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Review

Recent advances in biosensors for antibiotic detection: Selectivity and signal amplification with nanomaterials

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ABSTRACT

Antibiotics are widely used in the prevention and treatment of infectious diseases in animals due to its bactericidal or bacteriostatic action. Residual antibiotics and their metabolites pose great threats to human and animal health, such as potential carcinogenic and mutagenic effects, and bacterial resistances. Therefore, it is necessary and urgent to accurately monitor trace amounts of antibiotics in food samples. Up to now, many analytical methods have been reported for the determination of antibiotics. Biosensors with the advantages of high sensitivity, rapid response, easy miniaturization, and low price have been widely applied to the detection of antibiotics residues in past decades. This review offered an in-depth evaluation of recognition elements for antibiotic residues in diverse food matrices. In addition, it presented a systematical and critical review on signal amplification via various materials, focusing on recently developed nanomaterials. Finally, the review provided an outlook on the future concepts to help upgrade the sensing techniques for antibiotics in food.

1. Introduction

Antibiotics play an important role in the treatment of diseases caused by bacterial infections. Due to a lack of comprehensive knowledge, antibiotics are regarded as “panacea”, resulting in unreasonable use even abuse in animal husbandry and medical industries. Improper use of antibiotics in clinical practice could change the function of certain organs and damage the nerve, kidney and blood system. It is more harmful for children, the elderly and patients with renal insufficiency. The abuse of antibiotics can also cause the production of drug-resistant super bacteria, posing a huge threat to global health. In addition, the abuse in aquaculture industry may lead to residues in animal-derived foods. Therefore, it is necessary and urgent to accurately detect trace antibiotics in complex matrices such as food and biological samples. So far, many analytical methods for antibiotics detection have been reported, such as high performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA) and sensor. Nevertheless, the application of these methods is usually restricted due to low selectivity, high consumption of time, and expensive apparatus requirement. The sensor, with the advantages of high sensitivity, rapid response, easy miniaturization and low price, has become available methods for antibiotic detection. When detecting antibiotic residues in food and biological samples, biosensors not only maintain the advantages of high specificity and sensitivity with simple assay, but also are ultra-portable. Therefore, biosensors have been widely used in real-time monitoring antibiotic residues.

The device of the sensor mainly includes a recognition element for selective identification of the target, and a transducer for signal conversion and amplification. Receptors, as molecular recognition elements in biosensor, could specifically bind to analytes, thereby resulting in highly specific detection, which also determine the important performance of biosensor–selectivity. The most common biological receptors are organic substances with biological recognition ability, such as antibodies(El-Moghazy et al., 2018), molecularly imprinted polymers (MIPs) (Ayankojo, Reut, Ciocan, Öpik, & Syritski, 2020), and nucleic acids(Gai, Gu, Hou, & Li, 2017). In addition, biological systems, including cells or organisms(Poghossian et al., 2018), are also reported as specific recognition elements. Besides selectivity, sensitivity is another important indicator of biosensor performance. In order to achieve sensitive detection, a variety of signal amplification strategies, including molecular biotechnology, enzyme-catalyzed reactions and nanomaterials, have also been used to construct antibiotic biosensors.

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Among them, nanomaterials have attracted much attention because of good thermal conductivity, excellent mechanical strength and stability, high specific surface area, fantastic photoelectric properties and superior electronic conductivity(F. Zhang, Ma, Huang, & Li, 2020; Zhou et al., 2019; Zhu et al., 2020). Nanomaterials could not only amplify significantly the signals of various types of biosensors, but also enhance the interaction between analyte and receptor due to high specific surface area. In view of the huge potential of nanomaterials in sensing applications, more and more studies have reported their application in biosensors. Until now, various biosensors based on signal enhancement of nanomaterials (such as electrochemical sensors, fluorescence sensors, and surface plasmon sensors) have been developed for rapid and sensitive detection of antibiotic residues.

The recent advances in electrochemical biosensors and whole-cell based biosensors for antibiotic detection have been summarized by a few authors, reviewing MIPs as the selective recognition elements in electrochemical sensing(Gui, Jin, Guo, & Wang, 2018), application of electrochemical biosensors in different kinds of antibiotics detection (Majdinasab, Yaqub, Rahim, Catanante, Hayat, & Marty, 2017), or nanostructured electrochemical platforms for antibiotic detection(Joshi & Kim, 2020). There was also a review that delivered an overview of whole-cell based biosensors, mainly focusing on the application of screening antibiotic residues in various matrices(T. Chen et al., 2017). However, there is still a requirement for a systematical and comprehensive overview of the selectivity and signal amplification strategies with nanomaterials for antibiotic-biosensors. Consequently, this review summarized the molecular recognition elements commonly used in biosensors for antibiotic detection, and focused on the application of nanomaterials in biosensing platforms. To this end, this article also described methods how to use different nanomaterials to design high-performance biosensing platforms for achievement of signal enhancement and effective detection of antibiotics in different matrix with diverse conversion elements. In addition, this review discussed in depth the current challenges of biosensors in the detection of antibiotics and the methods how to further improve the detection performance of biosensors. The concepts introduced in this review are expected to motivate new findings towards nanomaterials and recognition elements assisted biosensors for small molecule detection in the future.

2. Selectivity of antibiotic biosensors

Molecular recognition elements are the main determinants of biosensor specificity. Antibiotics are classic small molecule substances, and their molecular recognition elements mainly include antibodies, aptamers and MIPs, etc. The specific molecular recognition element combined with the corresponding sensing platform can achieve high specific detection in the complex matrices, which is the key of effective biosensors.

2.1. Antibody

Antibodies based methods can provide high reliability, selectivity, and detectability for analysis of many kinds of antibiotics. Pinacho et al. (Pinacho, Sánchez-Baeza, Pividori, & Marco, 2014) presented an amperometric magneto-immunosensor for the detection of fluoroquinolone antibiotics residues in milk samples. In this immunosensor, the antibody biomodified magnetic beads are captured by electrodes made of graphite-epoxy composite containing magnets, which act as transducer for the electrochemical detection. Although the matrix of milk is complex, the use of magnetic beads can effectively eliminate potential interferences, combining with the specific antibody to achieve high selective assay. Results obtained by Tomassetti et al.(Tomassetti et al., 2016) demonstrated the superiority of sandwich geometry (first molecule of immobilized antigen–antibody—second antigen molecule) as the best format of surface plasmon resonance (SPR) immunosensor. From the data of the selectivity tests, other tested antibiotics, including those of very different classes and similar structures to the class of β-lactam, exhibited no potential interferences. As shown in Fig. 1(A), an electrochemical immunosensor based on anti- chloramphenicol was constructed, which displayed a high specificity to chloramphenicol without secondary antibodies. No cross-reactivity was observed with other tested antibiotics(El-Moghazy et al., 2018). For certain applications such as the control of commercial pharmaceutical specialties, antibody should be combined with some signal amplification to obtain higher sensitivity since the molecular weights of antibiotic always are small. For example, chloramphenicol with molecular weight of 323.13 is a hapten, is not able to stimulate an animal to produce an antibody, and Li's group(P. Li, Yu, Zhao, Deng, & Li, 2020)employed diazotization method to prepare the immunogenicity chloramphenicol-protein conjugates as capture probes.

Polyclonal antibodies are produced by a series of immune cells, which can bind antigens at different epitopes and have different binding affinities. Therefore, they have low specificity and are prone to production of cross reactions. At the same time, due to the differences of antibody among batches, the detection repeatability and reproducibility are not good. Monoclonal antibodies are produced by a single parent cell and have affinity for the same epitope of the same antigen, while they have the disadvantages of relatively high cost, thermal instability, and limited targets. In addition, the antibody has a short shelf life and is not easy to be chemically modified. As a result, it is limited in the package way with the sensor platform.

2.2. Aptamer

SELEX (systematic evolution of ligands by exponential enrichment) is a classical process to obtain specific aptamer. As the specific oligonucleotide strands, Aptamers can bind to the analytes with high selectivity and affinity. Compared with traditional antibodies, aptamers have the unique features of relatively small size, simple synthesis, easy functionalization, and excellent chemical stability during long-term storage, which makes them desired receptors and sensing elements for constructing sensors.

The single-stranded DNA (ssDNA) aptamers can be adsorbed on the surface of gold nanoparticles (AuNPs) by the electrostatic forces. The aptamers could remain a stable state, even in high salt concentrations when attached on the AuNPs surface. Seo et al.(Seo, Kwon, Lee, Cullen, Noh, & Gu, 2015) presented a reflectance-based colorimetric aptasensor using AuNPs for the detection of oxytetracycline, which has the features of simple operation and easy detection with naked eyes. The study confirmed that, in spite of the structure of oxytetracycline similar to tetracyclines, the signal response occurred only for oxytetracycline, not for tetracyclines or other antibiotics with similar structures. Taghdisi et al.(Taghdisi, Danesh, Nameghi, Ramezani, & Abnous, 2016) also designed a fluorescent aptasensor for selective detection of streptomycin based on Exonuclease III (Exo III), SYBR Gold and aptamer complimentary strand. In the absence of streptomycin, the fluorescence intensity was weak. Upon addition of streptomycin, it was specifically recognized by the 79-nucleotide (nt) aptamer, leading to the release of complementary strand from aptamer and more protection against Exo III function. Following addition of SYBR Gold, strong fluorescence intensity was obtained. Cao's group(K. Zhang, Gan, Hu, Chen, Li, & Cao, 2018) employed gold stirring bars modified with many AuNPs with high specific area to modify aptamers for antibiotic detection, which could realize enrichment of the target and phase separation simultaneously. As a result, the matrix interference was obviously reduced.

Enzyme biofuel cells (EBFCs) have attracted considerable attention due to their mild operating conditions and application prospects as implantable power sources. A self-powered EBFCs aptasensor was constructed for ampicillin determination, with the advantages of simple instrumentation, low cost, anti-interference ability, excellent selectivity, good stability and featured excellent selectivity owing to high specificity of the aptamer(Gai et al., 2017). Chinnappan et al.(Chinnappan, Eissa,

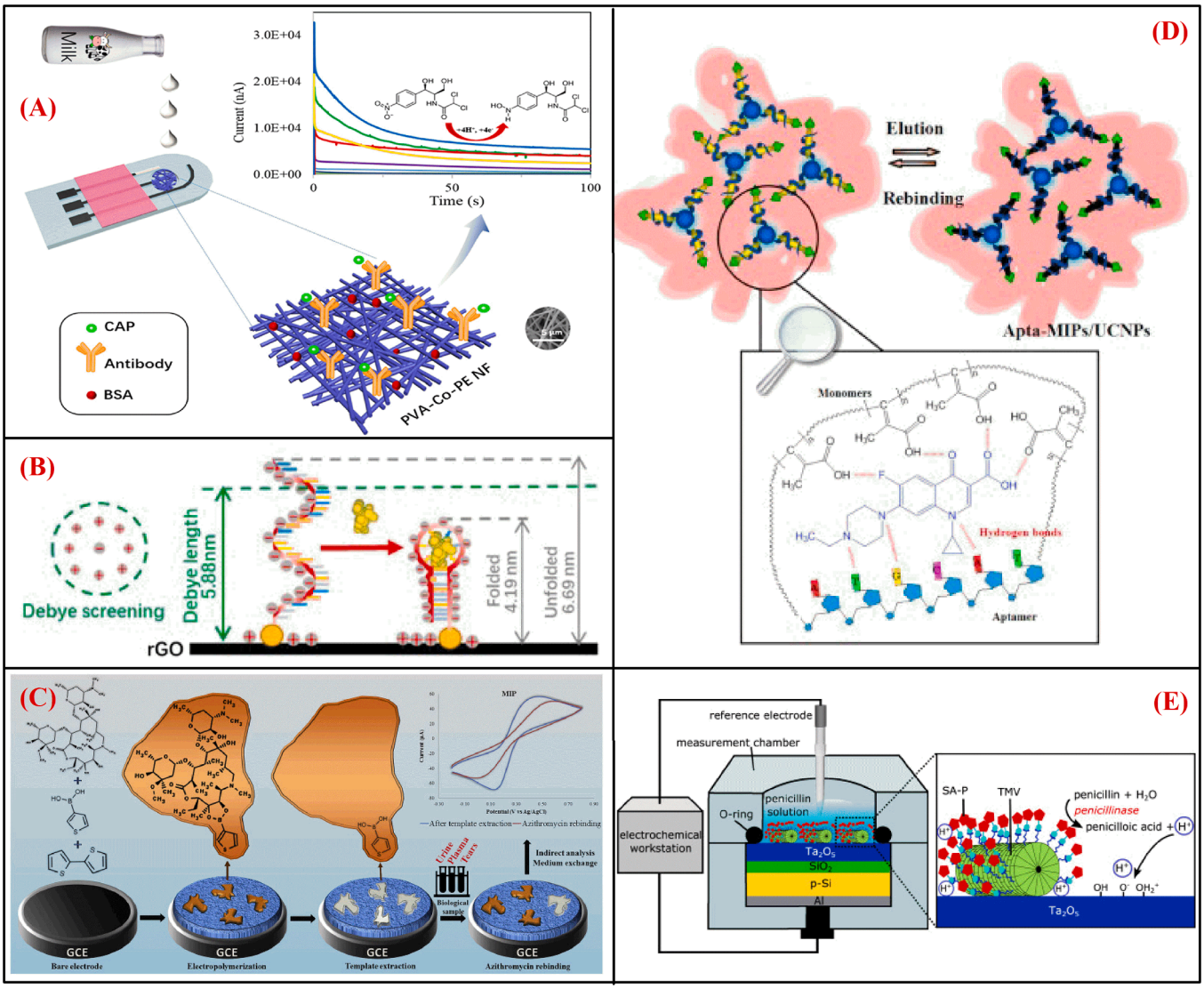

Fig. 1. Schematics of (A) antibody-based, (B) aptamer-based, (C) MIP-based,(D) dual recognition system, and (E) TMV-based sensors fabrication and their use for antibiotics analysis(X. Chen et al., 2019; El-Moghazy et al., 2018; X. Liu et al., 2017; Poghossian et al., 2018; Stoian et al., 2020).

Alotaibi, Siddiqua, Alsager, & Zourob, 2020) selected DNA aptamers against azlocillin using SELEX method, and characterized sociation constant of the selected aptamer (55 nM) with fluorescence-binding assays. This aptamer was employed to estabilish a competitive voltammetric aptasensor for azlocillin determination with a limit of detection (LOD) of 1.2 pg/mL as well as remarkable selectivity against potential interfering agents.

Raw aptamer sequences screened by SELEX, typically with the length of 70–130 nt, are usually too long to be suitable for practical application, which not only increases the cost of aptamer-based detection, but also induces uncertainty in 3D conformation and results in compromise affinity for targets in different solution systems. Therefore, truncation of aptamers in post-SELEX process is a critical step to obtain efficient aptamers. Nie et al.(Nie, Yuan, Jin, Han, Tian, & Zhou, 2018) obtained an aptamer of only 15 nt specific for tobramycin through rational truncation of a previously reported one. The K_d value of 42.12 nM indicates high affinity of this aptamer to tobramycin. The aptamer with the shortened length offers low cost and comparatively robust characteristics in application. The truncation strategy proposed in this study can also be utilized to obtain optimal aptamers for other analytes through post-SELEX process.

In order to further enhance the selectivity of sensor for antibiotic detection, Chen et al.(X. Chen et al., 2019) designed a RNA-aptamer electrochemical sensor with 6-mercapto-1-hexanol (MCH)/1-pyrenebutanol (PBA) blocking layer (BL) for structure optimization (Fig. 1 (B)). The results suggested that this blocking treatment effectively eliminated the nonspecific adsorption and improved the reliability and selectivity of the aptasensor.

Compared with antibodies, aptamers not only have the same or even higher sensitivity and selectivity, but also possess better stability and could be synthesized on a large scale. In addition, aptamers are easily modified by various functional groups, leading to excellent compatibility with biosensing platforms. However, the screening process of aptamers requires sophisticated equipment, and the required reagents are expensive. When the aptamer is employed in the detection of different matrix samples, its secondary structure may change, thus affecting its specific recognition ability.

2.3. *Molecularly imprinted polymers*

Molecularly imprinting polymers (MIPs) provide receptor-specific recognition and binding sites for a target analyte. MIPs are an excellent alternative material which has the advantages of easy preservation and good stability. Coating MIPs on nanoparticles could increase the

surface area-to-volume ratios and improve the target-binding kinetics. Chao et al.(Chao, Hu, & Chen, 2014) developed a fluorescent sensor based on CdTe quantum dots (QDs). In this study, MIPs–QDs composite, synthesized by the chain-growth polymerization of methacrylic acid (MAA) and an allyl mercaptan linker, was utilized as receptor to detect tetracyclines in bovine serum albumin and fetal bovine serum. The recoveries were 96% ($n = 5$, RSD = 3.6%) and 91% ($n = 5$, RSD = 4.8%), respectively, more accurate compared with the bare QDs materials used for the fluorometric tetracycline detection (recoveries of 135%, $n = 5$, RSD = 13.8%)(Poderys, Matulionyte, Selskis, & Rotomskis, 2011). MIPs–MAA–QDs composite, a material with higher specificity for tetracycline, possessed greater interactions between the template and its imprinted cavities than other MIPs–QDs in the simple phosphate buffer. Khataee's group(Jalili & Khataee, 2020; Jalili, Khataee, Rashidi, & Razmjou, 2020) combined MIPs with ratiometric fluorescent sensor that contained different colored carbon dots (CDs) as dual fluorophores for the detection of penicillin G and chloramphenicol residues, respectively. And their results exhibited that these ratiometric fluorescent sensors were promising in the in-situ antibiotic detection in milk. MIPs could also be applied in electrochemical biosensor. Li et al.(Y. Li et al., 2015) employed in-situ electro-polymerization to synthesize MIPs on the surface of gold electrode, so that a polymeric layer could easily grow directly on an electrode, and its thickness was controlled by adjusting the synthesis conditions. This method can achieve miniaturization of the sensor architecture with good reproducibility and rapid response. These methods were simple and could detect target antibiotics selectively. However, the insufficient adsorption capacity of MIPs system affected the performance of the sensor.

MIPs film (namely 2D MIPs system), prepared by fixing template molecules on 2D nanometer film, has high specific surface area. What's more, most template molecules are located on or near the surface of MIPs, which improves the binding ability of MIPs, and increases the probability of template entering the recognition site. Stoian et al.(Stoian et al., 2020) reported that reversible boronate ester bond-mediated, thin (~75 nm) MIPs-based biomimetic recognition layer, was electrodeposited in non-aqueous media onto the surface of a glassy carbon electrode (Fig. 1(C)). As it turned out, the sensor exhibited remarkable selectivity over a large number of structurally related and non-related antibiotics while employing indirect electrochemical determination in the presence of 10 mM ferro/ferricyanide as redox probe. Subsequently, they constructed a MIPs-based biomimetic electrochemical sensor for highly selective determination of azithromycin in biological fluids. This MIPs-based sensor could ensure the required thermodynamically and kinetically stable interactions between the functional monomer and the template molecule, due to the benefits of the covalent imprinting strategy via reversible boronate ester bonds. More recently, Ayankojo et al.(Ayankojo et al., 2020) integrated MIP films with screen printed electrode for electrochemical determination of erythromycin. And this sensor exhibited strong selectivity for erythromycin, both in buffer and environmental tap water samples, as against non-closely related antibiotics, demonstrating appreciable discrimination against very close analogue of the target. 2D colloidal array was also utilized as the platform to prepare OTC imprinted hydrogel film(Y. Wang et al., 2019). The surface of the resulting 2D-MIPs film has a monolayer with highly ordered spheres, which exhibits great optical diffraction and can be visually observed following the Bragg diffraction law. Furthermore, the use of nanotubes as molecularly imprinted microreactors can overcome the shortcomings of traditional MIPs templates such as incomplete elution, weak adsorption capacity, low mass transfer efficiency and irregular shape of materials. 3D MIPs system, constructed with 3D porous nanomaterials covered by an ultrathin MIP film, possessed a hierarchical porous structure and high surface area, thus could enhance detection performance. In consequence, Munawar et al.(Anam Munawar, Tahir, Shaheen, Lieberzeit, Khan, & Bajwa, 2018) functionalized carbon nanotubes (CNTs) with amino groups to generate reaction centers for the deposition of copper nanoparticles (CuNPs), and employed the resulting CNTs@CuNPs to design a nanohybrid material of MIP. Their research results successfully demonstrated the electrochemical sensor, which was designed based on a 3D CNTs@CuNPs@MIPs for chloramphenicol detection, delivered both superior sensitivity and selectivity.

In order to investigate the adsorption capacity and binding kinetics of MIPs, a large number of relevant studies have been conducted. An enrichment imprinted crystalline colloidal array (ICCA) was developed for chloramphenicol determination based on the wettability difference enrichment process(Sai, Wu, Yu, Sun, & Huang, 2016). In this assay, a 3D MIPs spheres array were inserted in a polydimethylsiloxane (PDMS) matrix to surround each hydrophilic MIPs sphere in a hydrophobic PDMS surrounding, thus providing a large HP interaction area. Thereby, the targets of interest can be efficiently enriched into the ICCA from the highly diluted solution, and were specifically captured by the MIPs microgel spheres to sensitively induce measurable optical signals based on the change of ICCA structure. Moreover, Okan et al.(Okan, Sari, & Duman, 2017) synthesized ciprofloxacin imprinted nanoparticles about 160 nm with high mono dispersity using mini emulsion polymerization technique. The results indicated that MIPs based nano-sensor has high selectivity and accuracy for ciprofloxacin detection. However, the sensitivity of this sensing platforms could be further increased by changing the immobilization strategy of MIPs nanoparticles, since blocking several groups during EDC/NHS activation might affect the sensitivity of the system.

The integration of nano-MIPs as synthetic affinity receptors into sensor devices has made a significant effect to the bio-assay field. Altintaset(Altintas, 2018) employed computational simulations and polymer composition to synthesize nano-MIPs targeting vancomycin. Subsequently, the synthetic receptors were employed for the establishment of SPR sensor for vancomycin assay in milk samples. Owing to nano-MIPs targeting vancomycin designed with computational simulations, the experimental screening time in the laboratory was reduced enormously. In order to quantify trace templates in complex samples accurately, MIPs of neomycin, containing both imprinted cavity and boronate affinity site, were synthesized on the surface of silica-modified QDs(Wan et al., 2018). This MIPs were applied in fluorescent chemosensor to realize rapid and high through-put neomycin monitoring in food and biological samples.

As a universal carrier material, MIPs have impressive versatility and practicality. In order to achieve accurate molecular recognition and adsorption, MIPs could be designed as complex functional substrates or coatings at different scales. How to improve the effectiveness of MIPs material is still a key for expanding application in antibiotic sensors. A large number of materials and methods could be utilized to achieve imprinting effects due to the designable ability of MIPs. However, how to evaluate the effectiveness of the materials and methods, and how to obtain MIPs with strong affinity are major focuses of MIP-based sensor development.

2.4. Dual recognition system

The selectivity of single recognition system might be compromised for the detection of samples with complex matrices. In order to achieve enhanced selectivity, dual recognition system in combination of MIPs with DNA aptamers was employed to construct electrogenerated chemiluminescence (ECL) sensor for lincomycin detection(Shuhuai Li, Liu, Yin, Zhang, Luo, & Wu, 2017). The ECL tests exhibited only minor changes (relative deviation < 5.0%) with or without addition of several other common veterinary drugs. Thus, drugs with similar structures to lincomycin are not identified by the dual recognition assay, strongly suggesting good selectivity of the aptamer-MIP sensor for lincomycin. A luminescent "dual recognition" sensor for the detection of enrofloxacin was also reported(X. Liu et al., 2017). In this study (Fig. 1(D)), the "dual recognition" imprinting cavities were built after removal of enrofloxacin, displaying recognition properties superior to that of traditional

molecularly imprinting or aptamer alone. Another feature of this strategy was simultaneous recognition and signal conversion by fabricating "double recognition" receptor onto the surface of up conversion nanoparticles (UCNPs) to form a hybrid sensing system of aptamer-MIP/UCNPs. However, both the stability of the DNA aptamer and the imprinted capacity in the sensor need further improvement.

2.5. Other recognition elements

Virus particles have been recognized as a very attractive nanometer-sized scaffolds for high-density immobilization of biomolecules (in particular, enzymes) in biosensing events. The *Tobacco mosaic virus* (TMV) surface possesses thousands of regularly positioned sites capable of coupling with various (bio-)chemical recognition elements. Modification of TMV particles with various functional molecules can enhance the detection selectivity towards the particular analyte of interest. It was shown that in comparison to conventional immobilization methods, the binding of enzymes on virus particles can provide an increased enzyme loading and enhanced reusability of sensors(Koch, Poghossian, Schöning, & Wege, 2018; Koch et al., 2015). TMV particles functionalized with recognition molecules can be easily integrated with different transducers, thus opening new opportunities for biosensing. Recently, a field-effect biosensor employing TMV particles as scaffolds for enzyme immobilization was successfully applied for penicillin detection in bovine milk samples (Fig. 1(E))(Poghossian et al., 2018). The biosensors possessed a LOD of 50 μM and a remarkable long-term stability. Repeated test one year later showed that the sensor performance was fully maintained. The results suggested a great prospect of an integration of electronic transducers with virus/biomolecule hybrids, thus providing new opportunities for novel label-free biosensing technique. However, this method sometimes had the defects of low specificity and slow response. Future experiments should be aimed at testing biosensors modified with TMV nanotubes with several other enzymes, which can enable simultaneous detection of multiple analytes, and improve the selectivity of the whole-cell biosensors.

It is well known that photonic crystal is an optical sensing material. However, the recognition groups attached to photonic crystal can achieve specific detection for some antibiotics. Ciprofloxacin contains piperazine group which can react with *o*-benzoquinone through Michael addition reaction. Based on this reaction, photonic crystal was utilized for pretreatment-free and label-free detection of ciprofloxacin(Y. Song et al., 2018). The recognition process was carried out by the Michael addition reaction between the piperazine group of ciprofloxacin and the *o*-benzoquinone group on the photonic crystal within 15 min. The ciprofloxacin-spiked fish farming water was detected by both the photonic crystal and LC-MS-MS methods, and the results demonstrated that this sensor presented good accuracy. The recognition groups, *o*-benzoquinone groups, can be easily attached to the photonic crystal through polymerization and oxidation, and very small amounts of organic solvents are used during both the preparation and the detection. This approach possesses promising prospects in food safety test, environmental monitoring, medicine analysis, and clinical diagnosis.

Another alternative recognition element for trace antibiotics detection is the microbial whole-cell, genetically engineered to generate a quantifiable signal in the presence of specific antibiotics. It demonstrated that *E. coli* strain harboring a plasmid-borne fusion of the *E. coli* recA gene promoter could specifically sense ciprofloxacin in milk, with a LOD of 7.2 ng/mL(Lu, Kao, Belkin, & Cheng, 2019). The shelf-life of the bacteria inside the chip is an important property of the whole-cell sensing system. Future efforts should be focused on the shelf life extension of immobilized bacteria.

In addition, Wang's study(J. Wang, Zha, Qin, & Ni, 2020) reported that Zn-MOFs could emit strong violet light at 445 nm under the excitation of 323 nm UV light, and the violet emission could be strongly quenched by some aromatic nitrophenols. Based on these findings, the researchers applied the as-obtained fluorescent Zn-MOFs for detecting antibiotic metronidazole in aqueous systems without the matrix interference. Nevertheless, the possibility of application in the samples with complex matrices remains to be investigated.

With continuous development of biochemistry, more and more molecular recognition elements can be used in sensors for antibiotic detection. However, food and biological samples usually contain a variety of interfering substances (proteins or carbohydrates), which may hinder the specific recognition of the target and the receptor. The traditional physical adsorption method for fixing recognition elements is characterized by poor stability and low sensitivity in capturing the target. In order to solve this issue, it is necessary to modify the surface of the sensor, which would enhance the stability of the recognition element and improve the specificity of the sensor. Therefore, the sensor can be better applied to high specific detection in complex samples.

3. Signal amplification

Sensitivity, as another key requirement of effective biosensors, is mainly affected by the types of bio-sensitive materials. Many kinds of sensors such as fluorescence sensors, electrochemical sensors, and SPR senor have been developed and widely applied in antibiotic detection because of their high sensitivity. With the gradual maturity of nanomaterial synthesis technique, more and more kinds of nanomaterials are employed as sensitization materials for sensors.

Many nanomaterials such as metal nanomaterials, silica nanoparticles, and carbon nanomaterials have been used in the construction of biosensors due to their ability to increase response speed and improve sensitivity. In recent years, scholars have developed fluorescent biosensors, colorimetric biosensors, electrochemistry biosensor and SPR biosensors based on nanomaterials for the detection of antibiotic residues in animal-derived foods, providing an effective approach for the miniaturization of biosensors as well as the rapid and sensitive detection of antibiotic residues.

3.1. Fluorescent sensors

Fluorescent sensors are widely applied in the fields of chemistry and biochemistry due to their excellent sensitivity, good selectivity, and adjustable fluorescence. In recent years, it has been demonstrated that fluorescent nanomaterials, with the advantages of high fluorescence quantum yield, good light stability, excellent water solubility and biocompatibility, could significantly improve the analytical performance of fluorescent sensors. At the same time, with the further improvement of nanomaterial synthesis technique, the size and function of nanomaterials can be controlled precisely, which can significantly improve the application prospects of nanomaterials in fluorescent sensors.

3.1.1. Quantum dots

Many quantum dots (QDs) and their derivatives have been successfully applied as fluorescence probes to detect ions, enzymes, proteins, and cells. Compared with organic dyes, Carbon quantum dots (CQDs) with sizes below 10 nm and strong fluorescence emission are excellent in terms of environmental friendliness, toxicity, simple synthetic routes and low cost. Akhgari et al.(Akhgari, Samadi, & Farhadi, 2017) proposed a method based on the complexation reaction between cefixime (CEF) and palladium ion (Pd (II)) in the presence of acidic buffer solution (pH = 4). The results suggest that the absorption of Pd (II)-CEF composite overlapped with the excitation spectra of the synthesized CQDs. Then, the fluorescence intensity of CQDs was decreased in the presence of CEF and Pd(II) through the inner filter effects. Since the changes in the absorbance of the absorber can be translated into exponential changes in fluorescence of the fluorophore, an enhanced sensitivity and decreased detection limit was obtained. In addition, fluorescence detection based chemical sensing was proved an extremely outstanding strategy to detect analytes fast and efficiently in recent

decades. As shown in Fig. 2(A), Xu et al.(Z. Xu, Wang, Liu, Yan, Ren, & Gao, 2020) fabricated a dual-channel fluorescence sensor array based on two CQDs to distinguish four tetracyclines, including tetracycline, oxytetracycline, doxycycline, and metacycline. Through applications of machine learning methods such as linear discriminant analysis (LDA) and support vector machine (SVM), four tetracyclines can be effectively differentiated at 1.0 μM. What's more, this sensor array can remarkable differentiate the individual tetracyclines and binary mixtures. Jia et al. (L. Jia et al., 2021) also developed a fluorescent stick-like nano-sensor, by integrating natural nano-clay (Atta) and CQDs, for tetracycline detection with the LOQ of 8.7 nM. In this study, a logic gate for semi-quantitation of the concentration of tetracycline was designed, which made it possible for the application of the nano-sensor in the field of smart devices.

Fluorescent MIPs (fMIPs) using QDs to give fluorescent signal have also attracted considerable attentions in recent years. The QDs-based fMIPs combine the outstanding fluorescent properties of QDs and the high selectivity of MIPs. Silica-modified QDs (QDs@SiO_2) is able to eliminate QDs coagulation during MIP polymerization and allow precise control of the thickness of the silica shell ,so that to acquire better binding properties of MIPs. In parallel, the silica shell was optically transparent and could improve the photostability of QDs. When combined with a fluorescent microplate reader, the QDs@SiO_2fMIP sensor showed a good linear concentration-dependent fluorescence quenching in response to neomycin in the range of 2–1000 g/L, with a LOD of 0.16 g/L(Wan et al., 2018).

In summary, QDs have a wide range of excitation wavelengths, so they are suitable for use as fluorescent materials. Meanwhile, when QDs are excited, a narrow distribution of fluorescence emission peaks can be obtained. In addition, different QDs can be excited at the same time, and their emission spectra will not interfere with each other in spite of their different spectral characteristics, which is beneficial for multi-antibiotic detection in food or environmental samples(Jalili & Khataee, 2020). QDs also have the advantages of high fluorescent intensity and biocompatibility. Nevertheless, there are still many problems in the application of QDs as fluorescent biomaterials. For example, quantum dots are difficult to be well coated. As a result, their fluorescent signals are easily quenched. Therefore, it is very important to find an appropriate coating method for QDs. Moreover, it is also crucial to improve the specific binding effect of QDs and biomolecules.

3.1.2. *metal–organic frameworks*

As a new class of porous crystalline materials, metal – organic frameworks (MOFs) are synthesized with organic ligands and different metal clusters, and have been applied as a potential energy and charge transfer media. Compared with conventional organic dye molecules or QDs fluorescent sensors, Lanthanide metal–organic frameworks (Ln-MOFs) have superior luminescent behaviors with high color, purity long lifetime and intense sharp emissions in the near-infrared and visible regions, Zhang et al.(Feng Zhang, Yao, Zhao, Li, Zhang, & Yang, 2017) developed an effective luminescence sensor based on Ln-MOFs incorporated with mixed matrix membranes (MMMs) for sensitive detection of nitrofuran antibiotics (Fig. 2(B)). As the results showed, MOFs used as filler particles in MMMs applications could significantly improve the selectivity and permeability of sensor. Blue-emitting CQDs (B-CQDs), green-emitting CQDs (G-CQDs) and the mixture (m-CQDs) providing

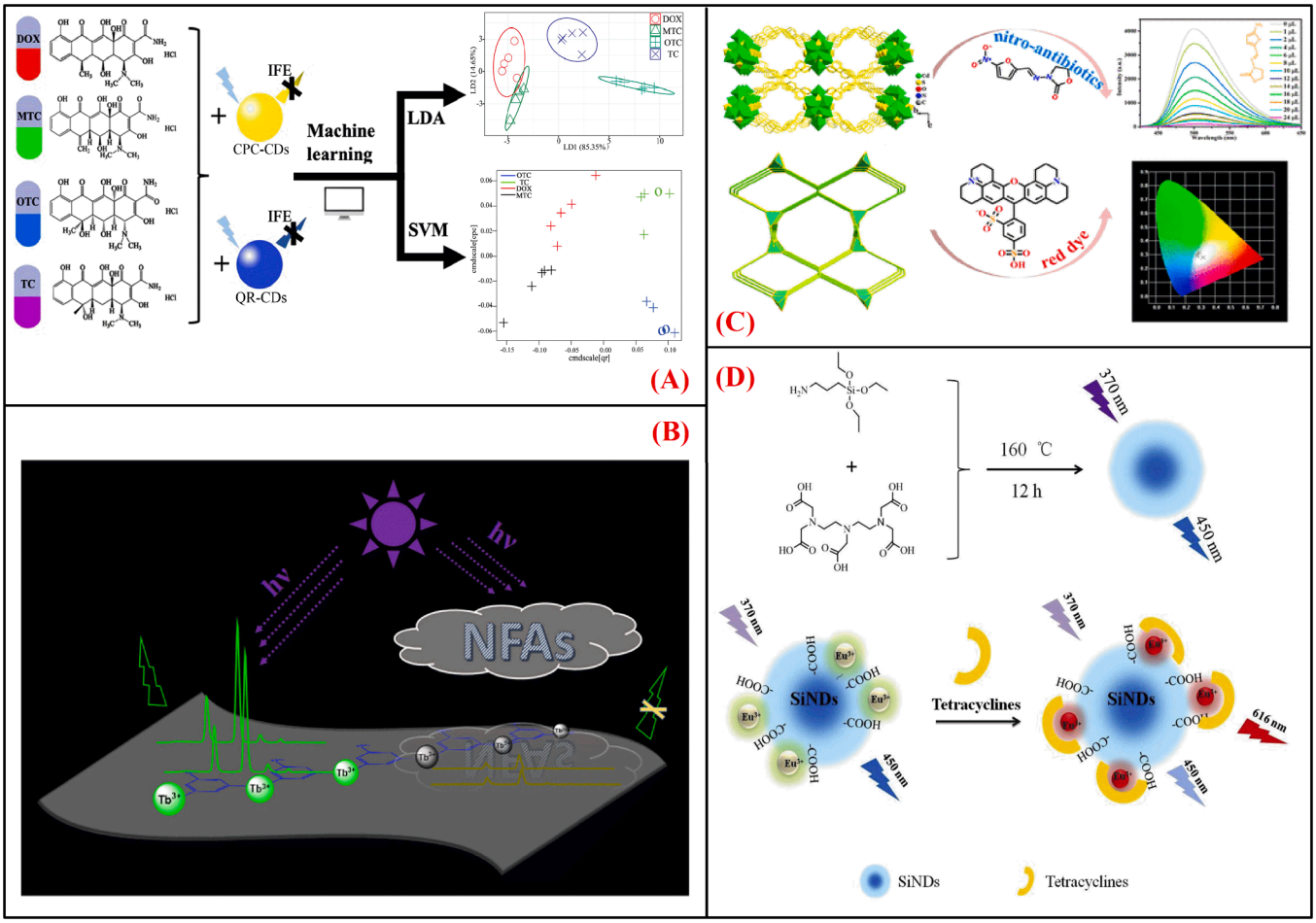

Fig. 2. Antibiotics-fluorescent sensing mechanisms based on (A) QDs, (B) Ln-MOFs, (C) 3D MOFs, and (D) SiNDs-Eu^{3+}(Wei et al., 2019; Z. Xu et al., 2020; Feng Zhang et al., 2017; Zhao et al., 2019).

four emission peaks were employed as four sensing elements to construct a quadruple-channel fluorescent sensor array, which could achieve the detection of four kinds of tetracyclines at a low concentration of 1 μM(Long et al., 2019). This fluorescent sensor array performs well in distinguishing binary mixtures and could distinguish four kinds of tetracyclines efficiently in milk. However, the fluorescence intensity of Ln-MOFs is usually adynamic. Xiong et al.(Xiong, Yang, Gao, Zhu, Chen, & Tan, 2019) employed 1H-1,2,4-triazole-3,5-diamine (Hdatrz) to improve the fluorescent behavior of europium -MOF (Eu-MOF) and equipped Eu-MOF as a dual mode probe for ratiometric fluorescent sensing of berberine hydrochloride and tetracycline. This strategy eliminated the interferences of system noise and source instability and achieved the visual sensing of target analytes for obvious fluorescent signal in aqueous solution. In addition, Li et al.(C. Li et al., 2020) developed a Ln-MOF sensor for immediate detection of oxytetracycline and tetracycline. The sensing can be accomplished immediately and visualized by the naked eyes, making it a superior candidate to monitor target analytes in actual application with LODs of oxytetracycline and tetracycline at 1.95 and 2.77 nM, respectively. When Ln-MOF is excited by the excitation light, the organic ligand coordinates with the rare earth ion absorbs energy, and the ligand molecule efficiently transfers the energy to Ln^{3+}, which can emit strong and sharp characteristic fluorescence. If the sensitization efficiency is low, the fluorescence emission peaks of ligand and Ln^{3+} may appear at the same time, which would decrease the sensitivity of sensor. Therefore, the selection and design of organic ligands are crucial for the synthesis of Ln-MOF.

Due to sheet structures and ultrathin thickness, two dimensional MOFs (2D-MOFs) exhibit a large number of unique properties different from traditional bulk MOFs. Cu-TCPP nanosheets, as one of novel nanosheets, was applied in fluorescence resonance energy transfer (FRET) aptasensor In this study, Cu-TCPP nanosheets were utilized to quench the background fluorescence, and circular strand replacement DNA polymerization (CSRP) was used for signal amplification. The results confirmed that the established sensor provided negligible background signals and 7.5-fold improved S/N compared with a graphene oxide (GO)-based FRET aptasensor(Q. Yang et al., 2018). The segmentation and confinement effect of MOFs could dimmish sharply the aggregation-caused quenching and exciton − exciton annihilation process of organic dyes. As Fig. 2(C) demonstrated, the two dimensional MOFs (2D-MOF), $[Cd_7(SO_4)_6(tppe)_2]$ $(2DMF{\cdot}2H_2O)$, with high porosity was prepared via the immobilization of tetraphenylethylene and served as fluorescent probes for furazolidone detection (Zhao et al., 2019). This research not only provided one electron-rich MOFs, but also confirmed that the great prospect of the introduction of tetraphenylethylene can supply the energy transfer platforms and light-harvesting for nitro-antibiotics detection. In order to further improve the surface area and porosity, 3D MOF with the advantages of adjustable structure and function was synthesized. Xu et al.(N. Xu, Zhang, & Zhang, 2019) prepared a Cd-based luminescent MOF (Cd-CBCD), a 3D supramolecular framework built on its stacked 2D layers, based on carbazole-functionalized ligand (H_3CBCD) and Cd(II) ions. In this study, Cd-CBCD exhibited an intense blue-light characteristic emission and was utilized to develop a highly effective fluorescent sensor for nitrofurans detection, which was ascribed to the energy transfers and coexistence of electron.

The detection accuracy of MOF-based sensor is always affected by the deviation between the environment and the optical components. Moreover, the fluorescence change caused by the target analytes may be too weak to be monitored. On the other hand, molecules with similar structures or electronic properties may produce similar signal changes, thereby producing false-positive results. In contrast, ratiometric fluorescent sensor can offer more accurate detection, due to two emission bands detection with self-calibration, which has become the focus in the latest years.

3.1.3. Nanodots for ratiometric fluorescent probes

Silicon nanodots (SiNDs) not only have the advantages of surface tailorability, strong fluorescence, ultrahigh photostability, and great stability, but also reveal intrinsic dominances such as low toxicity and satisfactory biocompatibility, which makes SiNDs extensively applied as promising fungible organic dyes and heavy-metal-containing (e.g. II-VI, III-V, IV-VI) QDs. Based on tetracyclines containing a β-diketonate structure which can bond Eu^{3+} and sensitize Eu^{3+} emission, Wei et al. (Wei, He, Wang, & Kong, 2019) constructed a ratiometric method based on SiNDs and Eu^{3+} system for highly sensitive fluorescent sensing of tetracyclines (Fig. 2(D)). Generally, the emission intensity variation of Eu^{3+} would be influenced by instrumental and environmental factors, which may lead to relatively low sensing reliability and selectivity. However, this ratiometric fluorescent sensor determined the concentrations of tetracyclines by measuring the emission ratios at two wavelengths. This could not only eliminate false signals generated from environmental influences compared with single channel analysis strategy, but also could eliminate the fluctuations of different probe concentration and excitation light intensity since carboxyl groups on the surface of SiNDs are able to coordinate to the Eu^{3+}. Furthermore, CDs that could emit different fluorescent spectrums are also a desirable choice for constructing ratiometric fluorescent sensors. Jalili et al.(Jalili, Khataee, et al., 2020) encapsulated both yellow-emissive CDs (Y-CDs) and blue emissive CDs (B-CDs) into the mesoporous molecularly imprinted polymer to fabricate a visual sensor. This fluorescent intensity ratio variation produced a continuous fluorescence color change from yellow to blue which can be observed by naked eyes. The results suggested that ratios of fluorescent intensities at two wavelengths could be used for the determination of penicillin G residue at trace level in milk. However, Nanodots have certain toxicity and poor biocompatibility.

3.1.4. Other nanomaterials

Covalent organic frameworks (COFs) are a kind of crystalline porous polymer with advantages of large surface area, well-defined structural regularity, and tunable pore structure. Zhou et al.(Zhou et al., 2019) synthesized Ce-MOF and COF nanohybrids, where COF was prepared via the reaction of melamine and cyanuric acid (MCA). Subsequently, the obtained Ce-MOF and MCA nanohybrid (denoted by Ce-MOF@MCA) were exploited as a scaffold of oxytetracycline aptasensor with a LOD of 17.4 fg/mL within a wider linearity of oxytetracycline concentration within 0.1–0.5 ng/mL. This Ce-MOF@MCA hybrid would be an outstanding aptasensor and has application potentials in the fields of biomedicine, food safety and environmental monitoring.

Photonic crystal is a kind of highly ordered material with periodic structure in accordance with the Bragg diffraction laws, which enables to reflect visible light depending on the particle area. Combining the molecularly imprinted hydrogel with the 3D-photonic crystal, the 2D-molecularly imprinted photonic crystal hydrogel (MIPCH) could serve as optical sensors for oxytetracycline determination(Y. Wang et al., 2019). This portable MIPCH sensor was available for oxytetracycline determination in milk, while the linear range was narrow (from 0 to 60 mM), which limited the application in various samples.

Few- or single-layer Molybdenum disulfide (MoS_2) nanosheets with 2D-layered structures, a typical layered transition metal sulfide, exhibit unique chemical and fluorescent properties. Jia et al.(P. Jia et al., 2019) published a feasible synthesis method for MoS_2, which possessed advantages of superior water stability, strong blue fluorescence, and high quantum yield of 7.74%. Subsequently, a facile quenching fluorescence sensor was constructed on the basis of MoS_2 for detecting tetracyclines. The methodology presented a low detection limit of 0.032 μM and could be applied to milk, milk powder and bovine muscle samples. MoS_2 with this ambient hydrothermal reaction didn't require dangerous reagents or long-term pretreatments. Nevertheless, the preparation of MoS_2 with higher quantum yield is still a challenge.

Carbon nanotubes (CNTs) also can be integrated in fluorescent sensors due to their function as quenchers for different fluorophores,

resulting in low background and high signal-to-noise ratio. Although the fluorescent sensors based on CNTs for antibiotic detection has not been reported, they would be a good direction for future research.

3.2. Electrochemical sensors

Electrochemical sensors have been gradually becoming alternative analytical strategies with several advantages, including portability, simplicity, and low cost, making them attractive as alternative analytical strategies. Their accurate and rapid responses without pretreatment makes it possible to direct on-site detect of particular analytes with intuitive devices. At present, a large number of studies have reported antibiotic electrochemical sensors, mainly involving the research of electrode modification materials. Nanomaterials have become an important choice for electrode modification materials in the construction of electrochemical biosensors due to their unique properties.

3.2.1. Carbon nanotubes

Carbon is a kind of material widely applied in the construction of electrochemical sensors based on the screen-printed electrodes (SPEs) due to its low background current, wide potential window, readily renewable surface, inexpensiveness, chemical inertia and versatility. In particular, carbon nanotubes (CNTs) are considerably potential electrode nanomaterials with the advantage of high electrical conductivity, unique electrocatalytic properties and significant mechanical strength. And CNTs can be employed to modify the surface of carbon working electrodes (WEs) and enhance the selectivity and sensitivity of the electrochemical system. In Quinaz's study(Couto & Quinaz, 2016), SPEs with carbon WEs (SPCEs) were modified with multi-walled CNTs (MWCNTs) and Nafion, and utilized to electrochemical portable sensor for the detection of low-level ethambutol in food and biological samples. Nafion, as a sulfonated tetrafluoroethylene based anionic copolymer with cationic exchange properties, can easily modify the electrodes, which would play an important role in the protection of WEs surface, minimization of the interference of electroactive species, and enhancement of the analytical signal intensity. CuO nanoparticle decorated on single wall carbon nanotubes (CuO/SWCNTs) nanocomposite was also successfully used for the modification of carbon paste electrode. The

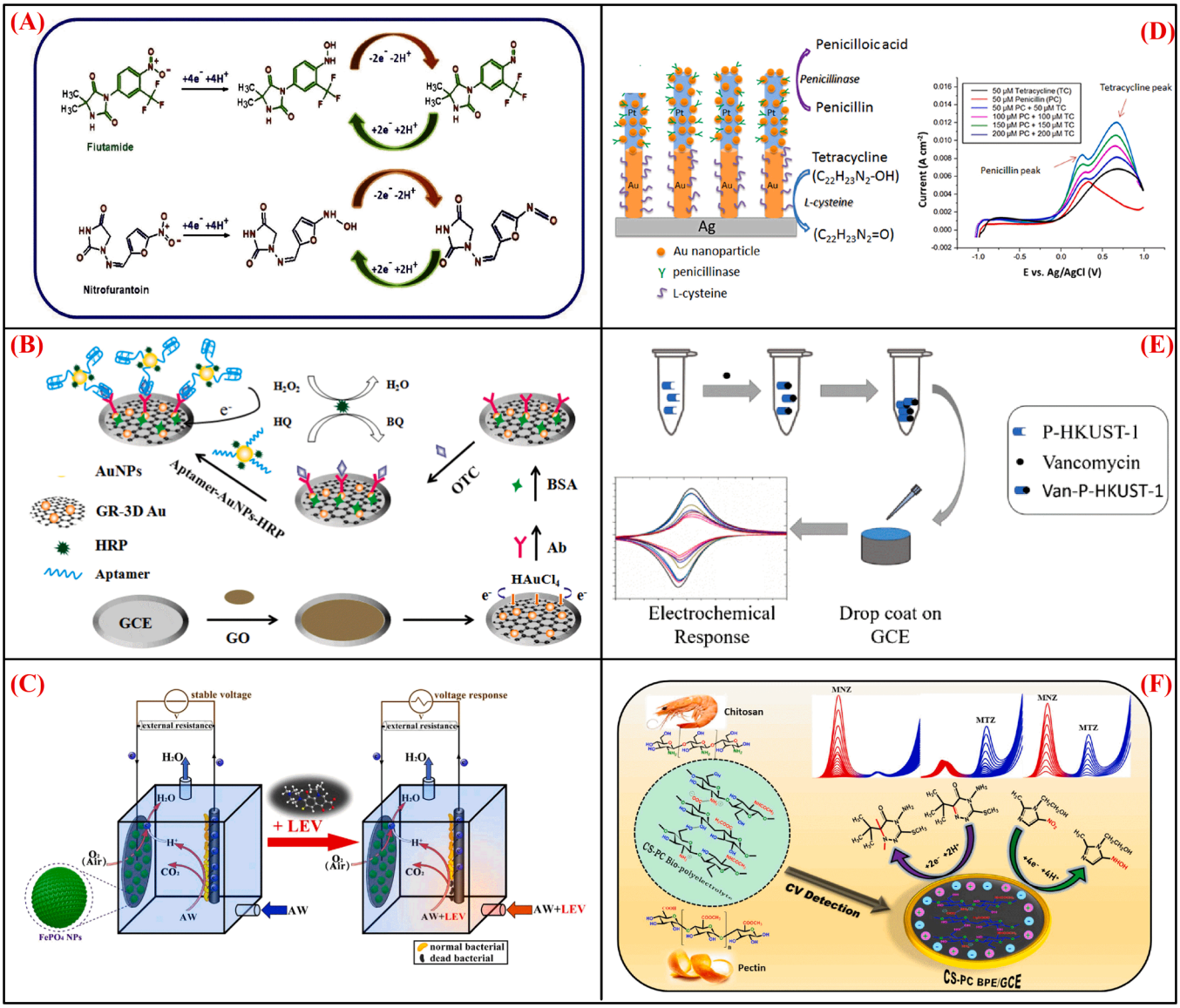

Fig. 3. Antibiotics-electrochemical sensing mechanisms based on (A) *N*-CQD@Co_3O_4/MWCNT hybrid nanocomposite, (B) GR-3D Au, (C) MFCs, (D)hybrid nanowire/nanoparticle array, (E) MOFs, (F) CS-PC BPE complex(Gill et al., 2020; Z. Li et al., 2019; S. Liu et al., 2017; Muthusankar et al., 2020; Ranganathan et al., 2019; Zeng et al., 2017).

obtained voltammetric data confirmed the significant enhancement of oxidation current and reduction of overvoltage for electro-oxidation of sulfisoxazole on a surface of CuO/SWCNTs(Karimi-Maleh, Amini, Akbari, & Shojaei, 2017). However, CNTs are easy to adhere to each other into clusters, resulting in losing the characteristics of nanostructures. The electrochemical properties of carbon nanomaterials can be further improved through functionalization and compositing with other inorganic or organic nanomaterials, which will expand their application.

Muthusankar et al.(Muthusankar, Devi, & Gopu, 2020) modified GCE with nitrogen-doped CQDs embedded Co_3O_4 with MWCNTs (*N*-CQD@Co_3O_4/MWCNTs) hybrid nanocomposite for simultaneous electrochemical sensing of flutamide and drug nitrofurantoin (Fig. 3(A)). The results obtained in this study evidenced that the hybrid nanocomposite offered high conductivity and a large number of reactive sites for the redox reaction of flutamide and nitrofurantoin. For now, there are still some fundamental problems in the preparation of carbon nanotubes, such as the chirality of CNTs and the control of the tube diameter, which limits the application of CNTs.

3.2.2. Graphene

As a novel class of carbon nanomaterial, graphene with the excellent properties, such as fast electron transfer kinetics, extraordinary electrical conductivity, high surface area and remarkable mechanical strength, is a promising electrode material for electrochemical sensing. Pinacho et al.(Pinacho et al., 2014) presented an electrochemical detection of fluoroquinolone antibiotics using a magnetic graphite epoxy composite (m-GEC) electrode. The immunosensor was able to detect up to seven different fluoroquinolones far below the MRLs. The main advantages of magnetic graphite epoxy composite in electrochemical immunosensors include easy manipulation, increased surface area, fast assay kinetics, improved separation and washing steps, possibility of renewing the surface of the electrode and perspectives for systematic automation and miniaturization. Due to strongπ-π interaction force between graphene layers, irreversible agglomeration is easy to occur, resulting in the reduction of effective specific surface area and ionic conductivity. In order to prevent agglomeration, graphene sheets can be modified with hydrophobic surface. An electrochemical sensor based on an electrochemically reduced L-methionine functionalized graphene oxide modified glassy carbon electrode (L-Met-ERGO/GCE), was reported for palmatine detection(Qiao, Wang, Ye, Li, & Li, 2015). Owing to high conductivity and large surface area of GO, the proposed sensor with the L-Met-ERGO/GCE electrode had a linear relationship with palmatine concentration in the range of 1×10^{-7} to 5×10^{-5} mol/L with a LOD of 6×10^{-8} mol/L. Additionally, it was also feasible for the detection of palmatine in human urine samples, medicinal tablets and the Chinese herb *Fibrauraerecisa* Pierre with satisfactory results. 2D-graphene nanosheets usually stack and form agglomerates, resulting in a decrease of surface area that hindered the practical application. Shortly afterwards, 3D reduced graphene oxide (3D-RGO) was synthesized and applied in the construction of electrochemical biosensor based on 3D-RGO-modified glass carbon electrode (3D-RGO/GCE)(X. Zhang, Zhang, & Zhang, 2016). The present 3D-RGO/GCE sensor showed largely increased electroactive surface area and lower electro-transfer resistance, and enhanced the sensitivity towards chloramphenicol detection with a detection limit of 0.15 μmol/L. Fig. 3(B) exhibited that Liu et al.(S. Liu et al., 2017) fabricated an electrochemical sensor based on graphene three dimensional nanostructure gold nanocomposite (GR-3D Au) and aptamer-AuNPs-horseradish peroxidase (aptamer-AuNPs-HRP) nanoprobes as signal amplification. Subsequently, this electrochemical sensor was applied for sensitive and selective detection of oxytetracycline with a LOD of 4.98×10^{-10} g/L. The aptamer and HRP modified AuNPs provide high affinity and ultrasensitive electrochemical probe with excellent specificity for oxytetracycline. Different nanomaterial supports and polymer have been utilized with GR to improve the catalytic activity and dispersion ability of GR. It's reported that *b*-cyclodextrin (*b*-CD), as a suitable dispersing agent for GR, was able to dramatically improve the dispersion ability of GR in aqueous system and avoid the re-stacking of GR sheets. As a result, an amperometric electrochemical sensor was fabricated using GR-*b*-CD/CuO complex modified electrode, which dramatically improved the electrocatalytic activity of GR(Velusamy et al., 2018). Those studies demonstrated that GR-based composites showed an improved surface area and electrochemical activity than pristine GR. As a future perspective, the integration of different polymer and nanomaterial supports with GR could be utilized for fabrication of other highly sensitive electrochemical biosensors. It's also reported that screen-printed electrode, affixed with Cu_2S nanosphere decorated reduced graphene oxide (rGO@Cu_2S) nanocomposite, exhibited tremendous electrocatalytic capability, and was applied in amperometric sensor. This amperometric sensor was able to detect chloramphenicol at the nanomolar level in real sample analysis(Govindasamy, Wang, Kumaravel, Ramalingam, & Al-Lohedan, 2019). Those studies confirmed that there would be a promising application in signal enhancement of electrochemical sensor with metal-GR/rGO. Currently, the graphene materials still face the problem of non-specific adsorption. It is still necessary to continue to explore graphene composite materials for constructing more sensitive and stable sensors.

3.2.3. $FePO_4$ nanoparticles combining with microbial fuel cells

Nowadays, microbial fuel cells (MFCs) were widely applied in the treatment of environmental pollutants. MFC is a bio-electrochemical device that recover electricity energy from wastewater using exoelectrogens as biocatalyst. Single chamber air cathode microbial fuel cell (SC-MFC) is commonly applied in MFC, with the advantages of producing higher power, membrane-free ion exchanging, and using more available oxygen in air and faster response. As displayed in Fig. 3(C), a bio-electrochemical sensor was established for levofloxacin detection based on a SC-MFC using $FePO_4$ nanoparticles as the cathode catalyst (Zeng et al., 2017). This SC-MFC showed an outstanding behavior in detection and degradation of levofloxacin, and exhibited high sensitivity (0.1 μg/L), low LOD and remarkable stability. In this biosensor device, $FePO_4$ NPs dramatically increased the electrooxidation of oxygen on the cathode, which helped to accelerate the voltage output from SC-MFC and could offer a powerful guarantee for levofloxacin detection. The $FePO_4$ NPs based SC-MFC could be developed as a promising biosensor for widespread applications in the future.

As green energy, MFCs technique is expected to play an important role in the field of electrochemical sensors. Whereas, the cost of bio-anode membrane is extremely high. How to reduce the production cost of the membrane, while maintaining the performance parameters of the membrane, is a key in future research.

3.2.4. Gold and platinum nanomaterials

Among the various kinds of nanomaterials, platinum nanoparticles (PtNPs) have been proved to the excellent electrocatalysts, and Au nanoparticles (AuNPs) have good conductivity. Au@Pt core shell nanoparticles have drawn a lot of attention owing to superior electrochemical performance than single metal nanoparticles, and they can prevent AuNPs from reuniting. He and Yan(B. He & Yan, 2019) described an aptasensor for kanamycin detection based on Au@Pt core shell nanoparticles, whose limit of detection was 0.16 pM. Owing to the simple preparation process, high surface areas for the load of sensing probes or aptamers, and high conductivity of Au@Pt core shell nanoparticles, the sensitivity of aptasensors are enhanced powerfully. Besides, Li et al.(Y. Li et al., 2015) developed a sensitive and selective electrochemical sensing protocol based on MIPs and nanoporous nickel (NPNi) for metronidazole assessment. The unique porous structure of NPNi allows it to serve as a great platform for loading the external imprinted membranes to identify the target molecules. In addition, NPNi with good conductivity could enhance the surface area and electron-transport ability of the sensor. Therefore, this hybrid sensor showed superior performance in terms of ultralow detection limit (2×10^{-14} M),

high selectivity, good repeatability over other sensors, and high selectivity. In Feizollahi's study(Feizollahi, Rafati, Assari, & Asadpour Joghani, 2021), the Cu-Ag core–shell nanoparticles were synthesized and used for the decoration of the glassy carbon electrode modified with graphene oxide. The electroanalytical measurements including cyclic voltammetry and square wave voltammetry were performed for the determination of sulfamethazine in cow milk, which showed good agreement with the results of HPLC.

The employment of nanofibers with ultrahigh surface area has resulted in the development of sensors with higher sensitivity and lower LOD. Poly (vinyl alcohol-*co*-ethylene) nanofiber membrane (PVA-*co*-PE NFM) is a commercial polymer possessing abundant active hydroxyl groups, which can be easily activated. In El-Moghazy's study(El-Moghazy et al., 2018), the immunosensor, by using a screen-printed carbon electrode laminated with a layer of PVA-*co*-PE NFM, exhibited high sensitivity for the determination of chloramphenicol in a range of 0.01–10 ng/mL, with a LOD of 0.0047 ng/mL. Compared with conventional PVA-*co*-PE casted membrane, the application of PVA-*co*-PE NFM decreased the electron-transfer-resistance by about 4 times. Afterward, an electrochemical biosensor based on hybrid gold nanowire/nanoparticle array with various bio-molecular receptors was also fabricated for simultaneous detection of penicillin and tetracycline (Fig. 3(D))(Z. Li, Liu, Sarpong, & Gu, 2019). Owing to the structure of hybrid nanowire/nanoparticle array, Au (L-cysteine)-Pt (penicillinase) nanowire array electrode prepared in this study showed remarkably high sensitivity and simultaneous detection ability for penicillin and tetracycline determination. Nonetheless, there are some limitations in highly selective detection of tetracycline owing to the influences of other non-target analytes. Furthermore, studies on functionalizing different bio-receptors with different segments of nanowire array should be carried out. Song et al.(J. Song et al., 2020) fabricated an ultrasensitive impedimetric aptasensor, utilizing the synergistic effect of (TiO_2-g-C_3N_4) and AuNPs, for amoxicillin detection. The thiol-aptamer was conjugated to AuNPs on the modified glassy carbon electrode (GCE) by the 'Au-S' bond, which can specifically recognize amoxicillin, thereby resulting in a rapid increase of the impedance signal. This sensor successfully achieved the detection of amoxicillin in the range of 0.5–3 nM with an ultra-low detection limit (0.2 nM).

Recently, simplex nanomaterials have been gradually replaced by composite nanomaterials in electrochemical sensor construction. The reason is that composite nanomaterials, combining nanomaterials with functional polymers, biomolecules, etc. could make full use of the advantages of different nanomaterials, which greatly improves the detection performance of electrochemical sensors.

3.2.5. Metal-Organic frameworks

Many MOFs could not only be used as fluorescent signal probes, but also be applied as electroactive signal probes for various analytes detection, owing to their electrochemical activity. The limited solubility/dispersibility of MOFs in water is still a hindrance. In order to overcome the dispersibility of MOFs and further increase its electrical conductivity, copper(II) benzene-1,3,5-tricarboxylate (BTC) MOF was modified with poly(acrylic acid) (PAA) (shown in Fig. 3(E)), which was developed to improve water solubility of materials and also showed the affinity towards vancomycin(Gill et al., 2020). The MOF with enhanced electrocatalytic properties was modified on a glassy carbon electrode. The reason was assumed to be the presence of the poly (acrylic acid) that formed a network between various HKUST-1 crystals through dimer formation between the carboxy groups of BTC and PAA. In addition, poly (acrylic acid) also resulted in better dispersion of the MOF and improved interaction between MOF and vancomycin.

In recent years, porous carbon materials, synthesized with MOFs as carbon precursors, have gradually been used in electrochemical sensors. Among various carbon materials, Printex 6L Carbon, also called carbon black (CB), was investigated because it is one of the most inexpensive carbon materials and presents favorable electrochemical properties. Wong et al.(Wong, Santos, Cincotto, Moraes, Fatibello-Filho, & Sotomayor, 2020) developed an electrochemical device based on a combination of nanomaterials such as Printex 6L Carbon and cadmiumtelluride quantum dots within a poly (3,4-ethylenedioxythiophene) polystyrene sulfonate film for sensitive determination of amoxicillin. Under the optimized experimental conditions, the proposed sensor exhibited repeatability, high sensitivity and stability for amoxicillin determination, with a low LOD of 50 nmol/L. He et al.(Y. Q. He et al., 2021) reported a sensitive electrochemical method for bleomycin determination, based on DNAzyme and the adsorption of signal probes by MOF modified electrode. Attributing to high catalytic capacity of DNAzyme and excellent electrochemical performance of MOF modified electrode, this method revealed an impressive limit of detection as low as 4 pM with a linear range of 5–2000 pM.

The incorporation of appropriate amount of carbon material could improve the stability of the material and prevent the structure of MOFs from collapsing during the carbonization and activation process. However, excessive carbon material would also exert some negative effects on MOFs, which can lead to the formation of irregular composite particles. Hence, it's still a technical difficulty in controlling carbon material participation.

3.2.6. Other materials

Recently, biopolymers derived polyelectrolytes (PEs) with excellent electrical ability was widely applied in fuel cells and supercapacitor. In the long-term inventory of biopolymer materials, two polysaccharides, chitosan (CS) and pectin (PC), are the most promising bio polyelectrolytes (BPEs) materials for the electrochemical sensor applications. Ranganathan et al.(Ranganathan, Mutharani, Chen, & Sireesha, 2019) utilized CS-PC BPE composite for the simultaneous electroreduction of metronidazole and metribuzin. As a proof of notion, the developed sensor taken place on GCE via CS-PC BPE as an electrocatalyst, exhibited an improvement in electron transfer kinetic process, thus leading to an enhanced electrocatalytic reduction of metronidazole and metribuzin on the surface of modified GCE. This sensor revealed attractive advantages including simplicity, biocompatibility, and low production cost.

Lutetium vanadate ($LuVO_4$) is another potential material for electrochemical application due to its good electrocatalytic activity and conductivity. $LuVO_4$/graphene sheet (GRS) nanocomposite, where $LuVO_4$ was encapsulated with an ultrathin GRS to form a hierarchical structure ($LuVO_4$/GRS), was synthesized and utilized to construct an electrochemical sensor, with suitable surface area, high redox reaction, excellent electrical conductivity and large numbers of electron transport (Kokulnathan & Chen, 2020). As shown in the results, the obtained sensor could detect nitrofurantoin with a low LOD (0.001 μM) and wide linearity (0.008–256.0 μM). The $LuVO_4$/GRS nanocomposite can serve as a favorable candidate for developing electrochemical sensor and play an important role in widespread fields.

With the in-depth research on nanomaterials, the nanomaterials-based electrochemical sensors have obtained more and more extensive application. However, there are still some shortcomings in nanomaterials when applied to electrochemical sensors. Firstly, although the sensitivity of nanomaterial-based electrochemical sensors can meet the requirements when detecting only one analyte, these sensors are vulnerable to interference when two or more analytes were detected at the same time. Secondly, the fixation between nanomaterials and sensor components mostly adopts physical adsorption methods, which are unstable and even easy to fall off.

3.3. Photoelectrochemical sensors

Recently, photoelectrochemical (PEC) sensors have attracted increasing interests due to the merits of simple device, high sensitivity, and easy miniaturization. Generally, PEC sensors are fabricated using photoactive electrodes which can convert photoirradiation to electrical

signal. Hence, photoactive materials are crucial for the performance of PEC sensors. Quantum dots and graphitic carbon nitride are commonly used as photoactive materials to construct PEC sensors for antibiotic detection.

3.3.1. Quantum dots

Semiconductor quantum dots are also good materials for electrode modification of electrochemical sensors. Zeynali et al.(Asadpour-Zeynali & Mollarasouli, 2017) offered a feasible strategy for the synthesis of polyvinyl pyrrolidone (PVP) capped $CoFe_2O_4$@CdSe core–shell. The photoluminescence (PL) spectroscopy study of $CoFe_2O_4$@CdSe has shown remarkable PL quenching by the formation of $CoFe_2O_4$ core inside CdSe, which indicated that $CoFe_2O_4$ NPs were efficient electron acceptors with the CdSe. Subsequently, the synthesized PVP capped $CoFe_2O_4$@CdSe was cast on the surface of GCE to fabricate novel electrochemical biosensor for the determination of rifampicin (RIF) with very low detection limit (4.55×10^{-17} M). The electrochemical oxidation of RIF on PVP capped $CoFe_2O_4$@CdSe showed higher signals than those on bare GCE and $CoFe_2O_4$/GCE, revealing excellent electrocatalytic activity of this film due to large surface area, abundant active sites and adsorptive capacity of PVP capped $CoFe_2O_4$@CdSe. Also, BiO nanostructure-modified SPEs were confirmed to exhibit greater stability, electrocatalytic activity, and reproducibility for simultaneous detection of antibiotics over unmodified (bare) SPEs(Mahmoud, Khairy, Rashwan, & Banks, 2017).

With the advantages of high sensitivity, user friendly operation, and rapid analysis, QDs-based PEC sensor has been expanded to wider research scope. There are many active sites on the surface of QDs, therefore QDs might be instable, highly active, and easy to produce non-specific interaction with other substances. As a result, the accuracy of the sensor would be affected negatively.

3.3.2. Graphene quantum dots

Graphene quantum dots (GQDs) have attracted much interest because of their good biocompatibility, robust chemical inertness, stable photoluminescence, and high dispersibility in water(Shuhua Li, Li, Cao, Zhu, Fan, & Li, 2014). Liu et al.(Liu, Yan, Okoth, & Zhang, 2015) prepared nitrogen-doped graphene quantum dots (*N*-GQDs) through a facile one-step hydrothermal method, and explored *N*-GQDs to achieve highly efficient photon-to-electricity conversion in PEC sensing. As shown in Fig. 4(A), GQDs in PEC sensing may offer efficient use of the visible range of solar energy, and prevent high background arising from direct UV photolysis of analytes. Besides, UV–visible absorption spectra indicated that nitrogen doping may obviously enhance the absorption of GQDs in visible light region. Additionally, the π-conjugated structure of *N*-GQDs provided an excellent platform for aptamer immobilization via π–π stacking interaction. Such an aptamer/*N*-GQDs based sensor showed a linear PEC response to chloramphenicol concentration in the range of 10–250 nM with a detection limit of 3.1 nM.

GQDs have the advantages of graphene and QD materials, including excellent fluorescence performance, good biocompatibility, low cytotoxicity, and chemical inertness. Nevertheless, the preparation procedure is more complicated, and the luminous efficiency can be influenced by many factors. Therefore, the preparation procedure of GQDs needs further optimization and improvement.

3.3.3. Graphitic carbon nitride

AS an organic semiconductor, Graphitic carbon nitride (g-CN) has aroused intensive attention in photochemical field recently. Due to the high thermal and chemical stability, visible light response ability, and layer structure like graphene, g-CN has been frequently utilized to enhance PEC response coupling with other semiconductors. However, as a photoactive material, bulk g-CN material still possess drawbacks, including unsatisfactory utilization of light energy and high electron-hole recombination rate, which restrict its practical application. The intrinsic vacancies modification in g-CN material is an effective selection for realization of material vacancy. It's published that nitrogen-deficient g-CN (ND-g-CN) could be utilized as a photoactive material for developing a PEC sensor under visible light irradiation(Yan et al., 2020). In this strategy, the ND-g-CN material possessed 2D thin sheet structure

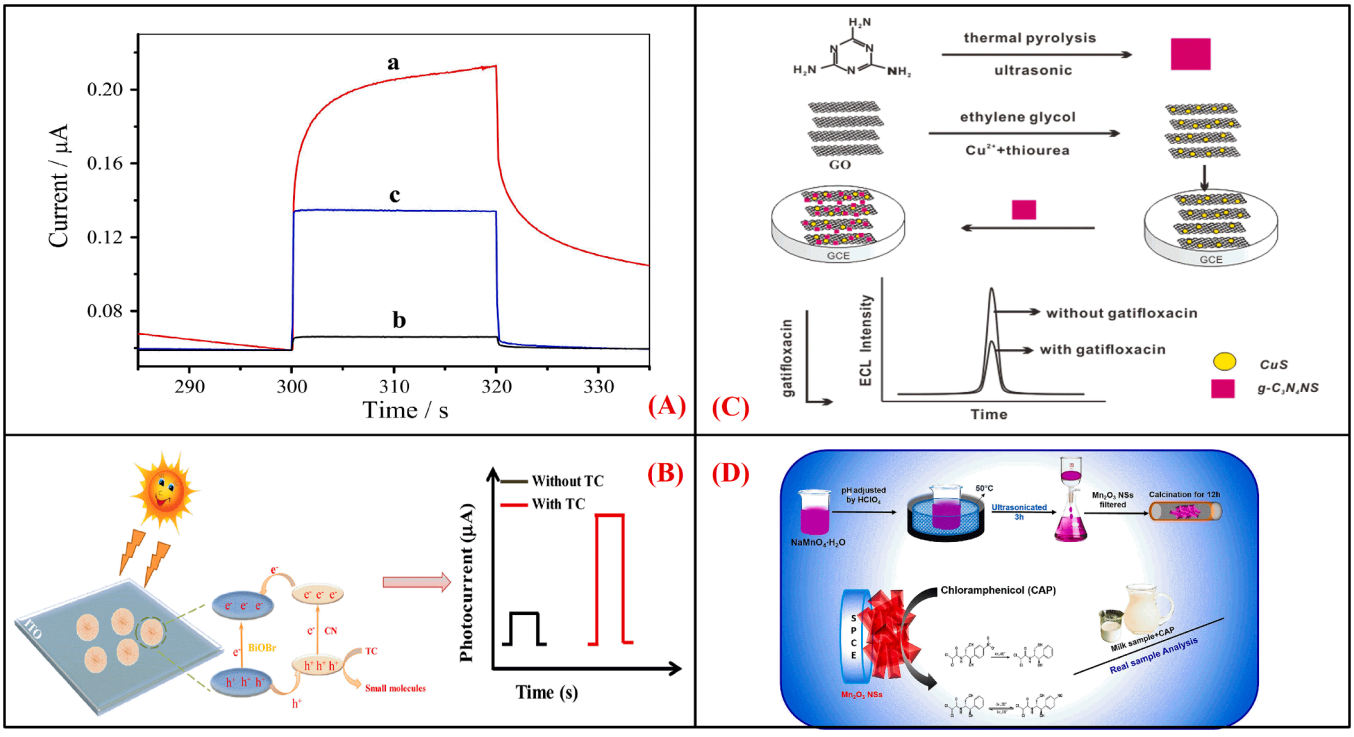

Fig. 4. Antibiotics-Photoelectrochemical sensing mechanisms based on(A) GQDs, (B) CN/BiOBr composites, (C) rGO-CuS composite, (E) Mn_2O_3 TNS:(a) *N*-GQDs/FTO, (b) FTO, and (c) GQDs/FTO electrodes,(Jiang et al., 2019; Liu et al., 2015; Rajaji et al., 2019. Yan et al., 2018).

with abundant nitrogen vacancies, which could enable effective charge separation and transfer, thus dramatically enhancing the PEC performance. The designed PEC sensor demonstrated low detection limit of 20 ng/L for ciprofloxacin analysis. This study presented a promising potential for the practical application in environmental monitoring. The UV light, which only accounts for 2–4% of solar energy, is a high-energy excitation light source that can easily result in fatal damage toward biomolecules. Therefore, it is important to develop visible light-responsive photoactive material in PEC biosensors. The combination of three-dimensional nitrogen doped graphene hydrogel (3D-NGH) and $BiPO_4$ is an important method to improve the photoactive property of $BiPO_4$. PEC aptasensor based on $BiPO_4$/3D-NGH nanocomposites was applied for sensitive and selective detection of tetracycline with a low detection limit of 0.033 nmol/L(Ge et al., 2018). The introduction of 3D-NGH could efficiently improve the visible light absorption of $BiPO_4$, and the energy band gap of $BiPO_4$/3D-NGH of 2.1 eV was greatly narrowed compared with pristine $BiPO_4$ with a band gap of 3.85 eV. This $BiPO_4$/3D-NGH nanocomposites would serve as a promising visible light-responsive photoactive material for the fabrication of PEC biosensors with high performance.

What's more, g-CN/BiOCl composite (g-CN/BiOCl) was designed for a facile and sensitive PEC monitoring platform of ciprofloxacin(L. Xu et al., 2016). As shown in the results, g-CN could enhance the PEC performance of BiOCl. In addition, the g-CN nanosheets could cover the surface of BiOCl microspheres, which could form heterojunction structures. Therefore, the g-CN/BiOCl composites possessed a high light response and exhibited much higher PEC response than that of pure BiOCl, and the LOD of the ciprofloxacin PEC sensor was significantly lowered to 0.2 ng/mL. BiOBr is another typical p-type semiconductor with tetragonal PbFCl-type layered crystal structure. The layer structure endows BiOBr with enhanced separation efficiency of photogenerated electron and hole, contributing to the superior photoelectrochemical properties and excellent optical and electrical properties. Yan et al.(P. Yan et al., 2018) constructed a signal-on photoelectrochemical sensor based on CN/BiOBr composites for the detection of tetracycline (Fig. 4 (B)). If combining CN with BiOBr, a high light response and excellent separation efficiency of photoinduced electron and hole could be obtained, beneficial for enhancing photoelectrochemical response of this composite. Research on the modification of g-C_3N_4 composite materials is still in its infancy. There are few reports on the application in electrochemical sensors, and the biocompatibility need further investigation.

3.3.4. Copper sulfide

Copper sulfide (CuS) is an important semiconductor with excellent physiochemical properties. Reduced graphene oxide-copper sulfide (rGO-CuS) composite could enhance the sensitivity for biosensing, which is attributed to its strong electrical conductivity, large capacity and good electrocatalytic ability. In addition, g-C_3N_4 nanosheets (g-C_3N_4 NSs) with high quantum yield, good electrochemiluminescence activity, fine stability and good biocompatibility, was extensively applied in many fields, such as mass spectrum, photo electrochemistry and electrochemiluminescence. A sensor for the determination of gatifloxacin by rGO-CuS composite coupled with g-C_3N_4 NSs modified glassy carbon electrode was reported(Jiang et al., 2019). As shown in Fig. 4(C), an ultra-thin (one layer or several layers) g-C_3N_4 NSs was employed to overcome the defects of massive g-C_3N_4, and the presence of rGO-CuS composite could establish a rapid electron transfer path to facilitate the direct electrochemistry response of g-C_3N_4 NSs with electrode. The signal intensity was enhanced four-fold after modified with rGO-CuS composite. However, so far there are few reports on the application of CuS composite nanomaterials, which may be due to the immature preparation technique of CuS composite.

3.3.5. Transition metal oxide

In recent years, transition metal oxide (TMO) based nanocatalyst has flourished in the nano-catalysis field for different potential applications. Among them, Manganese based TMOs were extensively investigated and used in various electronic applications due to high conductivity and various oxidation states. As shown in Fig. 4(D), Rajaji et al.(Rajaji et al., 2019) prepared and fabricated a porous and hierarchical manganese (III) oxide tiny nanostructures (Mn_2O_3 TNS) modified screen-printed carbon electrode (SPCE) for the determination of chloramphenicola. Compared with bare SPCE, Mn_2O_3 TNS modified SPCE showed much higher response towards chloramphenicol. What's more, the sonochemical synthesis method for Mn_2O_3 TNS was more simple, cost-effective and eco-friendly compared with hydrothermal and other methods. This study seems to support that nanosized metal oxides (NMOs) could also be used for nondestructive, non-invasive, and real-time analysis. The nanostructured yttrium oxide (nY_2O_3) has aroused great interest as biological immobilization matrix. nY_2O_3 is considered a suitable biosensing material with the advantages of chemical inertness, high dielectric constant, high surface-to-volume ratio, thermal stability, extremely rapid mobility of ions, biocompatibility, charge transfer capability, wide bandgap and interesting electrochemical properties. Thin film of nY_2O_3 will have strong conductivity due to low dielectric constant value. Therefore, nY_2O_3 is a probable aspirant for application towards biosensor development. Besides, nY_2O_3 was a desirable inorganic metal oxide composed of Y_2O_3 elements. The oxygen moieties in nY_2O_3 would help the functionalization and covalent immobilization of antibodies. However, the major problem of nY_2O_3 agglomeration to specific substrates containing biological molecules has resulted in the limitation in biosensing applications. To overcome this shortcoming, Yadav et al.(Yadav, Dhiman, Lakshmi, Berlina, & Solanki, 2020) developed a nanocomposite film biopolymer matrix by modifying nY_2O_3 with chitosan for biosensor application, in which chitosan as a biocompatible and biodegradable polymer with an excellent ability to form films, could be widely adopted in the nanocomposite fabrication for immobilization of biomolecules by affixing covalently to their amino/hydroxyl groups. The assay obtained a better sensitivity as high as 10.14 μA/μM*cm^2 when compared with above mentioned biosensors and commercial ELISA. Although there are many metal oxides with photoelectric conversion properties, the photoelectrochemical activity is greatly limited by low photoelectric conversion efficiency, low electron mobility, short hole diffusion distance, and easy recombination of electron-hole pairs. Velmurugan et al.(Velmurugan, Zhi-Xiang, T, & Juan, 2021) synthesized a visible light active p-stannic oxide/*n*-copper manganate (p-SnO(2)/*n*-CuMnO(2)) heterojunction and applied it for photoelectrochemical sensing of antibiotic tetracycline. The photoelectrochemical sensing performance of SnO(2)/CuMnO(2) microrods was 2.7 times higher than that of pure SnO(2) microrods, due to stronger visible light absorption ability and p-n heterojunction (synergy). Therefore, the designed photoelectrochemical sensor could give photocurrent signals for the detection of tetracycline in the range of 0.01–1000 μM with a LOD of 5.6 nM.

Currently, there are not many photoelectric materials that can be used in PEC sensors. It is a popular trend in the future to develop functional nanomaterials with high photocatalytic activity and photoelectric conversion properties.

3.4. Surface plasmon resonance sensors

SPR sensor has attracted extensive interests as a real time and label-free surface technique for molecular detection. When the metal surface is functionalized with a ligand, analyte binding will cause a local increase in refractive index (RI), which can be directly measured by a red-shift of the SPR. Due to small mass causes only minor RI changes on the surface, it's difficult to detect antibiotics. Therefore, signal amplification is an immediate research focus of SPR sensors for antibiotic detection.

Recently, taking advantages of SPR properties of noble metal nanoparticles (e.g. Au and Ag), analyte-induced aggregation of noble metal nanoparticles accompanied with color changes have been used as probes

for colorimetric determination. Compared with AgNPs, AuNPs are more stable, and have more controllable particle size. AuNPs, as substrates of colorimetric sensors, have been developed for facile tracking of antibiotics. Recently, a simple and rapid colorimetric biosensor for pazufloxacin mesilate detection based on glucose-reduced AuNPs was reported(Kong et al., 2016). As shown in Fig. 5(A), positively charged pazufloxacin mesilate as "molecular bridge" between the AuNPs can lead to the AuNPs aggregation through hydrogen-bonding interaction and electrostatic attraction, thereby causing absorption spectra and color changes of the sample solution. Compared with traditional methods, this method exhibits a wide linear range with a low detection limit of 7.92 pM. More importantly, it has rapid response rate without additional chemical modification or any complicated sample pretreatments. AgNPs with excellent SPR properties were also used for the performance enhancement of SPR sensors. A colorimetric sensor, based on chlortetracycline-coated silver nanoparticles (AgNPs–CTC) for streptomycin and kanamycin determination, was reported by Saratale et al.(Saratale et al., 2020). This assay could achieve an excellent picomolar-level sensitivity. The LODs for streptomycin and kanamycin were 2000 pM and 120 pM, respectively.

Although AgNPs have a stronger SPR property than AuNPs, the active chemical properties limit their application in SPR antibiotic sensors. Au@Ag shell-core composite nanomaterials, which not only have high SPR property of AgNPs and AuNPs, but also can protect AgNPs from oxidation by using AuNPs shell, would become a research focus of SPR antibiotic sensors in the future.

In the recent years, different shapes of gold nanomaterials are also investigated to further enhance the signal of SPR sensor, Cappi et al. (Cappi et al., 2015) developed a transmission configuration-localized SPR (*T*-LSPR) setup for direct measurement of tobramycin. With simple *T*-LSPR setup, the research results showed real-time and label-free detection of tobramycin in buffer with a measuring concentration down to 0.5 μM. Moreover, this label-free system can detect tobramycin in filtered undiluted blood serum, with a measuring concentration down to 10 μM and a theoretical detection limit of 3.4 μM. In this study, gold nanoislands (AuNIs) self-assembled on a glass slide were covered with a fluorine-doped tin oxide (FTO) layer, and functionalized with DNA aptamer, which allowed the sensor system not only to perform multiple regeneration cycles without critical degradation of the signal, but also to determine kinetic parameters that well matched those obtained with a commercial propagating SPR system (Fig. 5(B)). With the in-depth development of synthesis technique of nanomaterials, nanomaterials of various shapes with high SPR property have a huge application prospect in SPR antibiotic sensors.

3.5. *Surface enhanced Raman scattering sensors*

Surface enhanced Raman scattering (SERS) is a great increase in the Raman cross-section observed from molecules adsorbed in SERS substrates. As a powerful technique discovered in the 1970 s, SERS has numerous advantages and has been widely used in biochemistry and life sciences. Hong's group (Hong, de Albuquerque, Poppi, & Brolo, 2017) successfully employed the laser interference lithography fabricated nanogratings in SERS detection of enrofloxacin and its metabolite. The limit of quantitation (LOQ) obtained in this work (~1 ppm) was lower than those reported for SERS antibiotic detections, which ranged from

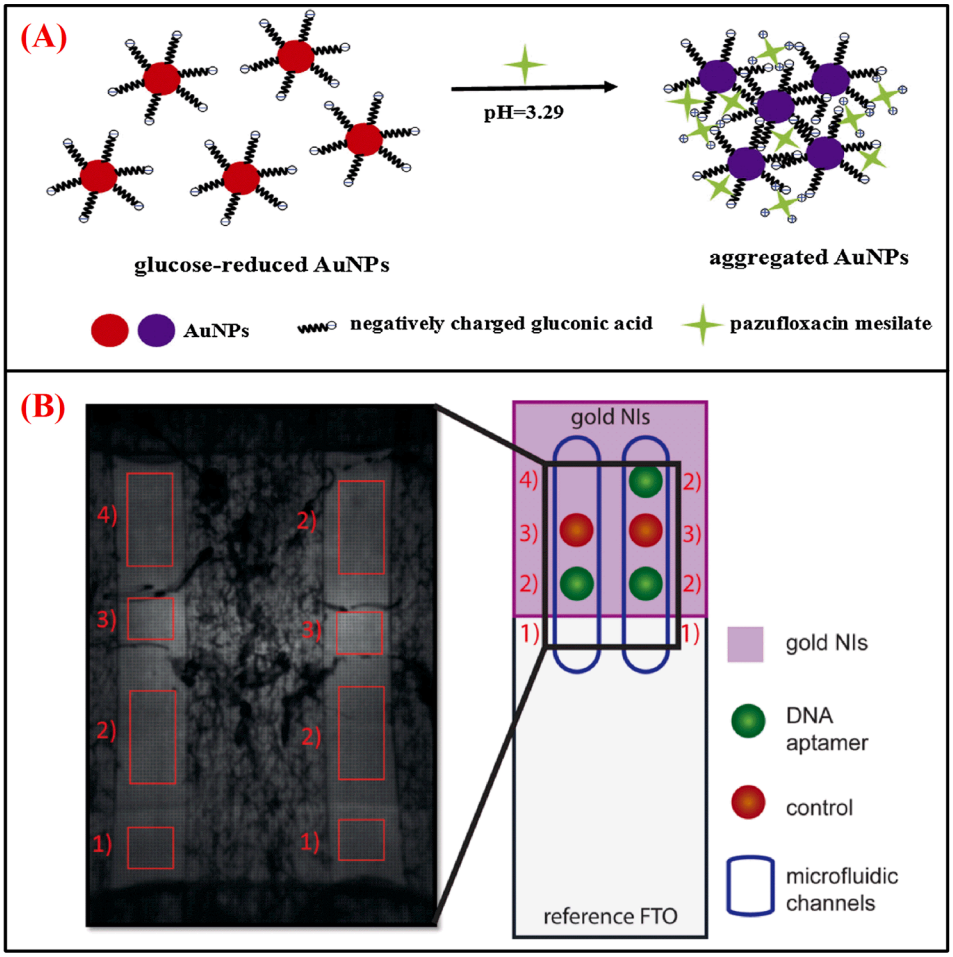

Fig. 5. Antibiotics-SPR sensing mechanisms based on (A) AuNPs, and (B) AuNIs(Cappi et al., 2015; Kong et al., 2016).

20 ppb to 100 ppb. This technique was proved successful in recovering the concentration and spectral profiles of the analytes, up to bi-mixtures. Besides traditional metal nanoparticles (such as Au, Ag, and Cu), heterogeneous metal nanomaterials and semiconductor materials have also been reported to construct SERS substrates for antibiotic detection.

3.5.1. Optical hollow fibers

The elaborated optical hollow fibers could guides light with low attenuation while providing a miniaturized sample container for the liquid analyte solutions. Therefore, a strongly improved interaction between the excitation light and the analyte molecules can be obtained. Yan et al.(D. Yan et al., 2018) developed a fiber-enhanced Raman spectroscopy filled hollow-core photonic-crystal fibers for detection of cefuroxime (Fig. 6(A)). Light in this fiber is strongly confined in the selectively filled liquid core, and Raman scattered signals are obtained with remarkable efficiency. The detection limit of cefuroxime in human urine was improved by 2 orders of magnitude (to μM level).

3.5.2. Gold nanostars

Compared to spherical NPs, such as gold NPs, gold @silver NPs and silver@gold NPs, gold nanostars (AuNSs) with multiple sharp branches acting as "hot-spots" for the "lightning rod" effect have shown the strongest SERS enhancement than that of spheres, cubes, and rods, when these substrates were used in SERS detection. Qian et al.(Qian, Xing, Ge, Li, Li, & Yan, 2020) developed a SERS sensor based on 4-ATP modified AuNSs nanotag for the analysis of trace tetracyclines shown in Fig. 6(B). The LOD for the Raman signal was 0.04 ng/mL, 100 times more sensitive than those of color intensity quantifications.

In order to obtain high-quality SERS spectra, a certain roughness is required for the surface of metal substrate. As we all know, rough metal surface obtained by various preparation methods is generally uneven, which causes different surface enhancement signals at different surface laser points. With the development of nano-self-assembly technology, it would become possible to prepare uniform and orderly SERS substrates.

3.6. Mass-sensitive sensors

The mass-sensitive sensor is another type of sensor based on the piezoelectric effect. Owing to its simplicity, convenience, inexpensive fabrication, real time response and label free detection, quartz crystal microbalance (QCM) is widely employed in mass-sensitive sensors. The principle of QCM sensors is based on the frequency change of the crystal

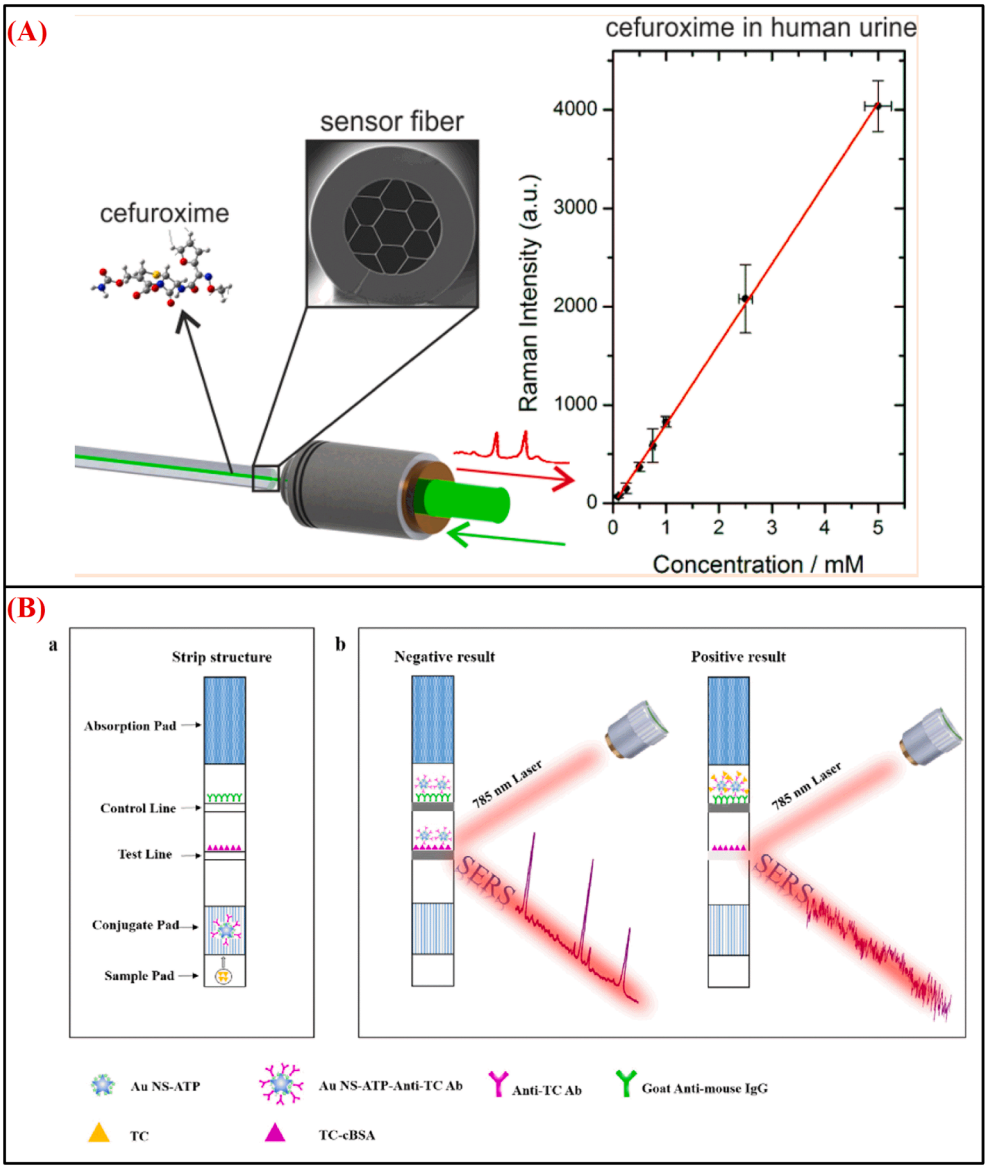

Fig. 6. Antibiotics-SERS sensing mechanisms based onhollow-core photonic-crystal fibers, and (B) AuNSs(Qian et al., 2020; D. Yan et al., 2018).

is inversely proportional to the mass change caused by the analyte binding on the surface of crystal. QCM has excellent adaptability to microfluidic techniques and good utility in a flow cell.

The QCM sensor integrated in a flow injection analysis (FIA-QCM) system has the advantages in terms of reproducibility, speed of analysis, control of contact time and concentration profiling in kinetic studies. Bhand et al.(Mishra, Sharma, & Bhand, 2015) developed an ultrasensitive biosensor for the detection of streptomycin residues in milk samples using the flow injection-electrochemical quartz crystal nanobalance (FIA-EQCN) technique, in which monoclonal antibody specific to streptomycin was immobilized onto the thiol modified gold quartz crystal surface. A broad dynamic range (0.3–300 ng/mL) was obtained for streptomycin with good linearity in the range of 0.3–10 ng/mL for PBS and 0.3–50 ng/mL for milk. Conventionally, either bare electrodes or the electrodes coated with metal nanoparticles of varying morphologies or polymer films are employed in QCM sensors. Munawar et al.(A. Munawar et al., 2019) first developed MWCNTs/Bi_2WO_6 nanocomposite as a sensor coating for the mass-sensitive detection of rifampicin. The developed sensor showed high sensitivity toward rifampicin with a detection limit of 0.16 μM, as well as excellent reproducibility and stability. This work opened up a new horizon for the exploration of unconventional nanomaterials bearing different morphologies for the detection of pharmaceuticals.

4. Conclusion and perspectives

The abuse of antibiotics in animal husbandry leads to excessive antibiotic residues in animal-derived foods, and then affects people's health. Therefore, it's necessary to develop detection methods for antibiotic restudies. Although with the advantages of rapid detection, low cost, and portability, biosensors do not require laborious sample preparation. In the last five years, a large number of literatures reported the studies on electrochemical sensors, fluorescent sensors, and SPR sensors for antibiotic assay. This review introduces the recent advances of recognition elements for high specificity and new nanomaterials for enhanced sensitivity in antibiotics biosensors.

The application of biosensors in antibiotic residue detection is still at a relatively immature stage, and many technical obstacles need to be resolved. Firstly, efficient, sensitive and applicable sensors, for trace and rapid detection of small molecule substances, would become the main goals of research. It is difficult to detect trace substances in complex samples only relying on a single signal amplification, so multiple signal enhancement strategies in biosensors should be emphasized. Various composite metal nanomaterials (such as Au@Pt core shell nanoparticles, Ln-MOFs, and g-CN/BiOCl) with multiple signal amplification abilities have also become the common materials for biosensor construction instead of traditional nanomaterials (such as PtNPs and AuNPs). What's more, nanomaterials combining with current advanced nanotechnology, including 3D technique and microfluidics technology, have been employed to construct successfully sensitive biosensors. However, it is necessary to carry out deeper theoretical research to better knowledge physical and chemical properties of new materials and apply them in biosensors. Secondly, high-throughput, real-time and rapid assay for multiple antibiotic residues detection, even antibiotics and other small molecular contaminants simultaneous detection is required for biosensor. With the development of MIPs and aptamers, especially multivalent aptamers(J. Yang, Li, Jiang, Yuan, & Xiang, 2020), the sensor of multi-target analysis has a great development prospect. Automated or portable antibiotics biosensor system is another important direction for future study, and the biosensor device tend to be smaller, simpler, and cheaper, with high throughput and integrated diversification. In addition, some techniques and methods are still in their infancy, such as nanoparticle collision electrochemistry and smart packaging, which can also provide novel ideas for the development of smart biosensors. In summary, the development of biosensor technique will inevitably lead to changes and innovations in antibiotic analysis, which has great value for the development and application in the fields of food safety and clinical diagnosis. The ideal sensors can not only provide real-time and reliable results with high sensitivity in a short time, but also distinguish specifically target antibiotics in complex matrices. Therefore, it is urgent to solve the problems so as to further improve the sensitivity, specificity, repeatability and stability of the antibiotic sensors. It is also quite important to reduce the cost and make sensors more portable and intelligent.

CRediT authorship contribution statement

Chen Zhou: Conceptualization, Writing - original draft. **Haimin Zou:** Visualization, Writing - review & editing. **Chengjun Sun:** Supervision. **Yongxin Li:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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