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Optical and Electrochemical Sensors and Biosensors for the Detection of Quinolones

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Abstract

One major concern associated with food safety is related to residual effects of antibiotics that are widely used to treat animals and results in antimicrobial resistance. Among different groups of antibiotics, the use of quinolones in livestock is of major concern due to the significance of these antimicrobial drugs for the treatment of a broad range of infectious diseases in humans. Therefore, it is highly desirable to develop reliable methods for rapid, sensitive and on-site detection of quinolone residue levels in animal-derived foods to ensure food safety. Sensors and biosensors are promising future platforms for rapid and on-site monitoring of antibiotic residues. In this review, we focus on recent advancements and modern approaches in quinolones sensors and biosensors.

29   **Keywords:** Quinolones, Optical, Electrochemical, Sensor, Biosensor, Nanomaterial

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The Importance of Quinolone Detection

Human health is greatly affected by the quality and nature of consumed food. The extensive use of antibiotics in animals, as therapeutics and growth promotion agents, can lead to antibiotic residues in animal-derived foods which affect the human health. More recently, antibiotic resistance has emerged as a serious and important issue worldwide. According to combined data from the Centers for Disease Control and Prevention (CDC), approximately 23,000 deaths occur annually in the United States due to infections caused by antibiotic resistant bacteria [1]. Various types of antibiotics are used in veterinary and livestock. Among these, the use of quinolones has become a major challenge due to the importance of this group to treat a wide variety of infections in humans [2]. Quinolones are a group of relatively newly developed synthetic antibiotics with broad-spectrum bactericidal activity against Gram-positive and Gram-negative bacteria [3, 4]. They are widely employed to treat bacterial infections in animals, poultry and fish. However, residues of these drugs in animal-derived foods such as meat, chicken, milk, egg and honey can lead to several side effects including the development of antimicrobial resistance, inefficiency of antibiotic therapy in humans with bacterial infections and gastrointestinal irritation [5]. The production and usage of quinolones is very high due to their low cost. For instance, the annual consumption of quinolones in USA, European Union (EU), South Korea and Japan is about 70 tonnes for generic quinolones and 50 tonnes for proprietary products. In China, annual consumption of quinolones in animals is estimated to be in the range of 470 tonnes and annual consumption is about 1,350 tonnes in human medicine [6]. Since 2000, quinolone use in animal production has progressively increased, which has inevitably resulted in residues in foods [7]. Due to the growing consumption and side effects of the residue of quinolones, regulatory authorities such as the EU have established maximum residue limits (MRLs) for quinolones in different animal-derived foods. The MRLs for eight quinolones regulated by the EU range between 30 and 800 $\mu\text{g kg}^{-1}$ [8]. These low levels require the development of analytical techniques that are sensitive enough to monitor and determine these antimicrobial drugs in biological samples. Although most conventional detection methods such as high-performance liquid chromatography (HPLC) [7, 9], enzyme-linked immunosorbent assay (ELISA) [10-12] and capillary electrophoresis (CE) [13-15] are sensitive, they are time consuming and labor intensive or require specialized and expensive instrumentation. To overcome many of the above-mentioned limitations, tremendous efforts have been employed to develop sensors and biosensors for the rapid,

sensitive and on-site monitoring of quinolones residue in animal origin foods to ensure food safety. The most important features of a biosensor are specificity and sensitivity. The specificity is influenced by an efficient coupling reaction between biological and transducer components, while the sensitivity is mainly affected by the bioreceptor (enzyme, antibody, RNA/DNA aptamer, synthetic MIP or bacterial cell), biomolecule immobilization procedure and transduction method [16]. One of the most important approaches to increase the sensitivity of a sensor/biosensor is application of nanomaterial. Nanomaterial-based sensors/biosensors provide reagent-free, low limit of detection (LOD) (see **Glossary**), one-step analysis and in some cases label-free assay with high sensitivity and small volume of sample [17-19]. Integration of nanotechnology in sensing can provide a future tool for diagnostic purposes in the area of monitoring antimicrobial drug residues. There is much ongoing research to explore nanomaterial-based sensors and biosensors for the detection of quinolones, yet there is no a comprehensive review to cover recent progress. In this review, we will focus on recent advances in sensors and biosensors that have been developed for the detection of quinolone residues in food samples (Figure 1, Key Figure). We will also evaluate advantages and disadvantages of various types of assays to assess the most rational and sensitive design for the determination of quinolones.

In recent years, different sensors and biosensors have been developed for the detection of quinolones; these apply various detection strategies including optical methods such as colorimetry [20-22], surface-enhanced Raman scattering (SERS) [23, 24], chemiluminescence (CL) [25], fluorescence [5, 26-28] and immunochromatographic assay (ICA) [3, 29, 30]; or electrochemical methods [31-34]. Here, we mainly discuss sensors and biosensors based on various nanomaterials for the detection of quinolones.

Optical Quinolone Sensors/Biosensors

Optical sensors have obtained notable interest for detection of antibiotic residues due to their simplicity of operation, high sensitivity and rapid detection [35]. Quinolone optical techniques are categorized based on the different optical detection methods including colorimetric, chemiluminescence, fluorescence, surface-enhanced Raman scattering and immunochromatographic assays.

Colorimetric Quinolone Sensors/Biosensors

Colorimetric assays are the simplest and most attractive sensing strategies among various optical methods. In these assays, analytes can be detected simply through a colored reagent, and the detection signal can be easily observed by the naked eyes without costly and complicated equipment [36]. The unique physical or chemical properties of metallic nanoparticles make them worthy indicators for colorimetric assays. Among these, gold nanoparticles (AuNPs) are widely employed in colorimetric assays due to size-distance-dependent optical features, catalytic activity, simple synthesis, easy functionalization and high extinction coefficient (1000 times higher than organic dyes) [37, 38]. Kong and coworkers reported a colorimetric assay based on color change of AuNPs for the detection of pazufloxacin mesilate (Figure 2A). In this assay, pazufloxacin mesilate with positive charge induced the aggregation of monodispersed glucose-reduced AuNPs with electronegative charge. The AuNPs aggregation led to color change of solution from red to purple which was easily detectable by naked eye or measurable with UV-vis spectrometer. The developed method was very simple, rapid, inexpensive and without the need for any complicated instruments [39].

In addition to AuNPs, a wide variety of nanomaterials such as cerium oxide nanoparticles, carbon nanotubes (CNTs), graphene oxide (GO), and conjugated polymers can also be used as indicator in colorimetric assays.

The catalytic activity of AuNPs as artificial enzymes means that they can replace natural enzymes in diagnostic process. For example, a colorimetric bioassay based on an aptamer as recognition element, 4-nitrophenol as colorimetric substrate, and surface catalytic activity of AuNPs was developed for the detection of ciprofloxacin (CIPR) (Figure 2B). In this method, AuNPs were modified with two types of DNA probes complementary with CIPR aptamer (cDNA1 and cDNA2). Upon addition of CIPR, aptamers dissociated from cDNA probes and preferentially bound to the target. Therefore, 4-nitrophenol could have access to the surface of AuNPs, resulting in the reduction of 4-nitrophenol to 4-aminophenol (due to the catalytic activity of AuNPs) and the color change of solution from yellow to colorless. The use of catalytic activity of AuNPs resulted in a highly sensitive assay [20].

Fluorescence-based Quinolone Sensors/Biosensors

Fluorescence assays are the most common optical detection techniques; they are extensively used in the design of bioassays and biosensors due to high sensitivity, high efficiency and simple operation [40]. Fluorescence assays can be divided into two groups including labeled and label-free assays. Labeled assays require at least one kind of fluorophores/chromophores and generally utilize fluorescence resonance energy transfer (FRET) to detect various analytes [41]. A variety of fluorophore donors and acceptors such as fluorescent proteins and non-protein organic fluorophores and fluorescent dyes can be employed as a part of FRET-based assay. Recently, nanomaterials with fluorescence and quenching properties are frequently used as alternative for dye labeled assays. In contrary, label-free assays do not need any chromophores or fluorophores in detection process. They include DNA intercalators, abasic-site-binding dyes and metal nanomaterials [42].

Quantum dots (QDs) with unique optical and electronic characteristics including broad absorption bands, long fluorescence lifetime, high resistance to photobleaching and large molar extinction coefficient are considered as novel fluorophores for the development of fluorescent assays [43]. Based on these properties, a nanocomposite containing carboxylic acid functionalized multi-walled carbon nanotubes (MWCNTs) and CdTe QDs incorporated into a molecularly imprinted polymer (MIP) was developed for the determination of CIPR (Figure 3A). The detection process was based on fluorescence quenching of QDs upon CIPR binding to the binding sites on the MIP part of developed nanocomposite. The method was highly sensitive and could detect low concentrations of CIPR in chicken muscle and milk (lower than the MRL values set by EU) [44].

Despite the many advantages of QDs, they suffer from several drawbacks, such as luminescence intermittency, which can cause blinking of the QDs and quantum yield deterioration of dots. However, this problem can be overcome by shell engineering around the core. Further disadvantages include synthesis cost and toxicity of the elements used in their structure. The toxicity of QDs is a main challenge for their application [45]. Upconversion nanoparticles (UCNPs) are considered as a new generation of fluorescent nanomaterials for their unique physicochemical characteristics including high resistance to photobleaching and photoblinking, long lifetime and sharp emission bands. Low toxicity, high color purity, multicolor tunable properties, great chemical stability and low background fluorescence make them ideal to construct fluorescence-based sensors [46]. Liu and colleagues introduced a novel hybrid probe

using double recognition of aptamer-MIP grafted on $\text{NaY}_{0.78}\text{F}_4\text{:Yb}_{0.2}, \text{Tm}_{0.02}$ UCNP for the enrofloxacin (ENR) detection (Figure 3B). The detection mechanism was based on decrease in fluorescence intensity of UCNP in the presence of target ENR. Application of double recognition elements increased the specificity, precision and sensitivity of the assay [47]. In another study, aptamer-functionalized Fe_3O_4 magnetic nanoparticles (MNPs) were used in conjugation with complementary DNA-functionalized UCNP for the detection of ENR (Figure 3C). In this method, the use of magnetic separation property of Fe_3O_4 NPs reduced background signals and increased the assay sensitivity [5].

Among various nanomaterials, two-dimensional nanostructures have considered as promising tools owing to their inherent superior light absorbance and high conductivity. Furthermore, their unique flat structure and large surface area increase loading efficiency of biomolecules. In the case of FRET-based assays, 2D nanostructures provide excellent fluorescence quenching ability by intrasheet energy or electron transfer. GO is one of the most attributed 2D nanomaterials which is commonly applied in FRET-based assays. As an electron acceptor, it can be used as a common quencher for different fluorescent substances [48]. Dolati and colleagues developed a label-free fluorescent assay based on specific aptamers and the fluorescence quenching ability of GO for the detection of ENR (Figure 3D). The native fluorescence of ENR was quenched by adsorption on GO; while ENR-aptamer complex showed less affinity toward GO. The method was very sensitive to detect ENR in milk with a LOD much lower than the MRL [28].

Chemiluminescence-based Quinolone Sensors/Biosensors

Chemiluminescence is the emission of light as a result of a chemical reaction which does not require an excitation source for sample radiation. Due to lack of an excitation source for sample radiation, the interference of light scattering, source instability and high backgrounds can be inhibited. Thus, CL-based sensors are superior to other optical methods such as fluorescence-based sensors [49]. CL assays are widely used for detection of various analytes due to high sensitivity and rapidity. Despite these advantages, only a few CL-based assays have been established for the detection of quinolones. A paper-based CL assay was developed for the detection of ofloxacin (OFL) [25]. In this assay, AgNPs and OFL were dropped on a wax-printed paper and CL signal was measured in the presence of luminol and H_2O_2 . The results showed that

the mixture of AgNPs (as catalyzer of CL reaction) and OFL significantly increased the CL signal.

Surface-Enhanced Raman Scattering-based Quinolone Sensors/Biosensors

Another trend in the field of food safety and bioanalysis is the development of SERS as a molecular fingerprint spectrum to identify each target. SERS is a surface-sensitive technique that relies on the increase in Raman scattering intensity produced by the molecules upon adsorption on rough nanostructured metal surfaces, metallic nanoparticles or by nanostructures such as plasmonic-magnetic silica nanotubes. SERS possesses several advantages including high speed and sensitivity, multiplexing ability, comparatively low cost and portability which enables this technique to be extensively used for sensitive, non-destructive and label-free detection of antibiotics [50]. Hong and coworkers introduced a SERS-based assay using silver-coated nano-gratings fabricated by laser interference lithography for the multiplexing detection of ENR and CIPR. However, the assay showed the high LOQs for both antibiotics [24].

Utilization of metallic nanomaterial in SERS-based assays increases the signal-to-noise ratio and improves LOD. Compared to nanostructured metal surface, noble metal NPs such as AuNPs are widely applied in SERS assays due to their extraordinary electro-optical features, long-term stability and simple synthesis. In this regard, Carrasco and colleagues developed a nanocomposite based on multibranched AuNPs as core, mesoporous silica as shell around AuNPs and MIP as recognition element in outer layer (bAu@mSiO₂@ MIP) for the label-free detection of ENR. Utilization of this nanocomposite resulted in a large enhancement of the Raman scattering of ENR upon binding to the MIP. The branched structure of gold core could act as intrinsic hot spots and localize electromagnetic field of excitation light at the sharp tips resulting in significant field enhancement for SERS [51].

Immunochromatographic-based Quinolone Assays

Immunochromatographic assay (also named as lateral flow assay) as a paper-based strip test is a popular diagnostic approach due to several advantages including simplicity, achieving results in a few minutes, on-site detection, low development costs, ease of production and the need for small volume of the sample. ICA strip is assembled of different parts including sample pad, conjugate pad, nitrocellulose (NC) membrane and absorbent pad pasted on an adhesive plastic

backing. [52]. Various nanomaterials have been explored as label for ICA strips in order to improve the assay sensitivity. Among these, AuNPs are extensively used in ICA for the visualization of analyte/recognition element interaction. Byzova and coworkers developed an ICA to detect OFL in food samples. The assay was based on the competitive binding of OFL and OFL-protein conjugate immobilized on the NC membrane to the AuNPs-labeled antibodies. The assay could detect low concentration of OFL corresponding to the MRL of OFL set by the EU [30].

ICA exhibits the major limitation of low sensitivity. To increase the ICA sensitivity, several strategies have been employed. One of the main strategies is to employ sensitive labels such as fluorescent nanomaterials. Fluorescent labels can increase the ICA sensitivity by at least 10-fold and in some assays up to 300-fold. In this regard, an ICA test based on multicolor QDs was developed for simultaneous detection of OFL, chloramphenicol and streptomycin in milk (Figure 4A). In this assay, monoclonal antibodies specific to each antibiotic were labeled with three types of water-soluble QDs with emission wavelengths at 625, 585 and 525 nm. The LODs obtained for OFL, chloramphenicol and streptomycin were 100, 2.5 and 1000 times lower than the MRL set by EU, respectively [29]. Utilization of QDs significantly improved the assay sensitivity. Moreover, the unique character of this system was multiplex detection on a single substrate which allows to apply it for simultaneous detection of various analytes in different diagnostic fields.

To increase the sensitivity of ICA, Shi and coworkers developed a SERS-based ICA for sensitive and multiplex detection of neomycin and quinolones (Figure 4B). In this assay, two monoclonal antibodies against neomycin and norfloxacin (NOR) were labeled with AuNPs conjugated to the 4-aminothiophenol (as Raman active molecule) and detection was performed through SERS of the 4-aminothiophenol-coated AuNPs captured in the test zone of ICA strips. NOR antibodies had a broad specificity and could react with 13 different quinolones. LODs obtained through SERS were much lower than visual LODs (by using of AuNPs) [3].

Several examples of developed optical sensors and biosensors for the detection of quinolones, including those described here as well as others, are listed in Table 1.

Electrochemical Quinolone Sensors/Biosensors

Electrochemical sensors are powerful analytical tools because of their high sensitivity and selectivity, rapid response time, low cost, ease of operation and the potential for miniaturization. The basic principle of detection in electrochemical sensors is electric current change generated by chemical reactions occurring on the surface of electrode [40]. Electrochemical biosensors incorporate a biological element, as recognition element, and a transducer to transform a biological reaction into a measurable electrochemical signal [16]. Based on the electroanalytical technique which is utilized to measure chemical/biochemical interaction, the electrochemical sensors/biosensors are classified into 4 groups; including conductometric, amperometric, impedimetric and potentiometric [53]. One of the recent trends in the development of electrochemical sensors/biosensors is to use nanomaterials leading to considerable enhancements in their performance in terms of sensitivity, selectivity and response speed of detection [54]. A variety of nanomaterials including carbon nanostructures (e.g., graphite, CNTs), metal and metal oxide nanoparticles, QDs, silica nanoparticles, and other NPs, have been investigated for their application in electrochemical sensors/biosensors [18].

Carbon nanostructures such as carbon nanotubes are a good candidate to construct electrochemical sensors/biosensors due to high chemical stability, great mechanical strength, high surface area, enhanced electron transfer and resistance to fouling. In this regard, He and colleagues developed an OFL electrochemical immunosensor based on dual amplification strategy using glassy carbon electrode (GCE) modified with MWCNT-Poly (L-lysine) (PLL) composite as a substrate and multi-HRP enzyme-antibody-labeled gold nanoflowers (AuNFs) as label [55]. As shown in Figure 5A, modified GCE was applied for the immobilization of OFL antigen as target antigens. In the presence of low amount of OFL target, an immunocomplex was formed between primary antibody, immobilized OFL and multi-HRP–AuNFs–secondary antibody. Electrochemical signal was generated with the aid of hydroquinone as the redox mediator and H_2O_2 .

Carbon black (CB) is a carbon-based nanostructure produced by incomplete combustion of hydrocarbons. Recently, it has been gained considerable attention to fabricate electrochemical sensors due to several advantages such as high surface area, high conductivity and low cost compared with other carbon nanostructures (e.g., CNTs and graphene). CB can be used in combination with metal NPs to enhance the electrochemical signal. Wong and coworkers used CB together with silver nanoparticles (AgNPs) and a conducting polymer named poly(3,4-

ethylenedioxythiophene):poly(4-styrene sulfonate) (PEDOT:PSS) for the surface modification of GCE and voltammetric detection of levofloxacin (LEV). Employing AgNPs provided several advantages such as enhanced electron transfer, fast mass transport, efficient catalysis and increased sensor surface area [56]. The distinctive feature of this sensor was the use of low-cost nanomaterials including AgNPs and CB to improve performance and assay sensitivity.

Carbon dots (CDs) are a class of carbon-based nanomaterials which have attracted a considerable attention in diagnostic purposes. Graphene quantum dots (GQDs) are a group of CDs with excellent properties such as high specific surface area, unique electrical and optical features, low production cost, low toxicity and chemical biocompatibility. Owing to the small size of GQDs, they exhibit several unique properties over micrometer-sized graphene materials. They are a good candidate to apply in electrochemical sensors due to more efficient electron transfer. According to the excellent properties of GQDs, a voltammetric sensor was developed for the detection of LEV in milk samples based on a GCE modified with poly(o-aminophenol)-GQDs nanocomposite (Figure 5B). This nanocomposite provides a high specific surface area and strongly promotes the oxidation current of LEV [32].

Metal nanoparticles play a key role to design electrochemical sensors/biosensors due to several advantages including ease of synthesis and functionalization, high surface area, the enhancement of electron transfer and catalysis of electrochemical reactions [17]. Vanadium oxide (V_2O_5) nanoparticles are a kind of metal NPs with unique electrical, catalytic and optical characteristics. Using electrical and catalytic properties of V_2O_5 NPs and CNTs, our group designed a new sensitive electrochemical aptasensor to detect CIPR in milk samples. In this method, screen printed carbon electrode (SPCE) was modified with CNTs- V_2O_5 NPs-chitosan nanocomposite. Then, CIPR aptamers were immobilized on the surface of modified electrode through electrostatic interactions with cationic chitosan (Figure 5C). Utilization of chitosan improved the electrode stability by forming a film on the electrode surface [57].

Several examples of developed electrochemical sensors and biosensors for the detection of quinolones, including those described here as well as others, are listed in Table 2.

Comparison of Different Types of Sensors/Biosensors

The five most popular optical methods used to detect quinolones are colorimetry, fluorescence, chemiluminescence, SERS and ICA. Each optical detection method possesses its own unique

features. The difference between methods can be related to several factors that affect the biosensor applicability and performance. These include the type of recognition element, sensor compositions and structure, type of sample tested, and measurement procedure used. General goals in the design of all types of biosensors include increased sensitivity and selectivity, reduced detection time, reduced cost, ease of use, miniaturization, portability and eventually commercialization capability.

Among the different optical methods, colorimetric and fluorescence assays are the most popular signal transduction methods. According to the reported LODs of various optical methods, fluorescence assays exhibited the highest sensitivity for the detection of quinolones. This high sensitivity can be attributed to low background fluorescence and sharp emission bandwidths of new-generation nanoparticle labels. For instance, UCNPs fluorescent labels resulted in assays with the highest sensitivity. Similar results have been obtained in the application of UCNPs labels in detecting other analytes. According to the reported data, fluorescent assays that have not used a bioreceptor (antibody, aptamer, etc.) are less sensitive, indicating that bioreceptors are key factors to develop a biosensor. Generally, colorimetric assays that employ AuNPs to produce a visible signal display low sensitivity. In this case, the silver enhancement strategy or a pre-concentration step using MNPs can increase the detection signal and result in a reduced LOD. Another approach to increase the sensitivity of colorimetric assays is the use of nanomaterials with peroxidase-mimicking activity, including metal oxide NPs (CeO_2 , Co_3O_4 , ZnFe_2O_4), noble metal nanomaterials (AuNPs, Ag/Pt NPs, Au/Pd NPs) and carbon-based nanostructures (CNTs, GO and reduced GO), to catalyze a colorimetric reaction through a chromogenic substrate. An ongoing trend in the field of antibiotic detection is the development of sensors/biosensors for point-of-care (POC) testing. Among colorimetric assays, ICA is a prominent example of on-site detection methods that has been commercialized for various analytes. This method suffers from a primary disadvantage of low sensitivity. As reported in Table 1, several strategies such as using QDs instead of AuNPs and combining this method with a sensitive technique (*i.e.*, SERS, chemiluminescence and fluorescence) have been able to overcome this limitation. Generally, ICA is considered a qualitative method, although it can be quantified by a flatbed scanner or smartphone. The basic principle of this method is relying on high-resolution camera of smartphone. Smartphone camera acquires an image of test strip, which is analyzed and processed by a dedicated app installed on the smartphone (Box 1).

In addition to optical assays, electrochemical sensors and biosensors have been frequently used for the detection of quinolones. Overall, electrochemical methods have demonstrated better sensitivity than optical methods. However, as reported in Table 2, electrochemical biosensors represent a higher sensitivity compared to electrochemical sensors due to application of receptors that specifically bind to the antibiotic target. In this review, CIPR electrochemical biosensor based on aptamer-immobilized SPGE and single-stranded DNA-binding protein, and also OFL biosensor using GCE modified with MWCNTs-PLL exhibited the lowest LOD. The high sensitivity of these biosensors can be attributed to high sensitivity and specificity of aptamer (as bioreceptor), application of nanomaterials for the electrode modification, and enhanced amount of immobilized HRP (as electrochemical signal producer) due to high specific surface of nanomaterials.

A main characteristic in the fabrication of electrochemical sensors/biosensors with high efficiency is the appropriate selection of transducer surface. Good electrode materials not only possess high conductivity and catalytic activity to accelerate signal transduction, but also amplify detection events with specifically designed signal labels, resulting in high sensitivity. As mentioned previously, modification of electrodes with different nanomaterials has increased the conductivity, response speed and sensitivity to obtain a lower LOD for the detection of quinolones in complex samples. Recently, enormous efforts have been made to fabricate nanocomposite-based electrodes using noble metals or metal oxide nanoparticles combined with carbon nanostructures or polymer materials. The resulted nanocomposites not only are excellent platforms for the immobilization of bioactive molecules (e.g., enzyme and aptamer), but also enhance the sensitivity due to the synergistic effect of nanomaterials.

Concluding Remarks and Future Perspectives

Widespread usage of quinolones in livestock production and quinolone residues in animal-derived foods can lead to the development of antimicrobial resistance and increasing concerns related to human health. Some recent studies have focused on the development of on-field detection of quinolones to prevent their abuse. However, the number of studies conducted on quinolones is limited compared to other antibiotics. The conventional analytical methods for quinolones are sensitive and specific enough, but they are not suitable for rapid and on-site detection. Moreover, they are time consuming and labor intensive. Therefore, design and

development of new diagnostic methods such as sensors/biosensors with improved characteristics are required to overcome these limitations. In this regard, sensors and biosensors based on nanomaterials offer several advantages such as real-time analysis, easy-to-handle, low LOD and low volume of required sample for analysis. However, developing nanomaterial-based sensors/biosensors for real sample analysis requires determining the main goal of application. For qualitative and semi-quantitative detection, colorimetric methods such as ICA can be good candidates due to fast detection and simplicity which results can be observed by the naked eyes. However, colorimetric assays suffer from low sensitivity. To avoid this problem, fluorescence assays with high sensitivity can be chosen. In this case, a fluorophotometer is required which sophisticated this method. However, many efforts have been made to design a portable fluorophotometer to overcome this limitation. For the accurate and quantitative detection of low concentrations of antibiotics, electrochemical methods are a suitable option, although complex sample pretreatments are required. Thus, each type of biosensor should be selected according to its own advantages and limitations and based on our goals in order to obtain the best results (see Outstanding Questions). Some quinolone biosensors are already commercially available. For instance, Bioo Scientific Company developed rapid strip tests based on lateral flow assay (LFA) or ICA for the detection of fluoroquinolones residues in milk. The assay is semi-quantitative and uses a competitive colloidal gold based format with a detection time of 4 minutes. Charm Scientific® has also produced LFA strips for the detection of 11 quinolones in milk within 3 minutes. LFA strips developed by Elabscience® can detect quinolones in honey and different tissues. The limited number of commercial products indicate that there is still an urgent need to research and develop quinolone biosensors with commercialization potential. In fact, research in the field of antibiotics biosensors and especially quinolones biosensors is still immature compared with other biosensing fields. In the case of nanomaterial-based biosensors which are growing in recent years, many technical hurdles such as biocompatibility of nanomaterials with the bio-recognition elements, the effect of non-uniform nanomaterials on the performance of biosensors, suitable connection between nanomaterial and bio-recognition element and cross reactions within antibiotics, should be considered [43]. In addition, the main challenge in practical application of biosensors is their application in real and complex samples. Most biosensors are restricted to the laboratory scale and have not reached the end user. In many cases their sensitivity and selectivity are influenced by real sample conditions such as interfering

components (e.g., lipids, proteins, vitamins, and carbohydrates), ionic strength, pH and viscosity. Furthermore, non-specific interaction of bio-recognition molecule with sample components can lead to false positive results. Therefore, in most biosensors, sample pretreatment is required, which should be simplified as much as possible with the aim of to be tested in the future in real and complex samples. Moreover, research efforts should be focused on improving the bio-recognition elements to increase resistance towards environmental conditions. The design of and application of receptors that specifically bind to the antibiotic of interest is critical to develop biosensors with high sensitivity and specificity. Thus, biosensors are more sensitive than chemical sensors developed for the detection of quinolones (see Table 2). As discussed in this review, antibodies and DNA aptamers are the most commonly used bioreceptors to design various types of biosensors. Each of these receptors possesses its own advantages and disadvantages. Unlike aptamers, antibodies are less stable towards adverse environmental conditions such as pH, ionic strength and temperature; they are not as complicated to engineer; and their stability is not affected by modification [58]. Due to sophisticated chemical and biological modification of aptamers and antibodies, there is a growing interest in developing synthetic molecular recognition elements such as MIPs, which are expected offer strong recognition but so far lack the specificity offered by their natural counterparts. To overcome the lack of specificity, a combination of various bioreceptors is recommended to develop a biosensor with high specificity. Simultaneous application of multiple recognition elements increases the specificity, precision and sensitivity of the assay.

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Table 1. Representative examples of recent optical sensors/biosensors for the detection of quinolones

Detection method	Strategy	Target	LOD (ng mL ⁻¹)	Linear range (ng mL ⁻¹)	Assay time	Sample	Ref.
Colorimetry	Aggregation of glucose-reduced AuNPs	Pazufloxacin	2.32	28.65-222.80	15 min	-	[39]
Colorimetry	Reduction-catalyzing activity of aptamer/cDNA-functionalized AuNPs	Ciprofloxacin	0.43 0.86 1.06	1.3-165.7	1 h	Water, serum and milk	[20]
Fluorescence	Fluorescence quenching of QDs incorporated into MIP upon target binding to MIP	Ciprofloxacin	0.07	0.1-1 and 1-100	7 min	Chicken muscle and milk	[44]
Fluorescence	Double recognition of aptamer-MIP grafted on NaY0.78F4:Yb0.2, Tm0.02 UCNPs	Enrofloxacin	0.04	0.5-10	nr	Fish	[47]
Fluorescence	Aptamer-functionalized Fe ₃ O ₄ MNPs in combination with cDNA-functionalized UCNPs	Enrofloxacin	0.06	1-10	nr	Fish	[5]
Fluorescence	Label-free assay based on specific aptamers and the fluorescence quenching ability of GO	Enrofloxacin	1.3	1.8-89.8	nr	Milk	[28]
Fluorescence	An immunoassay based on coating-antigen-modified polystyrene particles as immunesensing probes and antibody-coated UCNPs as fluorescent-signal probes	Norfloxacin	0.01	0.01-10	50 min	Milk, chicken, pork kidney	[59]
Fluorescence	Fluorescence quenching of silver nanocluster by Cu ²⁺ in the absence of quinolones	Nalidixic acid Cinoxacin Ciprofloxacin Ofloxacin	0.11 0.11 0.012 0.018	0.23-23 0.26-21 0.03-39.76 0.04-28.8	10 min	Serum, urine	[60]
Fluorescence	Fluorescence quenching of CdTe QDs by sparfloxacin	Sparfloxacin	83.7 8	280-40 × 10 ³	10 min	Water, serum	[61]
Fluorescence	Fluorescence quenching of the 3-mercaptopropionic acid capped CdS QDs by Cu ²⁺ in the absence of ciprofloxacin	Ciprofloxacin	13	43-49702	5 min	Pharmaceutical and serum	[62]
Fluorescence	Competitive reaction between	Enrofloxacin	0.20	1-80	nr	Water	[27]

	dissolved fluoroquinolones and AuNPs labeled with corresponding antigen for binding to antibody-labeled UCNPs	Ciprofloxacin Norfloxacin	0.19 0.32	nr nr			
Chemiluminescence	Paper assay based on enhancement of CL intensity of luminol-H ₂ O ₂ system by AgNPs	Ofloxacin	0.3	1-1000	nr	Eye drop	[25]
Surface-enhanced Raman scattering (SERS)	Label-free assay based on silver-coated nano-gratings	Enrofloxacin Ciprofloxacin	1000	nr	nr	Water	[24]
SERS	Label-free assay based on multibranched Au-mesoporous silica nanoparticles coated with MIP	Enrofloxacin	0.54	nr	10 min	-	[51]
SERS							
Immunochromatographic assay (ICA)	A competitive assay based on AuNPs-labeled antibodies	Ofloxacin	30	0.2-50	10 min	Milk	[30]
ICA	Simultaneous detection of several antibiotics using three types of QDs as label	Ofloxacin Chloramphenicol Streptomycin	0.3, 0.12, 0.2	1.5-200, 0.14-10, 0.3-500	10 min	Milk	[29]
ICA	SERS-based ICA using AuNPs conjugated to the 4-aminothiophenol as label	Norfloxacin Neomycin	0.37×10^{-3} 0.55×10^{-3}	0.0001-1.0	nr	Milk	[3]
ICA	Near-infrared fluorescence based multiplexed ICA using monoclonal antibodies conjugated with NIR dye	Enrofloxacin	4	0.08-2	20 min	Milk	[63]
ICA	Two types of ICA using monoclonal antibodies conjugated with two kinds labels including dyed polymer microspheres and QDs	Enrofloxacin	1, 5, 10	nr	20 min	Buffer, animal tissue, milk	[64]

nr: Not reported

Table 2. Representative examples of recent electrochemical sensors/biosensors for the detection of quinolones

Detection method	Strategy	Target	LOD (ng mL ⁻¹)	Linear range (ng mL ⁻¹)	Assay time	Sample	Ref.
Cyclic voltammetry (CV)	Antibody immobilization on the surface of GCE modified with MWCNTs-PLL and the use of multi-HRP enzyme-antibody-labeled AuNFs as label	Ofloxacin (<i>R</i> -OFL and <i>S</i> -OFL enantiomers)	0.30 and 0.15	0.37-12.8 and 0.26-25.6	60 min	-	[55]
Electrochemical impedance spectroscopy (EIS) and CV	GCE modified with CB, AuNPs and PEDOT:PSS film	Levofloxacin	5.06	242.1-4336.4	nr	Water	[56]
Differential pulse voltammetry (DPV)	GCE modified with poly(o-aminophenol)-GQDs nanocomposite	Levofloxacin	3.61	18.07-36137	nr	Milk	[32]
EIS and CV	Aptamer immobilization on the surface of SPCE modified with CNTs- V ₂ O ₅ NPs-chitosan nanocomposite	Ciprofloxacin	0.5	0.5-64.0	3 h	Milk	[57]
DPV	Aptamer immobilization on the surface of AuNPs-coated GCE	Ofloxacin	0.4	18-7227	24 s	Water, plant sewage	[65]
CV	Oxidation moxifloxacin hydrochloride by electrocatalytic activity of carbon paste electrode modified with AgNPs	Moxifloxacin hydrochloride	1.3	306-78821	nr	Tablet, urine	[66]
DPV	Inhibition of SSB interaction with ciprofloxacin aptamer immobilized on SPGE and access of redox probe to the electrode surface	Ciprofloxacin	0.09	0.3-132	< 1 h	Milk, serum	[67]
DPV	CPE modified with β -cyclodextrin and L-arginine	Ciprofloxacin Ofloxacin Norfloxacin Gatifloxacin	4.4 14.4 12.8 7.5	21.9-43800 36.1-36100 31.9-12760 22.5-37500	nr	Serum, tablet	[68]
DPV and CV	CPE modified with AgNPs and electrospun CeO ₂ -Au composite nanofibers	Levofloxacin	3.6 8	10.8-3614	nr	Serum, urine	[69]
Square wave voltammetry (SWV)	Electrochemical sensor based on boron doped diamond electrode	Levofloxacin	1041	3614-28909	nr	Serum, urine	[70]

DPV	GCE modified with electro-polymerized β -cyclodextrin/ reduced graphene oxide	Gatifloxacin	7.5	18.8-56309	nr	Urine, tablet	[71]
SWV	CPE modified with graphene oxide and ionic liquids	Ofloxacin	0.2	2.5-253	nr	Urine, ophthalmic samples	[72]
DPV	GCE modified with MIP polypyrrole-graphene-AuNPs	Levofloxacin	191	361-36100	4 min	-	[73]
CV and SWV	SPCE modified with AuNPs/Chitosan composite film	Ciprofloxacin	0.4	44-65684	nr	Serum, plasma, urine	[74]
Anodic stripping voltammetry (ASV)	GCE modified with CdS QDs	Ciprofloxacin	9.6	44-4379	nr	Urine	[75]
ASV	GCE modified with graphene	Ciprofloxacin	26	44-4379	3 min	Tablet	[76]
CV	GCE modified with MIP/ mesoporous carbon composite nanoparticles	Ofloxacin	29	180-36137	6 min	-	[77]
SWV	GCE modified with graphene oxide and nickel oxide nanoparticles	Ciprofloxacin	2.6	17.5-424.8	nr	Serum, urine	[78]

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nr: Not reported

Box 1

Smartphone-based sensors/biosensors

Currently much efforts have been focused on miniaturization of sensors/biosensors. In this way, smartphone-based biosensors have been introduced as a new generation of analytical devices to achieve real-time and point-of-care (POC) detection of analytes [79]. Smartphone has been extensively integrated with sensors/biosensors including sensor chips and test strips for detection processes due to its portability, rapid sensing, low cost, simple to perform and ubiquitous availability [80]. Smartphone-based biosensors are designed based on two major formats, where the smartphone can be served as detector or as instrumental interface. In the first case (smartphone as detector), smartphone is combined with a device that includes the elements of an apparatus in a simplified format. The smartphone camera is used for the detection of output signal. In the latter case (smartphone as instrumental interface), smartphone is interfaced with the bioanalytical apparatus through a micro USB, Bluetooth, or Wi-Fi. In this approach, the apparatus accomplishes the measurement and the smartphone controls the experimental setup and displays the result on the screen, such as a mini laptop computer [79]. A variety of smartphone-based biosensors with different detection strategies such as colorimetric (e.g., absorbance, reflectance), luminescence (e.g., bioluminescence, chemiluminescence, electrochemiluminescence, photoluminescence) and electrochemical detection have been developed for various analytes. Smartphone-based colorimetric biosensors are the most common systems using smartphone camera as a detector [79]. Due to advantages and performances of smartphone-base biosensors, they are widely applied in healthcare diagnosis, food quality evaluation, drug screening, biosecurity and environmental monitoring [79, 80]. Several smartphone-based devices have been commercially developed for colorimetric detection using smartphone camera as colorimeter. The AssayColor app. produced by Alidans s.r.l. can be used for colorimetric analysis in microplate. A mobile diagnostic reader, named mReader™, and Instantaneous Analysis™ software was designed by Mobile Assay Inc. for reading and colorimetric analysis of ICA strips using the smartphone [79]. Despite many advantages of smartphone-based biosensors, only a few POC systems have been developed for antibiotic detection especially quinolones. Thus, much effort should be further taken to establish such systems to simplify the detection and quantification of antibiotics including quinolones.

Glossary

Aptamer: Single-stranded nucleic acid (DNA or RNA) ligand obtained from in vitro selection named Systematic Evolution of Ligands by Exponential Enrichment (SELEX), which can bind to a target with high affinity and specificity.

Carbon dots (CDs): Small-sized carbon nanoparticles with a diameter of less than 10 nm and some forms of surface passivation.

Carbon nanotubes (CNTs): Allotropes of carbon which take the form of hollow seamless cylinders with a diameter of less than 1 nm and lengths up to several centimeters. They are composed of one or more layers of graphene defined single-wall, SWCNT, or multiwall, MWCNT.

Cyclic voltammetry (CV): A type of electrochemical technique which measures current as a function of the applied voltage.

Differential pulse voltammetry (DPV): An electrochemical method where the current is measured before each potential change, and the current difference is plotted as a function of potential.

Electrochemical impedance spectroscopy (EIS): An electrochemical method which current is measured versus as a function of the applied potential at different frequencies.

Fluoroquinolones: They are produced by addition of fluoride to the original quinolone antibiotics and exhibit an increased antimicrobial activity and improved pharmacokinetic characteristics.

Fluorescence resonance energy transfer (FRET): One of the most common techniques used to design fluorescent labeled assays. It is based on the utilization of two sets of particles including fluorescence particles as donors and quencher particles as acceptors. The fluorescence of the donor can be quenched by the acceptor when the donor and acceptor come to close proximity (< 10 nm).

Glassy carbon electrode (GCE): A type of electrode which combines glassy and ceramic characteristics with graphite.

Graphene: An allotrope of carbon consisting of a single layer of carbon atoms arranged in a rigid hexagonal configuration.

Limit of detection (LOD): The lowest quantity of a measured analyte which can be detected by an analytical approach.

Molecular imprinted polymer (MIP): A polymeric matrix produced by the molecular imprinting technique which forms cavities in the polymer matrix fit to shape and functional groups of template molecule. These polymeric materials can recognize a given target with high affinity.

Quantum dots (QDs): Semiconductor small particles (with diameters in the range of 2-10 nm) made out of the elements from II-VI, III-V, and IV-VI groups. They possess unique optical and electronic characteristics.

Screen-printed electrode (SPE): A disposable combined electrode (including reference, working, and counter electrodes) based on gold, carbon, silver, platinum or CNTs inks.

Upconversion nanoparticles (UCNPs): Nanoscale particles (1–100 nm) that exhibit photon upconversion (absorbance and conversion of several low energy photons, such as NIR, into one emitted photon with higher energy, such as visible or UV. UCNPs are usually composed of lanthanide- or actinide-doped transition metals.

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Figure Legends

Figure 1. Schematic illustration of formation and application of optical and electrochemical sensors/biosensors for the detection of quinolones.

Figure 2. Colorimetric assays for detection of antibiotics. (A) colorimetric detection of pazufloxacin mesilate based on AuNPs aggregation; (B) colorimetric detection of ciprofloxacin (CIPR) using AuNPs modified with complementary strands and CIPR aptamer. Reproduced from [20, 39] with permission.

Figure 3. Different fluorescent biosensors based on nanomaterials. (A) COOH@MWCNT-MIP-QDs nanocomposite for the detection of ciprofloxacin; (B) preparation of aptamer-MIP/UCNPs hybrid probe and enrofloxacin detection; (C) hybrid of aptamer-MNPs and UCNPs nanoprobe for the detection of enrofloxacin; (D) label-free fluorescent assay based on GO for the enrofloxacin detection. Reprinted from [5, 28, 44, 47] with permission. Abbreviations: MWCNT, multi-walled carbon nanotube; MIP, molecular imprinted polymer; QDs, quantum dots; UCNPs, upconversion nanoparticles; GO, graphene oxide.

Figure 4. Nanomaterials-based ICA for detection of antibiotics. (A) simultaneous detection of three antibiotics using ‘traffic light’ ICA (1. test line for streptomycin (STM); 2. test line for chloramphenicol (CAP); 3. test line for ofloxacin (OFL); 4. QD-STM mAb conjugate; 5. QD-CAP mAb conjugate; 6. QD-OFL mAb conjugate; 7. control line; (B) SERS-based ICA for the detection of neomycin (NEO) and norfloxacin (NOR). Reproduced from [3, 29] with permission.

Figure 5. Different electrochemical sensors/biosensors based on nanomaterials. (A) ofloxacin immunosensor based on MWCNTs/PLL substrate and multi-HRP–AuNFs-antibody bioconjugates as the label in the presence of hydroquinone electron mediator (HQ) and H_2O_2 ; (B) levofloxacin voltammetric sensor based on GCE coated with electropolymerized PoAP/GQDs nanocomposite; (C) ciprofloxacin aptasensor based on SPCE coated with CNTs-V2O5-chitosan nanocomposite. Reproduced from [32, 55, 57] with permission. Abbreviations: MWCNTs/PLL, multi-walled carbon nanotubes/Poly (L-lysine); HRP, horse radish peroxidase; AuNFs, quantum gold nanoflowers; GCE, glassy carbon electrode; PoAP/GQDs, poly(o-aminophenol)/graphene quantum dots; SPCE, screen printed carbon electrode; CNTs, carbon nanotubes.

Detection

Nanomaterials

Sensor

Optical

Electrochemical

Figure 2

(A)

(B)

(C)

Figure 3

Figure 4

(A)

(B)

(C)

Figure 5