	Colorimetric	AuNPs	(Chen et al., 2014)
Hg^{2+}	Fluorimetric	AuNPs and QDs	(Li et al., 2011)
Cd^{2+}	Colorimetric	AuNPs	(Yin et al., 2011)
Pb^{2+}	Electrochemical	DNA and Pt@Pd nanocages	(Zhao et al., 2017)

(T) and Hg^{2+}, Chen et al. created a colorimetric sensing platform on microfluidic paper-based analytical devices for Hg^{2+} detection through coordination of T-Hg^{2+}-T by utilizing the photoelectric and chemical characteristics of AuNPs. AuNPs were conjugated with oligonucleotide sequences, which decreased the zeta potential of AuNP surfaces, and thus reduced the electrostatic repulsion between adjacent AuNPs. Once the salt solution was added, AuNPs tended to form aggregation, causing the color change of AuNPs (Chen et al., 2014). Li et al. (2011) developed a fluorescent sensor composed of QD/DNA/AuNPs assembly for Hg^{2+} detection by taking advantage of the photostability, high quantum efficiency and size-tunable optical properties of QDs (Fig. 3a). The presence of Hg^{2+} in samples induced the formation of T-Hg^{2+}-T and the linkage between QDs and AuNPs through T-Hg^{2+}-T interaction, and subsequently surface energy transfer occurred between QDs and AuNPs, resulting in the quenching of QDs. This biosensor exhibited excellent limit of detection (LOD, 0.4 ppb) and high selectivity towards Hg^{2+} in mixed samples. Yin et al. (2011) developed a surface-enhanced Raman scattering (SERS) sensor for Cd^{2+} detection by virtue of the interparticle plasmonic coupling generated with selective self-aggregation of AuNPs induced by Cd^{2+} (Fig. 3b). In this system, AuNPs were first coated with a Raman Tag, followed with a layer of polymer brush via surface-initiated atom transfer radical polymerization (SI-ATRP). These AuNPs remained spectrally silent when staying as single particles; if the analytical samples contained Cd^{2+}, whereas, self-aggregation of AuNPs occurred, leading to turning-on of the SERS finger print signal, with up to 90-fold enhancement. It was notable that other metal ions did not trigger self-aggregation of AuNPs and turning-on of SERS signal. Zhao et al. demonstrated a sensitive electrochemical biosensor based on catalytic hairpin assembly and synergistic amplification to specifically detect Pb^{2+}. Pb^{2+} was first recognized by Pb^{2+}-specific DNAzymes, inducing the strand replacement reaction and the formation of dendritic structure DNA on surface of the electrode. Pt@Pd nanocages and electroactive toluidine blue was then captured onto the surface of the electrode by DNA hybridization, forming the dendritic structure DNA to facilitate the immobilization of manganese(III) meso-tetrakis (4-N-methylpyridiniumyl)-porphyrin (MnTMPyP). The signal enhancement of Pb^{2+} detection biosensor was achieved through synergistic catalysis of Pt@Pd nanocages and MnTMPyP to H_2O_2 reduction (Zhao et al., 2017).

Table 3
Biosensors for the detection of pesticide residues.

Analytes	Biosensors	Nanomaterials	Ref.
Organophosphorus pesticide	Electrochemical	CNTs	(Yu et al., 2015)
Organophosphorus pesticides	Electrochemical	AuNPs and graphene oxide	(Yang et al., 2014)
Organophosphate insecticide	Electrochemical	MNPs	(Dominguez et al., 2015)
Glyphosate	Colorimetric	AuNPs	(Tan et al., 2017)
Methylparathion	Fluorimetric	CdTe QDs	(Chouhan et al., 2010)
Paraoxon-ethyl	Optical	Carbon dots	(Chang et al., 2017)

4. Pesticide residues

Pesticides are widely used in agricultural field, most of which are carcinogens, permanently residing in food. Pesticide residues accumulate in organs for long periods and cannot be digested, remarkably damaging human health (Alavanja et al., 2004). Since 1970s, the traditional gold standard methods for the detection and quantification of pesticide residues have been performed by chromatography methods, such as GC/LC combined with MS. With the increasing demands for the determination of pesticide residues, immunoassay and capillary electrophoresis were utilized as well (Bogialli and Di Corcia, 2009; LeDoux, 2011; Watanabe et al., 2013; Xu et al., 2014). However, these methods have some disadvantages such as complicated pretreatment, short storage time, not easily adaptable for in situ monitoring, and requiring expensive equipments and skilled experts. In recent years, to overcome the limitations of traditional methods, nanomaterials-based biosensors have been applied to detect pesticide residues (Table 3).

Yu et al. fabricated CNTs based electrochemical biosensors to detect organophosphorus pesticides (OPs). Amino functionalized CNTs were modified with acetylcholinesterase (AChE), which not only served as electronic bridge and signal amplifier, but also controlled the efficiency of AChE immobilization. Quantitative determination could be realized by measuring UV light absorption of the unbound acetylthiocholine chloride, resulting from the hydrolysis of acetylthiocholine chloride catalyzed by AChE modified biosensors (Fig. 4a) (Yu et al., 2015). Similarly, Yang and coworkers developed an AChE biosensor for rapid detection of OPs by using electrode modified with Au-polypyrrole-reduced graphene oxide (Au-PPy-rGO) nanocomposite. This biosensor not only showed high conductivity but also exhibited specific affinity for thiocholine (the hydrolysis product of AChE). The electrochemical response increased as the concentration of acetylthiocholine chloride increased, while the response decreased in the presence of AChE

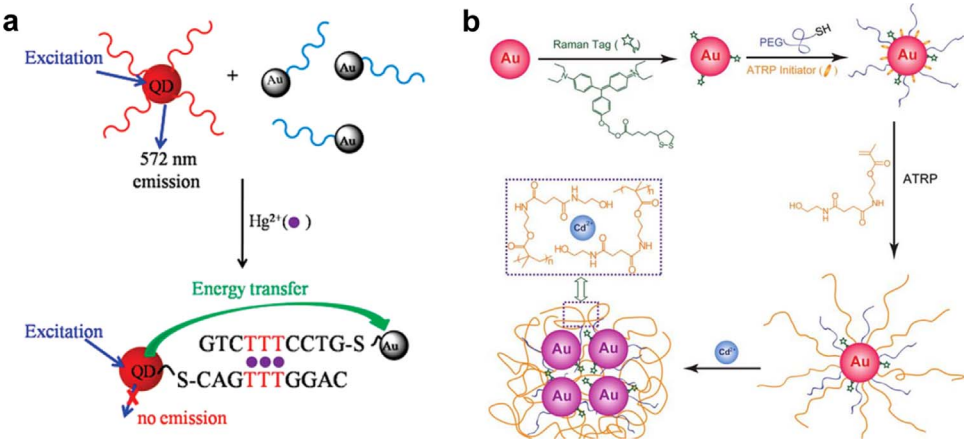

Fig. 3. Detection of heavy metals. (a) QD/DNA/AuNP sensor for Hg^{2+} detection (Li et al., 2011). (b) SERS nanosensor for Cd^{2+}detection (Yin et al., 2011).

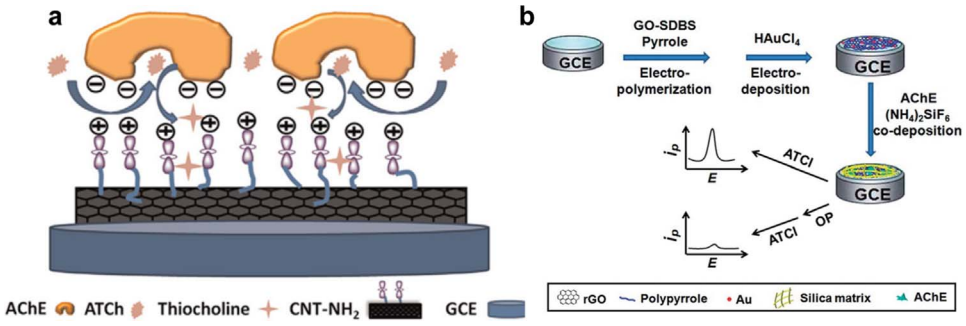

Fig. 4. Detection of pesticides. (a) CNTs based electrochemical AChE biosensors for OPs detection (Yu et al., 2015). (b) Au-PPy-rGO nanocomposite based AChE biosensor for OPs detection (Yang et al., 2014).

inhibitor-OPs (Fig. 4b) (Yang et al., 2014). Dominguez et al. designed a MNPs based sensing surface integrating with an automatic flow based platform to realize regeneration of sensors and on-line monitoring of OPs (Dominguez et al., 2015). Tan and coworkers used metal carbonyl conjugated AuNPs biosensor for detection of glyphosate. The surface of AuNPs was bound by organometallic osmium carbonyl clusters, making the NPs free from biomolecule interference, therefore being utilized as non-interference SERS NPs. In the presence of glyphosate, the activity of AChE mediating the hydrolysis from acetylthiocholine to thiocholine was inhibited. Subsequently, the thiocholine induced the aggregation of metal carbonyl conjugated AuNPs, which caused the color change of NPs solution and variation of intensity of SERS signal (Tan et al., 2017). Chouhan and coworkers detected methylparathion (MP) via CdTe QDs combined with antigen-antibody reaction, free MP and QDs bioconjugated MP showed competitive binding with anti-MP IgY antibodies and the fluorescence intensity of bioconjugated MP was directly proportional to the free MP concentration (Chouhan et al., 2010). Chang et al. developed a single-shot optical biosensor for the detection of paraoxon-ethyl. This biosensor made use of carbon based nanoparticles, commonly known as carbon dots, as sensing receptor. With the addition of paraoxon-ethyl, the strong yellow fluorescence of carbon dots quenched dependent with the concentration of paraoxon-ethyl. The LOD of the biosensor achieved 0.22 ± 0.02 μM (Chang et al., 2017).

5. Veterinary drugs

Veterinary drugs are broadly used to control bacterial infections and prevent the outbreak of diseases of livestock. Furthermore, residues of these drugs and metabolites accumulate in livestock products, such as meat, eggs and milk. Food quality is subsequently affected, causing negative health effects on consumers, such as anaphylactic shock, skin allergies and microbial resistance (Baynes et al., 2016; Reig and Toldra, 2008). In order to obtain safety and high-quality edible tissues, the European Union (EU) has established a set of maximum residue limits (MRLs) for veterinary drugs such as antibiotics, sulfa drugs, furan drugs, coccidiostat, hormone drugs and anthelmintics. The detection of veterinary drugs and residues is of great importance for the food quality control. A variety of nanomaterials-based biosensors have been demonstrated (Table 4).

Verheijen et al. detected streptomycin by using a one-step strip test, basing on the AuNPs coated with monoclonal anti-streptomycin antibodies. Streptomycin conjugated in capture reagent, which was immobilized on the test device, could compete to the streptomycin in the sample to bind to the anti-streptomycin antibodies in detector reagent, resulting in the acquirement of readouts by naked eyes (Verheijen et al., 2000). Ding and coworkers demonstrated an indirect competitive fluorescence-linked immunosorbent assay (cFLISA) for the detection of sulfamethazine (SM_2) in chicken muscle tissue, by using QDs as the fluorescence label coupled with secondary antibody (Ding et al., 2006). The same method could also be applied to detect enrofloxaci (Chen et al., 2009). Ramezani et al. used a fluorescent biosensor based on catalytic recycling activity of exonuclease III (Exo III), AuNPs and FAM-Labeled complimentary strand of aptamer (CS) to detect kanamycin. Without kanamycin, aptamer bound to CS to form a double-stranded DNA (dsDNA) which left the surface of AuNPs. When Exo III was added, aptamer was recycled from dsDNA, increasing the intensity of fluorescence in the solution. Upon addition of kanamycin, aptamer bound to the target and CS remained on the surface of AuNPs, leading to a weak fluorescence emission (Ramezani et al., 2016). Govindasamy and coworkers developed a hybrid electrochemical biosensor that consisted of molybdenum disulfide nanosheets coated on functionalized MWCNT for the determination of chloramphenicol (CAP), a broad-spectrum antibacterial veterinary drug. The nanocomposite modified electrode showed excellent electrocatalytic ability to CAP and performed well in wide linear concentration range from 0.08 μM to 1392 μM (Govindasamy et al., 2017).

Table 4
Biosensors for the detection of veterinary drugs.

Analytes	Biosensors	Nanomaterials	Ref.
Streptomycin	Immuno	AuNPs	(Verheijen et al., 2000)
Sulfamethazine	Fluorescentimmuno	QDs	(Ding et al., 2006)
Kanamycin	Fluorescent	Exonuclease III and AuNPs	(Ramezani et al., 2016)
Chloramphenicol	Electrochemical	MWCNTs	(Govindasamy et al., 2017)

6. Illegal additives

Food safety incidents caused by the abuse of illegal food additives emerged frequently. Overuse or misuse of food additives poses a threat to health and raises concerns about food safety. Typical illegal additives include melamine, clenbuterol and Sudan I. For the detection of these chemicals, various nanomaterials-based biosensors have been developed (Table 5).

Melamine, a trimer of cyanamide that is commonly used in flame-resistant products, textile industries and the production of pesticides, has been intentionally and illegally adulterated in milk, infant formula

Table 5
Biosensors for the detection of illegal additives.

Analytes	Biosensors	Nanomaterials	Ref.
Melamine	Colorimetric	AuNPs	(Ai et al., 2009)
Melamine	Colorimetric	AgNPs	(Ma et al., 2011)
Melamine	Fluorimetric	CdTe-Doped Silica NPs and AuNPs	(Gao et al., 2012)
Clenbuterol	Immunochromatographic	Magnetic nanobeads	(Wu et al., 2014)
Clenbuterol	Immuno	AuNPs	(Kabiraz et al., 2017)
Sudan I	Electrochemical	MWCNTs	(Gan et al., 2008; Mo et al., 2010)
Sudan I	Electrochemical	PtNPs	(Palanisamy et al., 2017)

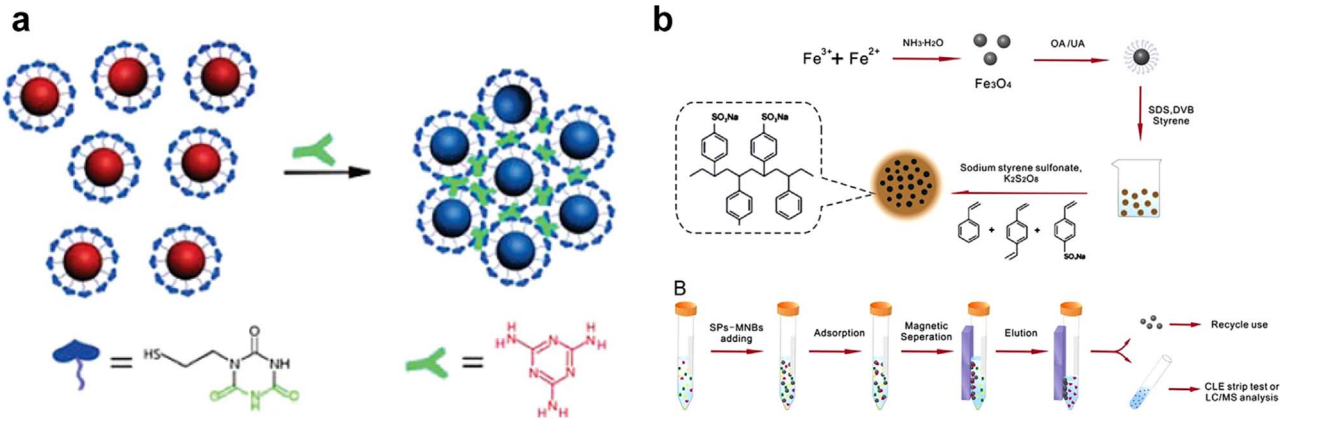

Fig. 5. Detection of illegal additives. (a) MTT stabilized AuNPs for melamine detection (Ai et al., 2009). (b) Magnetic nanobeads coupled with AuNPs for clenbuterol detection (Wu et al., 2014).

and pet foods due to its low cost and high nitrogen content. Ingestion of melamine at levels above the safety limit (2.5 ppm in USA and EU; 1.0 ppm for infant formula in China) induces renal failure and even death in infants (Guan et al., 2009). Therefore, it is of importance to develop a reliable and highly sensitive method to detect trace melamine in food. The traditional approach is chromatography including HPLC (Zhang et al., 2014), GC-MS (Li et al., 2009) and LC-MS/MS (He et al., 2014). Ai et al. developed a colorimetric sensor for on-site and real-time detection of melamine in milk products by using AuNPs modified with 1-(2-mercaptoethyl)-1,3,5-triazinane-2,4,6-trione (MTT). Upon exposure of the MTT-stabilized AuNPs to melamine, hydrogen-bonding recognition between melamine and MTT resulted in the aggregation of AuNPs, inducing the color change from wine red to purple, which was consistent with the change of UV–vis spectra (Fig. 5a) (Ai et al., 2009). Similarly, Ma et al. (2011) used dopamine-stabilized silver NPs (AgNPs) as a colorimetric readout to detect melamine. In their design, melamine bound with dopamine through Michael addition and Schiff base reactions, leading to the aggregation of AgNPs and inducing a colorimetric response from bright yellow to red. Gao and coworkers reported a quantitative method for the determination of melamine in milk via fluorescence energy transfer (FET) system between CdTe QDs (donors) and AuNPs (acceptors). CdTe@SiO2-AuNPs assemblies formed when AuNPs were added into CdTe@SiO_2, and the fluorescence of QDs quenched due to energy transfer. Upon addition of melamine, the fluorescence of CdTe QDs was recovered because of the strong covalent interactions between the amino group of melamine and AuNPs, so that the content of melamine in the sample could be calculated by fluorescence enhanced efficiency (Gao et al., 2012).

Clenbuterol (CLE), also named as brown meat essence, is a banned drug which has been misused as a nutrient repartitioning agent in the livestock industry in the past decades (Prezelj et al., 2003). CLE eventually resided in livestock products, threatening consumers' health. Wu et al. utilized magnetic nanobeads to adsorb CLE via magnetic solid-phase extraction method, realizing efficient clean-up and enrichment of CLE from sample in 30 min after MNPs adsorbing CLE (Fig. 5b), and subsequently detected CLE with AuNPs based immunochromatographic assay (Wu et al., 2014). Kabiraz et al. developed a surface plasmon resonance (SPR) biosensor by using an antibody labeled with AuNPs, combined with an indirect competitive inhibition immunoassay. The immunosensor had an extremely low LOD with 0.05 pg/mL (Kabiraz et al., 2017).

Sudan I is a carcinogen, which has been widely used as food additive, especially in chili powder because of its attractive red color and low cost. Gan and Mo modified the electrode with CNTs thin film to achieve the fast and sensitive detection of Sudan I because of the attractive characteristics of MWCNTs such as strong adsorption properties, good electrical conductivity and large surface area (Gan et al., 2008; Mo et al., 2010). Palanisamy et al. reported a sensitive and low level electrochemical biosensor for Sudan I detection in food samples, by utilizing PtNPs conjugated graphene-β-cyclodextrin modified electrode. (Palanisamy et al., 2017).

7. Conclusions and perspectives

Food safety is undoubtedly one of the major global concerns that human beings have to confront and are continuously fighting for. In this review, we clearly show the prominent performance of nanomaterials-based biosensors in the detection of food contaminants, whereas which is still at the nascent phase. We summarize the representative nanomaterials used in biosensors for detection of food contaminants including food pathogens/toxins, heavy metals, pesticides, veterinary drugs and illegal additive. We aim at stimulating a broader interest in developing nanomaterials-based biosensors and improving their applications in food safety detection. We hope to provide a bridge to connect the gap between food science and nanotechnology, thus with collaborative endeavors of scientists/engineers in both fields, more novel nanomaterials-based biosensors will be designed and new solutions will spring up. At last, we emphasize that a general concern regarding biosafety of nanomaterials might not be a problem due to the in vitro nature of food safety detection.

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