Trends in Biotechnology

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REVIEWS

Review

Optical and Electrochemical Sensors and Biosensors for the Detection of Quinolones

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One major concern associated with food safety is related to residual effects of antibiotics that are widely used to treat animals and result in antimicrobial resistance. Among different groups of antibiotic, the use of quinolones in livestock is of major concern due to the significance of these antimicrobial drugs for the treatment of a range of infectious diseases in humans. Therefore, it is desirable to develop reliable methods for the 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 quinolone sensors and biosensors.

Highlights

Detection of quinolone residues in animal-derived foods is vital to ensure public health and avoid antimicrobial resistance.

Electrochemical and optical sensors and biosensors are powerful analytical tools for real-time analysis of various samples.

Immunochromatographic strip-based optical assays are useful for the rapid and on-site detection of quinolones.

Electrochemical sensors with high sensitivity and selectivity have the potential for miniaturization and fabrication of portable devices, which are preferred in diagnostic fields, such as food quality control.

Integration of nanomaterials in sensors and biosensors results in assays with higher sensitivity and rapid response.

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 both therapeutics and growth-promotion agents, can lead to antibiotic residues in animal-derived foods, which affect 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), ~23 000 deaths occur annually in the USA due to infections caused by antibiotic-resistant bacteria [1]. Various types of antibiotic 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 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 -negative bacteria [3,4]. They are widely used to treat bacterial infections in animals, including poultry and fish. However, residues of these drugs in animal-derived foods, such as meat, chicken, milk, eggs, and honey, can lead to several adverse effects, including the development of antimicrobial resistance and inefficiency of antibiotic therapy in humans with bacterial infections and gastrointestinal irritation [5]. The production and usage of quinolones is high due to their low cost. For instance, the annual consumption of quinolones in the USA, European Union (EU), South Korea, and Japan is ~70 tons for generic quinolones and 50 tons for proprietary products. In China, the annual consumption of quinolones in animals is estimated to be in the range of 470 tons and annual consumption is ~1350 tons 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 adverse effects of the quinolone residues, 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 from 30 to 800 $\mu g\ kg^{-1}$ [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 HPLC [7,9], 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

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 https://doi.org/10.1016/j.tibtech.2019.01.004

above-mentioned limitations, tremendous efforts have focused on the development of sensors and biosensors for the rapid, sensitive, and on-site monitoring of quinolone residues in animal-origin foods to ensure food safety.

The most important features of a biosensor are its 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** (see Glossary), 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 or biosensor is the application of nanomaterials. Nanomaterial-based sensors and biosensors provide reagent-free, low **limit of detection** (LOD), one-step analysis, and, in some cases, label-free assays with high sensitivity and requiring a small sample volume [17–19]. The integration of nanotechnology in sensing can provide a future tool for diagnostics for monitoring antimicrobial drug residues. Despite ongoing research to explore nanomaterial-based sensors and biosensors for the detection of quinolones, a comprehensive review of this recent progress has been lacking. Therefore, we focus here 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 also evaluate the advantages and disadvantages of various types of assay 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 assays (ICAs) [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 and Biosensors

Optical sensors have been the focus of research for the 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 used, including colorimetric, CL, fluorescence, SERS, and ICAs.

Colorimetric Quinolone Sensors and Biosensors

Colorimetric assays are the simplest and most attractive sensing strategies among the various optical methods available. In these assays, analytes can be detected simply through a colored reagent, and the detection signal can be easily observed by the naked eye without costly and complicated equipment [36]. The unique physical or chemical properties of metallic nanoparticles (NPs) make them useful indicators for colorimetric assays. Among these, gold NPs (AuNPs) are widely used in colorimetric assays due to size–distance-dependent optical features, catalytic activity, simple synthesis, easy functionalization, and high extinction coefficients (1000 times higher than organic dyes) [37,38]. Kong and coworkers reported a colorimetric assay based on color changes of AuNPs for the detection of pazufloxacin mesilate (Figure 2A). In this assay, pazufloxacin mesilate, which has a positive charge, induced the aggregation of monodispersed glucose-reduced AuNPs with an electronegative charge. AuNP aggregation led to a change in the color of the solution from red to purple, which was easily detectable by the naked eye or measurable with a UV–vis spectrometer. The developed method was very simple, rapid, inexpensive, and without the need for any complicated instruments [22].

Glossary

Aptamer: single-stranded nucleic acid (DNA or RNA) ligand obtained from *in vitro* selection [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 NPs with a diameter of <10 nm and some form of surface passivation.
Carbon nanotubes (CNTs): allotropes of carbon that take the form of hollow seamless cylinders with a diameter of <1 nm and lengths of up to several centimeters. They comprise one or more layers of graphene, defined as single-wall CNTs (SWCNTs) or multiwall CNTs (MWCNTs).
Cyclic voltammetry (CV): a type of electrochemical technique that 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 in which current is measured versus as a function of the applied potential at different frequencies.
Fluoroquinolones: produced by the addition of fluoride to original quinolone antibiotics; exhibit increased antimicrobial activity and improved pharmacokinetic characteristics.
Fluorescence resonance energy transfer (FRET): one of the most common techniques used to design florescent labeled assays. It is based on the utilization of two sets of particles: 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 into close proximity (<10 nm).
Glassy carbon electrode (GCE): a type of electrode that combines glassy and ceramic characteristics with graphite.
Graphene: an allotrope of carbon comprising a single layer of carbon

Key Figure

Schematic Illustration of the Formation and Application of Optical and Electrochemical Sensors and Biosensors for the Detection of Quinolones Residues in Animal-Derived Foods.

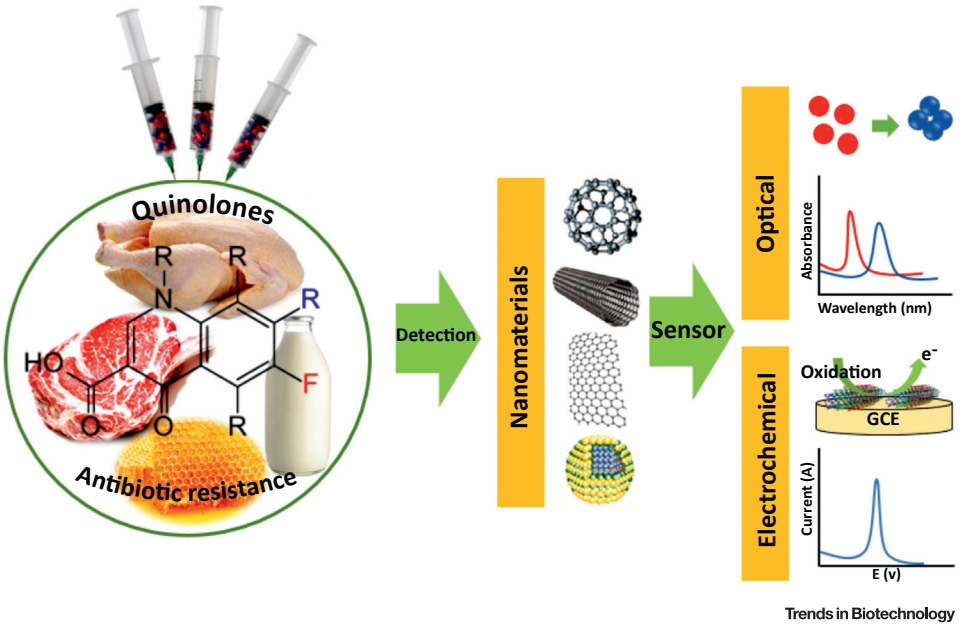


Figure 1.

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

The catalytic activity of AuNPs as artificial enzymes means that they can replace natural enzymes in diagnostic processes. For example, a colorimetric bioassay based on an aptamer as the recognition element, 4-nitrophenol as the colorimetric substrate, and the 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 probe complementary to the CIPR aptamer (cDNA1 and cDNA2). Upon addition of CIPR, aptamers dissociated from cDNA probes and preferentially bound to the target. Therefore, 4-nitrophenol had access to the surface of the AuNPs, resulting in the reduction of 4-nitrophenol to 4-aminophenol (due to the catalytic activity of AuNPs) and the color change of the solution from yellow to colorless. The use of the catalytic activity of AuNPs resulted in a highly sensitive assay [20].

Fluorescence-based Quinolone Sensors and Biosensors

Fluorescence assays are the most common optical detection techniques; they are extensively used in the design of bioassays and biosensors due to their high sensitivity, high efficiency, and

atoms arranged in a rigid hexagonal configuration.

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

Molecular imprinted polymer (MIP): a polymeric matrix produced by the molecular imprinting technique in the presence of template molecule. This technique 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) comprising the elements from II–VI, III–V, and IV–VI groups. They have unique optical and electronic characteristics.

Screen-printed carbon electrode (SPCE): a disposable combined electrode (including reference, working, and counter electrodes) based on Au, carbon, Ag, platinum, or CNT inks.

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

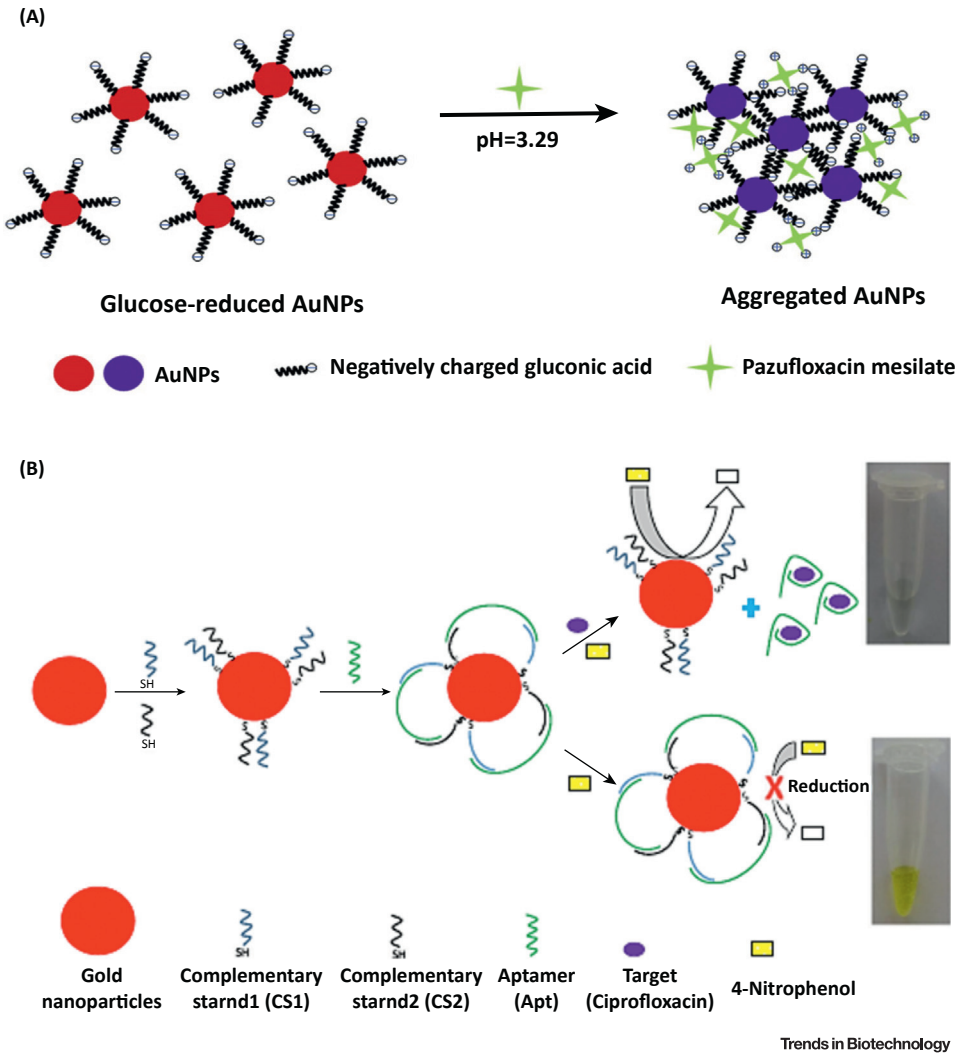


Figure 2. Colorimetric Assays for the Detection of Antibiotics. (A) Colorimetric detection of pazufloxacin mesilate based on gold nanoparticle (AuNP) aggregation; (B) colorimetric detection of ciprofloxacin (CIPR) using AuNPs modified with complementary strands and a CIPR aptamer. Reproduced, with permission, from [20,22].

simple operation [39]. Fluorescence assays can be divided into two groups, namely labeled and label-free assays. Labeled assays require at least one kind of fluorophore and/or chromophore and generally utilize **fluorescence resonance energy transfer** (FRET) to detect various analytes [40]. A variety of fluorophore donors and acceptors, such as fluorescent proteins and nonprotein organic fluorophores and fluorescent dyes, can be used as part of FRET-based assays. Nanomaterials with fluorescence and quenching properties are frequently used as alternatives for dye-labeled assays. By contrast, label-free assays do not need any chromophores or fluorophores for the detection process. They include DNA intercalators, abasic site-binding dyes, and metal nanomaterials [41].

Quantum dots (QDs), with unique optical and electronic characteristics including broad absorption bands, long fluorescence lifetime, high resistance to photobleaching, and large

molar extinction coefficients, are considered novel fluorophores for the development of fluorescent assays [42]. Based on these properties, a nanocomposite containing carboxylic acid-functionalized multi-walled CNTs (MWCNTs) and cadmium telluride (CdTe) QDs incorporated into a **molecularly imprinted polymer** (MIP) was developed for the determination of CIPR (Figure 3A). The detection process was based on the fluorescence quenching of QDs upon CIPR binding to the binding sites on the MIP part of the 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 the EU) [43].

Despite the many advantages of QDs, they have several drawbacks, such as luminescence intermittency, which can cause blinking of the QDs and quantum yield deterioration of dots. However, this 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 to their application [44]. **Upconversion NPs** (UCNPs) are a new generation of fluorescent nanomaterials owing to 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, high chemical stability, and low background fluorescence make them ideal for use in the construction of fluorescence-based sensors [45]. Liu and colleagues introduced a novel hybrid probe using double recognition of

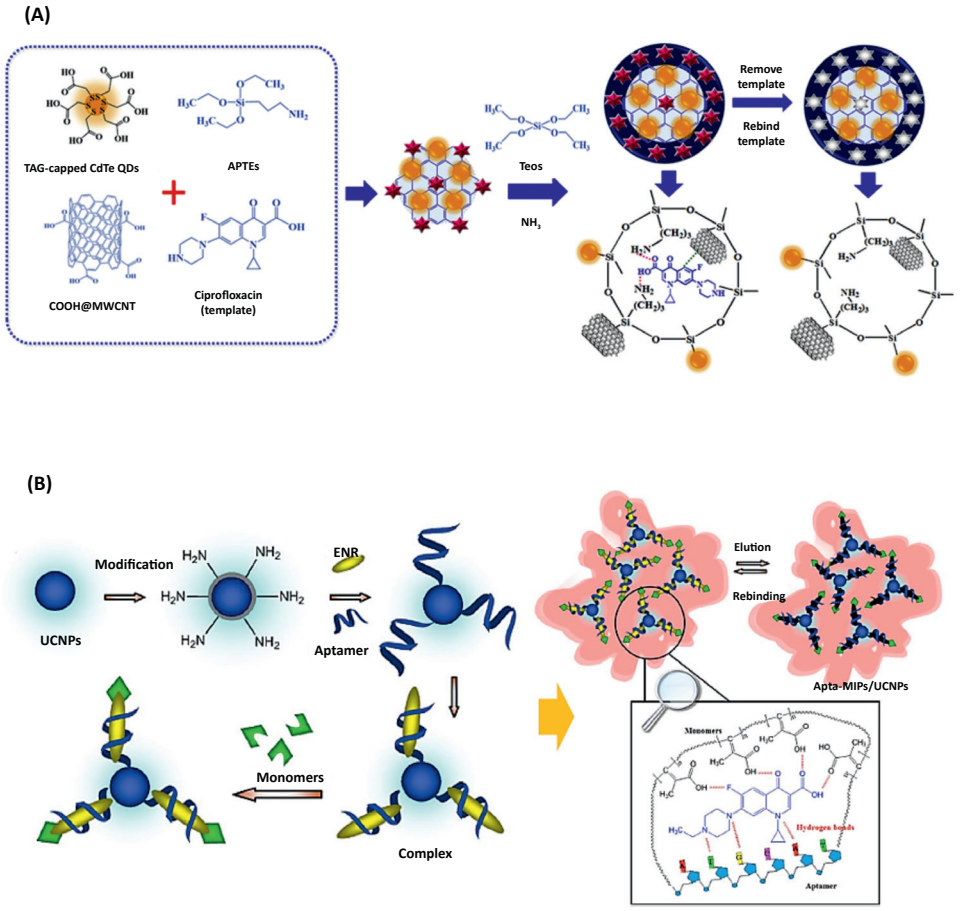
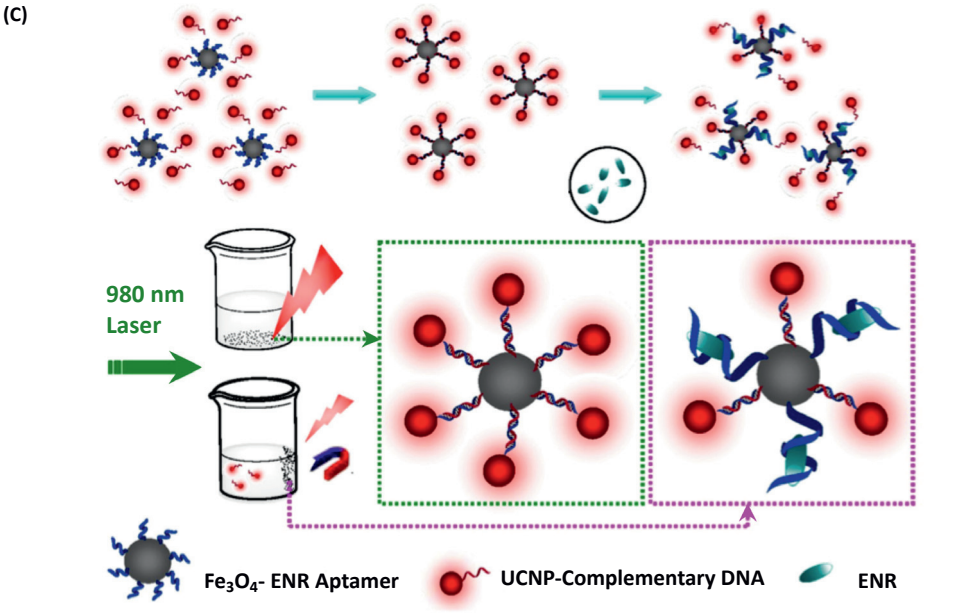


Figure 3. (Continued).



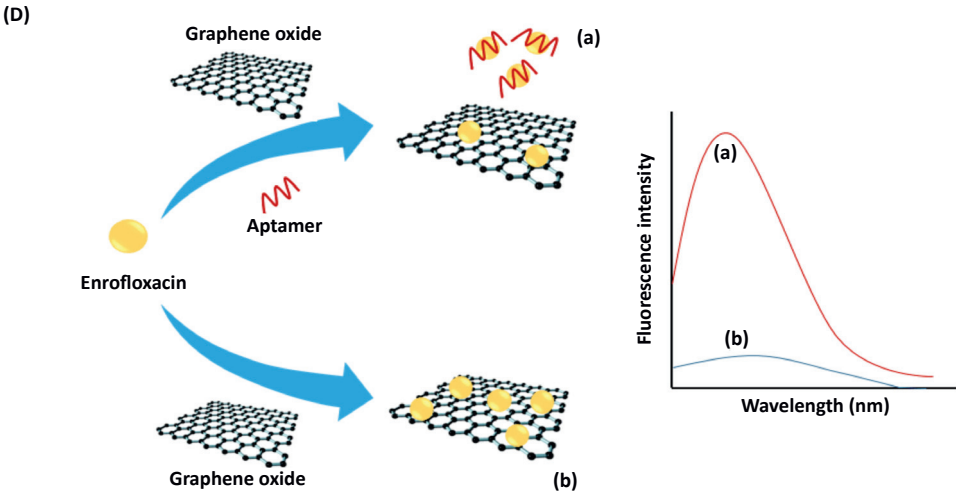


Figure 3. Different Fluorescent Biosensors Based on Nanomaterials. (A) COOH@multiwalled carbon nanotube (MWCNT)-molecularly imprinted polymer (MIP)-quantum dot (QD) nanocomposite for the detection of ciprofloxacin; (B) preparation of aptamer-MIP/upconversion nanoparticle (UCNP) hybrid probe for enrofloxacin detection; (C) hybrid of aptamer-magnetic nanoparticle (MNP) and UCNP nanoprobes for the detection of enrofloxacin; and (D) label-free fluorescent assay based on graphene oxide (GO) for enrofloxacin detection. Reprinted, with permission, from [5,28,43,46].

aptamer-MIPs grafted onto $NaY_{0.78}F_4$:$Yb_{0.2}$, $Tm_{0.02}$ UCNPs for the detection of enrofloxacin (ENR) (Figure 3B). The detection mechanism was based on a decrease in the fluorescence intensity of UCNPs in the presence of target ENR. The application of double recognition elements increased the specificity, precision, and sensitivity of the assay [46]. In another study, aptamer-functionalized Fe_3O_4 magnetic NPs (MNPs) were used in conjugation with complementary DNA-functionalized UCNPs for the detection of ENR (Figure 3C). In this method, the use of the magnetic separation properties of Fe_3O_4 NPs reduced background signals and increased the assay sensitivity [5].

Among various nanomaterials, 2D nanostructures are promising tools owing to their inherent superior light absorbance and high conductivity. Furthermore, their unique flat structure and large surface area increase the loading efficiency of biomolecules. In the case of FRET-based assays, 2D nanostructures provide excellent fluorescence quenching ability based on intra-sheet energy or electron transfer. GO is a 2D nanomaterial that is commonly applied in FRET-based assays. As an electron acceptor, it can be used as a common quencher for different fluorescent substances [47]. 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, whereas the ENR-aptamer complex showed less affinity toward GO. The method was very sensitive and able to detect ENR in milk with a LOD lower than that of the MRL [28].

Chemiluminescence-based Quinolone Sensors and Biosensors

CL is the emission of light as a result of a chemical reaction that does not require an excitation source for sample radiation. Due to the 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 [48]. CL assays are widely used for the detection of various analytes due to their 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, silver NPs (AgNPs) and OFL were dropped onto a wax-printed paper and the CL signal was measured in the presence of luminol and H_2O_2. The results showed that the mixture of AgNPs (as a catalyzer of the CL reaction) and OFL significantly increased the CL signal.

Surface-enhanced Raman Scattering-based Quinolone Sensors and 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 NPs, or by nanostructures, such as plasmonic-magnetic silica nanotubes. SERS has several advantages, including high speed and sensitivity, multiplexing ability, comparatively low cost, and portability, which enables this technique to be extensively used for the sensitive, nondestructive, and label-free detection of antibiotics [49]. Hong and coworkers introduced a SERS-based assay using Ag-coated nanogratings fabricated by laser interference lithography for the multiplexing detection of ENR and CIPR. However, the assay showed high LOQs for both antibiotics [24].

Utilization of metallic nanomaterials in SERS-based assays increases the signal:noise ratio and improves LOD. Compared with nanostructured metal surfaces, 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 the core, mesoporous silica as the shell around AuNPs, and MIP as the recognition element in the outer layer (bAu@mSiO_2@ MIP) for the label-free detection of ENR. Utilization of this nanocomposite resulted in significant enhancement of the Raman scattering of ENR upon binding to the MIP. The branched structure of the Au core can act as an intrinsic hot spot and localize the electromagnetic field of excitation light at the sharp tips, resulting in significant field enhancement for SERS [50].

Immunochromatographic-based Quinolone Assays

ICAs (also named as lateral flow assays) as paper-based strip tests are a popular diagnostic approach due to several advantages, including simplicity, ability to achieve results in only a few minutes, on-site detection, low development costs, ease of production, and the need for a small sample volume. ICA strips are assembled of different parts, including a sample pad, conjugate pad, nitrocellulose (NC) membrane, and an absorbent pad pasted on an adhesive plastic backing [51]. Various nanomaterials have been explored as labels for ICA strips to improve the assay sensitivity. Among these, AuNPs are extensively used in ICAs for the visualization of analyte–recognition element interactions. Byzova and coworkers developed an ICA to detect OFL in food samples. The assay was based on the competitive binding of OFL and an OFL-protein conjugate immobilized on the NC membrane to the AuNP-labeled antibodies. The assay could detect a low concentration of OFL corresponding to the MRL of OFL set by the EU [30].

The major limitation of ICAs are their low sensitivity. To increase this sensitivity, several strategies have been developed. One of the main strategies is to use sensitive labels, such as fluorescent nanomaterials. Fluorescent labels can increase the ICA sensitivity by at least tenfold and, in some assays, up to 300-fold. In this regard, an ICA test based on multicolor QDs was developed for the 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 QD 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 the 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 enables it to be applied for the 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 4-aminothiophenol (as the 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 have a broad specificity and can react with 13 different quinolones. LODs obtained through SERS were lower than those achieved with visual LODs (by use 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 and 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 an electric current change generated by chemical reactions occurring on the surface of an electrode [39]. Electrochemical

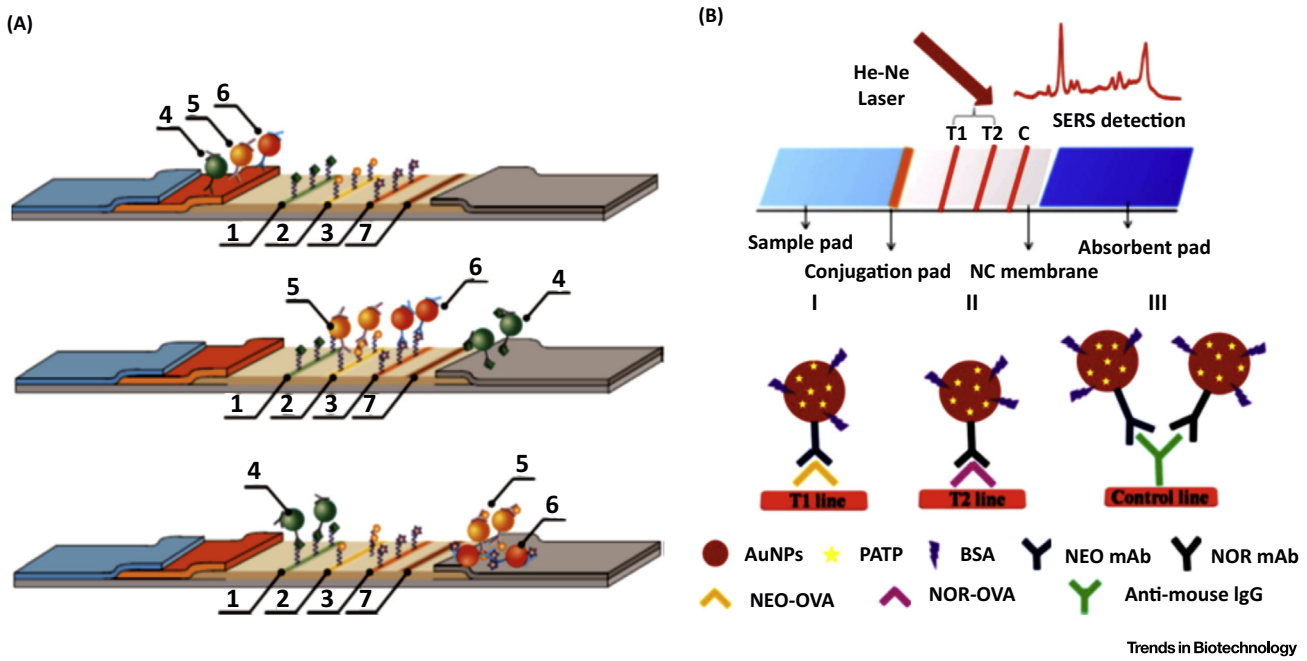


Figure 4. Nanomaterial-Based Immunochromatographic Assays (ICAs) for the Detection of Antibiotics. (A) Simultaneous detection of three antibiotics using 'traffic light' ICA [(1. test line for streptomycin (STM); 2. test line for chloramphenicol (CAP); 3. test line for ofloxacin (OFL); 4. Quantum dot (QD)-STM monoclonal antibody (mAb) conjugate; 5. QD-CAP mAb conjugate; 6. QD-OFL mAb conjugate; 7. control line]; and (B) surface-enhanced Raman scattering (SERS)-based ICA for the detection of neomycin (NEO) and norfloxacin (NOR). Reproduced, with permission, from [3,29].

Table 1. Representative Examples of Recent Optical Sensors and Biosensors for the Detection of Quinolones[a]

Detection method	Strategy	Target	LOD (ng ml^{-1})	Linear range (ng ml^{-1})	Assay time	Sample	Refs
Colorimetry	Aggregation of glucose-reduced AuNPs	Pazufloxacin	2.32	28.65–222.80	15 min	–	[22]
	Reduction-catalyzing activity of aptamer/cDNA-functionalized AuNPs	CIPR	0.43, 0.86, 1.06	1.3–165.7	1 h	Water, serum, milk	[20]
Fluorescence	Fluorescence quenching of QDs incorporated into MIP upon target binding to MIP	CIPR	0.07	0.1–1 and 1–100	7 min	Chicken muscle, milk	[43]
	Double recognition of aptamer-MIP grafted on NaY0.78F4: Yb0.2, Tm0.02 UCNPs	ENR	0.04	0.5–10	nr	Fish	[46]
	Aptamer-functionalized Fe_3O_4 MNPs in combination with cDNA-functionalized UCNPs	ENR	0.06	1–10	nr	Fish	[5]
	Label-free assay based on specific aptamers and fluorescence quenching ability of GO	ENR	1.3	1.8–89.8	nr	Milk	[28]

Table 1. (continued)

Detection method	Strategy	Target	LOD (ng ml^{-1})	Linear range (ng ml^{-1})	Assay time	Sample	Refs
	Immunoassay based on coating-antigen-modified polystyrene particles as immunosensing probes and antibody-coated UCNPs as fluorescent-signal probes	NOR	0.01	0.01–10	50 min	Milk, chicken, pork kidney	[58]
	Fluorescence quenching of Ag nanoclusters by Cu^{2+} in absence of quinolones	Nalidixic acid Cinoxacin CIPR OFL	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	[59]
	Fluorescence quenching of CdTe QDs by sparfloxacin	Sparfloxacin	83.7, 8	280–40 × 10^3	10 min	Water, serum	[60]
	Fluorescence quenching of 3-mercaptopropionic acid-capped CdS QDs by Cu^{2+} in absence of CIPR	CIPR	13	43–49 702	5 min	Pharmaceuticals, serum	[61]
	Competitive reaction between dissolved fluoroquinolones and AuNPs labeled with corresponding antigen for binding to antibody-labeled UCNPs	ENR CIPR NOR	0.20 0.19 0.32	1–80 nr nr	nr	Water	[27]
CL	Paper assay based on enhancement of CL intensity of luminol-H_2O_2 system by AgNPs	OFL	0.3	1–1000	nr	Eye drops	[25]
SERS	Label-free assay based on Ag-coated nanogratings	ENR, CIPR	1000	nr	nr	Water	[24]
	Label-free assay based on multibranched Au-mesoporous silica NPs coated with MIP	ENR	0.54	nr	10 min	–	[50]
ICA	Competitive assay based on AuNP-labeled antibodies	OFL	30	0.2–50	10 min	Milk	[30]
	Simultaneous detection of several antibiotics using three types of QD as label	OFL, chloramphenicol, streptomycin	0.3, 0.12, 0.2	1.5–200, 0.14–10, 0.3–500	10 min	Milk	[29]
	SERS-based ICA using AuNPs conjugated to 4-aminothiophenol as label	NOR Neomycin	0.37 × 10^{-3} 0.55 × 10^{-3}	0.0001–1.0	nr	Milk	[3]
	Near-infrared fluorescence-based multiplex ICA using monoclonal antibodies conjugated with NIR dye	ENR	4	0.08–2	20 min	Milk	[62]
	Two types of ICA using monoclonal antibodies conjugated with two kinds label, including dyed polymer microspheres and QDs	ENR	1, 5, 10	nr	20 min	Buffer, animal tissue, milk	[63]

[a]nr, not reported.

biosensors incorporate a biological element, a recognition element, and a transducer to transform a biological reaction into a measurable electrochemical signal [16]. Based on the electroanalytical technique utilized to measure chemical and biochemical interactions, the electrochemical sensors and biosensors can be classified into four groups: conductometric, amperometric, impedimetric, and potentiometric [52]. One of the recent trends in the development of electrochemical sensors and biosensors is to use nanomaterials leading to considerable enhancement of their performance in terms of sensitivity, selectivity, and response speed of detection [53]. A variety of nanomaterials, including carbon nanostructures (e.g., graphite and CNTs), metal and metal oxide NPs, QDs, silica NPs, and other NPs, have been investigated for their application in electrochemical sensors and biosensors [18].

Carbon nanostructures, such as CNTs, are a good candidate for use when constructing electrochemical sensors and biosensors due to their high chemical stability, great mechanical strength, high surface area, enhanced electron transfer, and resistance to fouling. He and colleagues developed an OFL electrochemical immunosensor based on a dual amplification strategy using **glassy carbon electrodes** (GCE) modified with a MWCNT-poly(L-lysine) (PLL) composite as a substrate and multi-horseradish peroxidase (HRP) enzyme-antibody-labeled Au nanoflowers (AuNFs) as a label [54]. As shown in Figure 5A, modified GCE was applied for the immobilization of OFL antigens as target antigens. In the presence of a low amount of OFL target, an immunocomplex was formed between the primary antibody, immobilized OFL, and multi-HRP–AuNF–secondary antibody. An 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 the incomplete combustion of hydrocarbons. Recently, it has received considerable attention for use in the fabrication of 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 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). The use of AgNPs provided several advantages, such as enhanced electron transfer, fast mass transport, efficient catalysis, and an increased sensor surface area [55]. The distinctive feature of this sensor was the use of low-cost nanomaterials, including AgNPs and CB, to improve the performance and sensitivity of the assay.

Carbon dots (CDs) are a class of carbon-based nanomaterials that have attracted considerable attention for use in diagnostics. Graphene QDs (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 for use 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 a poly(o-aminophenol)-GQDs nanocomposite (Figure 5B). This nanocomposite provided a high specific surface area and strongly promoted the oxidation current of LEV [32].

Metal nanoparticles have a key role in the design electrochemical sensors and 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

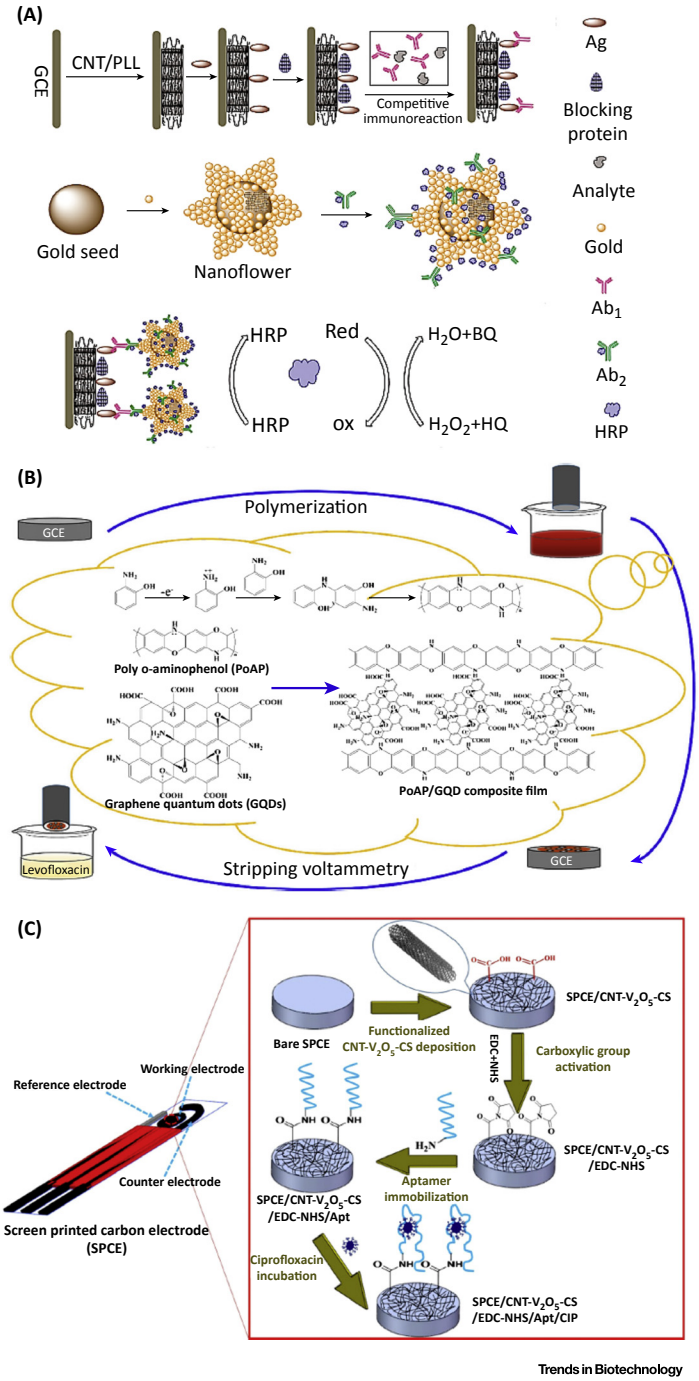


Figure 5. Different Electrochemical Sensors and Biosensors Based on Nanomaterials. (A) Ofloxacin immunosensor based on multiwalled carbon nanotube (MWCNT)/poly(L-lysine) (PLL) substrate and multi-horseradish peroxidase (HRP)–quantum gold nanoflowers (AuNF)-antibody (Ab) bioconjugates as the label in the presence of a hydroquinone electron mediator (HQ) and H_2O_2; (B) levofloxacin voltammetric sensor based on glassy carbon electrode (GCE) coated with an electropolymerized poly(o-aminophenol)/graphene quantum dot (PoAP/GQD) nanocomposite; and (C) ciprofloxacin aptasensor based on screen-printed carbon electrode (SPCE) coated with CNT-V2O5-chitosan nanocomposite. Reproduced, with permission, from [32,54,56].

oxide (V_2O_5) NPs are metal NPs with unique electrical, catalytic, and optical characteristics. Using electrical and catalytic properties of V_2O_5 NPs and CNTs, a new sensitive electrochemical aptasensor was designed to detect CIPR in milk samples. In this method, **screen-printed carbon electrodes** (SPCE) were modified with a CNT-V_2O_5 NP-chitosan nanocomposite. CIPR aptamers were then immobilized on the surface of the modified electrodes through electrostatic interactions with cationic chitosan (Figure 5C). Utilization of chitosan improved the electrode stability by forming a film on the electrode surface [56].

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

Comparison of Different Types of Sensor and Biosensor

The five most popular optical methods used to detect quinolones are colorimetry, fluorescence, CL, SERS, and ICA. Each optical detection method has its own unique features. The differences between methods are 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 biosensor 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 NP labels. For instance, UCNP fluorescent labels resulted in assays with the highest sensitivity. Similar results have been obtained in the application of UCNP labels in the detection of 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 in the development of a biosensor. Generally, colorimetric assays that use AuNPs to produce a visible signal display low sensitivity. In this case, the Ag enhancement strategy or a preconcentration 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, and $ZnFe_2O_4$), noble metal nanomaterials (AuNPs, Ag/Pt NPs, and 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 and 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 has 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, CL, 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 relies on the use of the high-resolution camera on a smartphone. The smartphone camera can be used to take an image of the 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

Table 2. Representative Examples of Recent Electrochemical Sensors/Biosensors for the Detection of Quinolones[a]

Detection method	Strategy	Target	LOD (ng ml^{-1})	Linear range (ng ml^{-1})	Assay time	Sample	Refs
Cyclic voltammetry (CV)	Antibody immobilization on surface of GCE modified with MWCNTs-PLL and multi-HRP enzyme-antibody-labeled AuNFs as label	OFL (*R*-OFL and *S*-OFL enantiomers)	0.30 and 0.15	0.37–12.8 and 0.26–25.6	60 min	–	[54]
Electrochemical impedance spectroscopy (EIS) and CV	GCE modified with CB, AuNPs, and PEDOT:PSS film	LEV	5.06	242.1–4336.4	nr	Water	[55]
Differential pulse voltammetry (DPV)	GCE modified with poly(o-aminophenol)-GQDs nanocomposite	LEV	3.61	18.07–36137	nr	Milk	[32]
EIS and CV	Aptamer immobilization on surface of SPCE modified with CNT- V_2O_5 NP-chitosan nanocomposite	CIPR	0.5	0.5–64.0	3 h	Milk	[56]
DPV	Aptamer immobilization on surface of AuNP-coated GCE	OFL	0.4	18–7227	24 s	Water, plant sewage	[31]
CV	Oxidation of moxifloxacin hydrochloride by electrocatalytic activity of carbon paste electrode modified with AgNPs	Moxifloxacin hydrochloride	1.3	306–78 821	nr	Tablet, urine	[64]
DPV	Inhibition of SSB interaction with ciprofloxacin aptamer immobilized on SPGE and access of redox probe to electrode surface	CIPR	0.09	0.3–132	$<$ 1 h	Milk, serum	[34]
DPV	CPE modified with β-cyclodextrin and L-arginine	CIPR OFL NOR Gatifloxacin	4.4 14.4 12.8 7.5	21.9–43 800 36.1–36 100 31.9–12 760 22.5–37 500	nr	Serum, tablet	[65]
DPV and CV	CPE modified with AgNPs and electrospun CeO_2-Au composite nanofibers	LEV	3.6, 8	10.8–3614	nr	Serum, urine	[66]
Square wave voltammetry (SWV)	Electrochemical sensor based on boron-doped diamond electrode	LEV	1041	3614–28 909	nr	Serum, urine	[67]
DPV	GCE modified with electro-polymerized β-cyclodextrin/reduced GO	Gatifloxacin	7.5	18.8–56 309	nr	Urine, tablet	[68]
SWV	CPE modified with GO and ionic liquids	OFL	0.2	2.5–253	nr	Urine, ophthalmic samples	[69]
DPV	GCE modified with MIP polypyrrole-graphene-AuNPs	LEV	191	361–36 100	4 min	–	[70]
CV and SWV	SPCE modified with AuNPs/chitosan composite film	CIPR	0.4	44–65 684	nr	Serum, plasma, urine	[71]
Anodic stripping voltammetry (ASV)	GCE modified with CdS QDs	CIPR	9.6	44–4379	nr	Urine	[72]
ASV	GCE modified with graphene	CIPR	26	44–4379	3 min	Tablet	[73]
CV	GCE modified with MIP/mesoporous carbon composite NPs	OFL	29	180–36137	6 min	–	[74]
SWV	GCE modified with GO and nickel oxide NPs	CIPR	2.6	17.5–424.8	nr	Serum, urine	[75]

[a]nr, not reported.

Box 1. Smartphone-based Sensors and Biosensors

Currently, many efforts are focused on the miniaturization of sensors and 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 [76]. Smartphones have been extensively integrated with sensors and biosensors, including sensor chips and test strips, for detection processes due to their portability, rapid sensing, low cost, simple use, and ubiquitous availability [77]. Smartphone-based biosensors are designed based on two major formats, where the smartphone can be served as either a detector or an instrumental interface. In the first case (as detectors), a 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 signals. In the latter case (as an instrumental interface), a 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 [76]. A variety of smartphone-based biosensors with different detection strategies, such as colorimetric (e.g., absorbance and reflectance), luminescence (e.g., bioluminescence, CL, electrochemiluminescence, and photoluminescence), and electrochemical detection have been developed for various analytes. Smartphone-based colorimetric biosensors are the most common systems using smartphone cameras as detectors [76]. Due to the advantages and performance of smartphone-base biosensors, they are widely applied in healthcare diagnosis, food-quality evaluation, drug screening, biosecurity, and environmental monitoring [76,77]. Several smartphone-based devices have been commercially developed for colorimetric detection using smartphone cameras as colorimeters. The AssayColor app. produced by Alidans s.r.l. can be used for colorimetric analysis on a microplate. A mobile diagnostic reader, the mReaderTM, and Instantaneous AnalysisTM software was designed by Mobile Assay Inc. for reading and colorimetric analysis of ICA strips using smartphones [76]. Despite their advantages, only a few POC systems have been developed for antibiotic detection, especially of quinolones. Thus, more research should focus on establishing such systems to simplify the detection and quantification of antibiotics, including quinolones.

Outstanding Questions

What type of optical or electrochemical sensor has the potential to be marketed?

What changes should be made for the development of sensors in accordance with market requirements?

How can we improve the performance of sensors for more efficient detection of low concentrations of antibiotics in complex samples, such as foodstuffs?

How can we simplify sample preparation before detection by sensors?

How can we improve the sensitivity of sensors by incorporating nanomaterials?

better sensitivity than optical methods. However, as reported in Table 2, electrochemical biosensors have higher sensitivity compared with electrochemical sensors due to the application of receptors that specifically bind to the antibiotic target. In this review, CIPR electrochemical biosensor based on aptamer-immobilized screen-printed gold electrode (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 the high sensitivity and specificity of the aptamer (as the bioreceptor), application of nanomaterials for the electrode modification, and enhanced amount of immobilized HRP (as electrochemical signal producer) due to the high specific surface of nanomaterials.

A main characteristic of the fabrication of electrochemical sensors and biosensors with high efficiency is the appropriate selection of the transducer surface. Good electrode materials not only have 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 NPs 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. Recent studies have focused on the development of techniques for the on-field detection of quinolones to prevent their abuse. However, the number of studies conducted on quinolones is limited compared with 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, the design and development of new diagnostic methods, such as sensors and 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, being easy to handle, low LOD, and low sample volume required for analysis. However, developing nanomaterial-based sensors and biosensors for real sample analysis requires determining the main goal of application. For qualitative and semiquantitative detection, colorimetric methods, such as ICA, are suitable candidates due to fast detection and simplicity, with results that can be observed by the naked eye. However, colorimetric assays have low sensitivity. To avoid this problem, fluorescence assays with high sensitivity can be chosen. In this case, a fluorophotometer is required and many efforts have been made to design portable fluorophotometers. 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 the end goals to obtain the best results (see Outstanding Questions). Some quinolone biosensors are already commercially available. For instance, the Bioo Scientific Company developed rapid strip tests based on lateral flow assays (LFA) or ICA for the detection of **fluoroquinolone** residues in milk. The assay is semiquantitative and uses a competitive colloidal Au-based format with a detection time of 4 min. Charm Scientific® also produced LFA strips for the detection of 11 quinolones in milk within 3 min. LFA strips developed by Elabscience® can detect quinolones in honey and different tissues. The limited number of commercial products indicates 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, especially quinolone biosensors, is still immature compared with other biosensing fields. In the case of nanomaterial-based biosensors, many technical hurdles, such as biocompatibility of nanomaterials with the biorecognition elements, the effect of non-uniform nanomaterials on the performance of biosensors, suitable connection between the nanomaterial and biorecognition element, and cross-reactions within antibiotics, should be considered [42]. In addition, the main challenge to the practical application of biosensors is their application in real and complex samples. Most biosensors are restricted to the laboratory scale and have not yet 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, nonspecific interactions of biorecognition molecules 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 so that it can be tested in the future in real and complex samples. Moreover, research efforts should focus on improving the biorecognition elements to increase resistance toward environmental conditions. The design 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 (Table 2). As discussed in this review, antibodies and DNA aptamers are the most commonly used bioreceptors in the design of various types of biosensor. Each of these receptors has its own advantages and disadvantages. Unlike aptamers, antibodies are less stable in 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 [57]. Due to sophisticated chemical and biological modifications of aptamers and antibodies, there is growing interest in developing synthetic molecular recognition elements, such as MIPs, which are expected to 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.

Acknowledgments

This study was supported by Shiraz University and University of Perpignan.

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