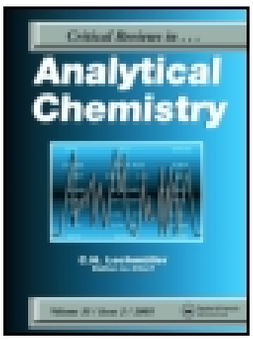

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Recent Development in Sample Preparation and Analytical Techniques for Determination of Quinolone Residues in Food Products

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Abstract

Used heavily in food animal production, quinolones occur widely in food products of animal origin. Development of highly sensitive and selective analytical techniques for the detection of quinolone residues, often at trace levels, in food samples is necessary to ensure food safety and understand their public health risk. With complex matrices, food samples typically require a series of pretreatment steps, such as powdering, homogenization, deproteinization, and filtration. This review summarizes the recent advances in extraction, concentration, and detection techniques for quinolones in food product samples, and briefly compares the advantages and limitations of major techniques. Recent development of quick, easy, cheap, effective, rugged,

and safe (QuEChERS) extraction method, and immunoassay- and biosensor-based detection methods for the determination of quinolones residues in food products are discussed in details. A perspective on the trends and needs of future research is also presented.

Keywords

Quinolones; food products; quick, easy, cheap, effective, rugged, and safe (QuEChERS) method; liquid chromatography-mass spectrometry (LC-MS); immunoassay; biosensor.

Abbreviations

AMI amifloxacin

BAL balofloxacin

BEN benofloxacin

CAD caderofloxacin

CIN cinoxacin

CIP ciprofloxacin

CLI Clinafloxacin

DAN danofloxacin

DIF difloxacin

ENO enoxacin

ENR enrofloxacin

FLE fleroxacin

FLU flumequine

FRE frefloxacin

GAR Garenoxacin

GAT gatifloxacin

GEM gemifloxacin

GRE grepafloxacin

LEV levofloxacin

LOM lomefloxacin

MAR marboflxacin

MOX moxifloxacin

NA Nalidixic acid

NOR norfloxacin

NOX noxacin

OA oxolinic acid

OFL ofloxacin

ORB orbifloxacin

PA piromidinic acid

PAZ pazufloxacin

PEF pefloxacin

PIP pipemidic acid

PRU prulifloxacin

RUF Rufloxacin

SARA sarafloxacin

SPA sparfloxacin

TRO Trovafloxacin

TOS Tosufloxacin.

1. Introduction

With broad antimicrobial spectrum, good oral absorption, and low cost, quinolones are considered as one of the most successful classes of synthetic antimicrobial drugs (Sharma et al. 2009). They act directly on bacterial DNA by inhibiting topoisomerase and have strong and fast antimicrobial effects (Andreu et al. 2007). Since the introduction of nalidixic acid in 1962, various quinolone compounds have been produced from modifications of the basic 4-quinolone structure (Figure 1) to improve antimicrobial activity and increase pharmacokinetic performance (Sharma et al. 2009). With the further expansion of their antibacterial spectrum, quinolones are divide into different generations. Currently, the quinolones have been developed to the fourth generation, fluoroquinolones, which are derived with the addition of a fluorine atom at the 6-position of the central ring structure (Sharma et al. 2009), while the second (ciprofloxacin, lomefloxacin, norfloxacin and enrofloxacin) and third generation (levofloxacin) of quinolones are the most commonly used ones (Table 1). Quinolones can have one or more ionizable functional groups, depending on their structures (Figure 1). For example, nalidixic acid has only one ionizable carboxylate group, whereas ciprofloxacin, lomefloxacin, and norfloxacin have both carboxylate group and 4'-amino group on the piperazine ring. With a carboxyl group, or both

carboxyl and amine groups, quinolones can undergo acid-base speciation in aqueous solutions. The zwitterion form predominates in neutral solutions, whereas the cationic and the anionic forms are predominant in acidic and basic solutions, respectively.

Quinolones are heavily used in human health care as therapeutic agents for general bacterial infections, and in animal farming as feed additives for disease prevention and/or growth promotion, and in aquaculture as antifungal drugs for inhibiting fungal growth (Hu and Cheng, 2015, 2016). The majority of quinolones administered to humans and animals are excreted unchanged in feces and urine (Migliore et al. 2003). Because of their strong adsorption potentials (K_{OC} = 496-61,000 L/kg for ciprofloxacin, norfloxacin and ofloxacin) (Picó and Andreu. 2007), most of quinolones are not degraded in wastewater treatment plants, but adsorb on the sludge, with small fractions remaining in the treated effluent (Golet et al. 2003, Tong et al. 2011). The undegraded quinolones are subsequently released into the environment with the sludge and effluent, while they are not very susceptible to microbial degradation in the environment (Halling-Sørensen et al. 2000, Marengo et al. 1997). With the continuous inputs of quinolones and their degradation products into the environment, they can disrupt the structure of soil microbial communities and induce selection and emergence of antimicrobial resistance (Hu and Cheng, 2014, 2015, 2016). As a result of their ubiquitous uses, quinolones have been widely detected in waters at concentrations in the ranges of ng/L to μg/L, and in soils, sediments, and organisms at μg/kg to mg/kg levels around the world (Hu et al. 2010b, Watkinson et al. 2009). In addition, quinolones in the environmental media (soil, water, and sediment) can be absorbed by plants, particular vegetables, and accumulate in their edible parts. It has been found that concentrations of quinolones can be up to several hundred μg/kg in vegetable samples collected from organic vegetable bases (Hu et al. 2010b) and vegetable cultivation fields (Li et al. 2014),

with the concentrations generally decreasing in the order of leaf > stem > root (Hu et al. 2010b). Certain fractions of quinolones administered to animals can be absorbed and metabolized in animal bodies, resulting in residues in animal food products (e.g., eggs, milks, and meats) when not fully eliminated. The wide use, particularly misuse and overuse of quinolones in factory farming, elevates the potential for excessive residues in the animal food products. Serious food safety problems can arise from these residues once they occur at levels beyond those considered safe for human consumption (Hu and Cheng, 2016). As a result, regular monitoring of the contents of quinolones in the food products of animal origin is necessary to protect the health of consumers (Hu and Cheng, 2015, 2016). To ensure food safety, maximum residue limits (MRLs) of several quinolones in animal-based foods have been established by regulatory agencies and government authorities worldwide (EU 2009, 2010, WHO 2003, MOA 2002, 2003). For quinolones in different types of tissues, MRLs ranging from 10 to 1,900 μg/kg have been set in these regulations, depending on the specific compounds.

The highly complex matrices of food samples usually require sample pretreatment, which typically involves homogenization, filtration, purification, extraction, and pre-concentration to remove any unwanted matrix components and enrich the analytes to concentrations appropriate for subsequent analysis. Quinolones in the prepared samples can then be identified and quantified using a range of analytical instruments or techniques. Derivatization of quinolones, which aims to improve the detection sensitivity for reducing matrix interference (Davydov et al. 2013, Phonkeng et al. 2012, Tong et al. 2015, Xia et al. 2013, 2014a) and/or the polarity of target analytes for increasing the extraction efficiency (Xia et al. 2014b), has been studied for analyzing trace quinolones in food samples. For detection with liquid chromatography (LC), off-line pre-column derivatization and on-line post column are often used, while mathematical derivatization

of chromatographic data has also been applied for resolving the overlapping peaks (Phonkeng et al. 2012). Most of current research efforts focus on developing new sample pretreatment and detection techniques rather than derivatization methods. Therefore, derivatization of quinolones is not discussed further in this review.

Advances made on analytical methods for quinolones in food and environmental samples between 2002 and 2006 have been systematically reviewed (Andreu et al. 2007). The study concludes that solvent extraction (SE) with subsequent solid phase extraction (SPE) was the mostly used extraction procedure, with the former being used for quinolone isolation and the latter for clean-up and analyte enrichment, respectively. Compared to ultraviolet (UV) and fluorescence detection, mass spectrometry (MS) is much more sensitive, selective, and specific. Ideally, an analytical methodology should detect as many quinolones as possible, require simple sample pretreatment, and have high sample throughput and low cost. Recent efforts on the analysis of quinolone residues in food samples have focused primarily on the development of inexpensive, less labor-intensive pretreatment, and fast detection methods. This review first gives a brief overview on the recent development of analytical methods for quinolone residues in food samples, focusing on studies over the past 8 years (since 2009). The advantages and limitations of the major methods for pretreatment and analysis of quinolones are discussed, with focuses on the recent development of quick, easy, cheap, effective, rugged, and safe (QuEChERS) extraction method, and immunoassay- and biosensor-based methods for detection of quinolones residues. Finally, an outlook on the future trends and research needs for determination of quinolone resides in food products is presented.

2. Sample Preparation Methods for Quinolones in Food Samples

Table 1 summarizes the separation and instrumental detection methods for quinolones in food products, including the quinolones analyzed, sample matrix, sample preparation procedure, separation setup, and method sensitivity, reported in peer reviewed literature since 2009. An analytical methodology for quinolones in food samples typically involves sample preparation, followed by detection using analytical instrument or other techniques. Sample preparation is a crucial step in qualitative and quantitative analysis of quinolones, which involves sample pretreatment and extraction for isolating quinolones from the sample matrix, concentrating or converting them into the forms tailored to the analytical tools.

2.1. Sample Pretreatment

As depicted on Figure 2, a series of pretreatment steps are often necessary before extraction of quinolones from food samples due to their complex matrices. For various food products, the difficulty of sample preparation can be largely different, with vegetables and honey being the easiest to handle. Vegetable samples are typically processed with ultrasound-assisted extraction (UAE) using methanol and hydrochloric acid (1:1, v:v) (Hu et al. 2010b), while honey samples could be processed with (Kaufmann et al. 2011) or without (Meng et al. 2014) pretreatment. Food products of animal origin (e.g., milk, fish, meats, and eggs) are typically rich in proteins and fat, on which quinolones can bind strongly because of their lipophilicity and formation of hydrogen bonds (Li et al. 2012). Thus removal of proteins and fat is necessary before extraction of quinolones from these types of samples. Unlike liquid food samples (i.e., milk) that can be extracted directly after deproteinization and filtration, solid food samples (such as meats and eggs) need to be first powdered and homogenized (before or simultaneously with

deproteinization), which can be achieved through grinding with purified sand (Martins et al. 2014) or in a food processor (Lombardo-Agüí et al. 2014a, Moema et al. 2012).

Various organic solvents can be used to cause precipitation of the proteins in food samples. Methanol can quickly extract quinolones from milk and muscle, but it has poor performance in protein and fat removal (Granelli et al. 2009, Kaufmann et al. 2011, Nebot et al. 2012). Acetonitrile is highly efficient at precipitating proteins and has low co-extraction of lipids, and the proteins are more denatured in aqueous-acetonitrile mixtures than in pure acetonitrile (Li et al. 2012). In pure acetonitrile, the secondary structure of protein remains essentially intact and analytes can be packaged as proteins quickly gather together. It has been reported that 90% acetonitrile solution can completely precipitate proteins of fish tissues with the quinolones well released (Li et al. 2012). Trichloroacetic acid (TCA)-induced protein precipitation is also a popular method, and 5% TCA has been shown to work well for extracting multiple classes of veterinary drugs, including quinolones, from chicken muscles (Chiaochan et al. 2010). Ethanol, which has low selectivity and can dissolve milk fat, can also be used as an extraction solvent due to its low toxicity, while addition of organic acids can improve the extraction yields of quinolones from milk samples (Martins et al. 2014, Watkinson et al. 2009). Inorganic acids (e.g., phosphoric acid and HCl (Springer et al. 2014)) and their mixtures with salts (e.g., mixture of NaCl and phosphoric acid (Gao et al. 2011)) can also purify milk, while $(NH_4)_2SO_4$ alone cannot effectively remove the matrix interference (Mi et al. 2014). Meanwhile, it has been shown that pH (Gao et al. 2011, Junza et al. 2014, Meng et al. 2014, Mi et al. 2014, Nebot et al. 2012) and temperature (Gao et al. 2011, Martins et al. 2014, Mi et al. 2013, Nebot et al. 2012) have negligible effect on the deproteinization efficiency.

2.2. Extraction of Quinolones

After the necessary pretreatment, the samples can be extracted by a solvent or solvent mixture. Various techniques, including UAE, microwave-assisted extraction (MAE), and accelerated solvent extraction (ASE), can be used to accelerate the extraction process and improve the extraction efficiency. MAE and ASE can have higher extraction efficiency and sample throughput compared to UAE, while the latter does not require expensive equipment (Dorival-García et al. 2013, Sturini et al. 2010). The extract obtained by these extraction techniques is typically centrifuged to remove the suspended particulates, followed by further treatment. An overview on extraction methods is first presented, followed by discussions of the important extraction techniques for quinolone residues in food products in the following section.

2.2.1. Overview of extraction methods

Liquid-liquid extraction (LLE) is a type of solvent extraction and partitioning method that is based on the relative solubilities of analyte in two immiscible solvents of different densities. A sufficient amount of extraction solvent is essential to capture the target analyte from the original sample. Dichloromethane is a commonly used solvent for quinolone extraction (Mi et al. 2013, 2014). Ethanol (ethanol: acetic acid, 96:4 v:v) (Martins et al. 2014), methanol (methanol: water 70:30 v:v with HCOOH 0.1%) (Martins et al. 2014), 70% methanol (Granelli et al. 2009), and acetonitrile (Garrido Frenich et al. 2010, Hu et et al. 2009), have been used in single organic solvent extraction (SOSE) for extracting quinolones from food samples due to the relative simplicity compared to two-phase LLE. To optimize the extraction process, multiple variant techniques of LLE have been developed, including modified-LLE (salting-out assisted liquid-liquid extraction, SALLE) (Dorival-García et al. 2015, Lombardo-Agüí et al. 2014b), modified liquid-liquid microextraction (salting-out induced liquid-liquid microextraction, SILLME) (Du et

al. 2014), dispersive liquid-liquid microextraction (DLLME) (Vázquez et al. 2012, Yan et al. 2011), and ionic liquid-based homogeneous liquid-liquid microextraction (IL-based HLLME) (Gao et al. 2011)).

Solid phase extraction (SPE) captures the target analyte based on its different interactions with the solid (stationary) phase and the liquid (mobile) phase. SPE is some time used as an additional clean-up step after LLE/SOSE (Huet et al. 2009). Various SPE-based techniques have also been developed, including modified-SPE (online SPE (Prieto et al. 2011), pipette tip SPE (PT-SPE) (Liu et al. 2013, Springer et al. 2014), dispersive micro-solid-phase extraction (DMSPE) (Tsai et al. 2009)), and improved solid-phase microextraction (SPME), such as SPME with novel fibers (Mirzajani et al. 2016) or micellar desorption (SPME-MD) (Esponda et al. 2009), electrochemically enhanced SPME (EE-SPME) (Liu et al. 2012), in-tube magnetic SPME (Manbohi et al. 2015), and stir bar sorptive extraction (SBSE) (Huang et al. 2010b).

The advantages and limitations of these extraction techniques are compared in Table 2. In general, they have the advantages of simple operation, fast extraction, low solvent consumption, low detection limits, high recoveries, and can be cost-effective. Despite of the recent development of various extraction techniques, SPE remains the most widely used sample preparation method, as most of the other techniques are still in the stage of development. Meanwhile, among the extraction methods that can be used for extracting quinolones from samples of food products, QuEChERS method has been gaining increasing popularity in recent years (Anastassiades et al. 2003b). Therefore, the relevant processes and key factors that influence the extraction efficiencies of the target analytes by SPE and QuEChERS are discussed in details.

2.2.2. SPE

Figure 3 depicts the general SPE procedures for extraction of quinolones from aqueous samples. The key factor determining the extraction efficiency in SPE is the sorbent, and various types of SPE sorbent materials have been developed for extraction and concentration of quinolones from aqueous samples. Prepacked SPE cartridges with different variants of solid phases are commercially available (Table 3), while novel packing materials, such as molecularly imprinted polymers (MIPs) that have excellent compound selectivity (Yang et al. 2014), surface-functionalized magnetic particles that allow easy operation (Xu et al. 2012), cigarette filters that cost little (Chen et al. 2012a), and graphene-derivatized silica that can be reused for at least 10 consecutive extractions without significant loss of efficiency (recovery >70%) (Speltini et al. 2015), have also been developed and tested in the laboratory. Nonetheless, these new materials have only been used in few laboratory studies, and their performance in routine samples analysis remains to be proven. The selection of SPE sorbents is based primarily on the interactions between quinolones and the sorbents, which influence the analyte selectivity and recovery. The functional groups of quinolones that can interact with SPE packing materials include the aromatic moiety, 4'-amino group of the piperazine ring and the protonated carboxyl group. The major types of interactions between SPE sorbents and quinolones include van der Waals (octadecyl, styrene-diviylbenzene and MIPs), polar/dipole-dipole (silica), hydrogen bonding (amino) and electrostatic (cation and anion exchange) (Figure 4). Satisfactory recoveries of quinolones can be achieved on Isolute C_{18} (octadecyl (end-capped) functionalized silica), Strata-X (modified poly(styrene-divinylbenzene)), and MIPs (Table 4), which suggests that van der Waals force is the most important interaction between the SPE sorbents and quinolone compounds.

2.2.3. QuEChERS extraction

Since its first introduction in 2003 for the extraction of pesticide residues in fruits and vegetables (Anastassiades et al. 2003b), QuEChERS has been extensively used in sample preparation for monitoring of quinolones in different matrices, including animal tissues (fish meat (Li et al. 2012, Lombardo-Agüí et al. 2014a, Lopes et al. 2012a), chicken meat (Lombardo-Agüí et al. 2014a, Stubbings et al. 2009), poultry muscles (Rocha et al. 2015)), kidneys (poultry (Rocha et al. 2015), porcine (Chen et al. 2014, Lucatello et al. 2015), turkey (Lucatello et al. 2015)), turkey lung (Lucatello et al. 2015), milks (Chen et al. 2014, Lombardo-Agüí et al. 2011, Martínez Vidal et al. 2010, Wang et al. 2012), honey (Wang et al. 2012), beehive products (Lombardo-Agüí et al. 2012), fruits (Kaewsuya et al. 2013), vegetables (Hu et al. 2014, Kaewsuya et al. 2013), and eggs (Capriotti et al. 2012, Garrido Frenich et al. 2010) (Table 5).

QuEChERS method usually involves extraction by an organic solvent with a high salt content to improve recovery and phase separation, followed by dispersive-SPE (dSPE) when cleanup is required, as illustrated on Figure 5. QuEChERS method has high flexibility, and allows selection of optimal conditions for a wide range of analytes. The extraction efficiency and recovery of analytes by QuEChERS method are influenced by many factors, including extraction phase composition (solvent (Hu et al. 2014, Lopes et al. 2012a, Lopes et al. 2012b), water content (Rocha et al. 2015, Stubbings et al. 2009)), pH (addition of buffering salts (Hu et al. 2014) or organic acids (Capriotti et al. 2012, Garrido Frenich et al. 2010, Lombardo-Agüí et al. 2011, 2012, 2014a, Lopes et al. 2012b, Martínez Vidal et al. 2010, Rocha et al. 2015, Stubbings et al. 2009, Wang et al. 2012)), cleanup procedure (Wang et al. 2012), and sorbents (Hu et al. 2014, Rocha et al. 2015)). Other factors, such as salts for partitioning (Lopes et al. 2012a) and re-composition media after clean-up (Lombardo-Agüí et al. 2011, 2012), can also influence the

performance of QuEChERS. As quinolones can form complexes with metal ions (stability constants: Fe^{3+}>Al^{3+}; Cu^{2+}>Fe^{2+}>Zn^{2+}>Mg^{2+}>Ca^{2+}) (Kawai et al. 1996), the extraction performance may be improved in the presence of ethylenediaminetetraacetic acid (EDTA) as a chelating agent. It has been reported that addition of EDTA could improve the extraction efficiency of antimicrobials (quinolones, benzimidazoles, and some sulfonamides and macrolides) that can easily chelate with the co-existing metal ions (Lopes et al. 2012b, Wang et al. 2012). Extraction of quinolones by QuEChERS method has been carried both with and without the addition of EDTA in the extraction solvent (with EDTA (Garrido Frenich et al. 2010, Martínez Vidal et al. 2010, Wang et al. 2012); without EDTA (Chen et al. 2014, Hu et al. 2014, Li et al. 2012)).

The above-mentioned factors are often optimized individually to improve analyte recovery and reproducibility of QuEChERS, while statistical models and factorial design have also been used to facilitate the optimization of arbitrary steps in QuEChERS (Capriotti et al. 2012, Lopes et al. 2012a) or the whole QuEChERS process (Rocha et al. 2015). The choice of extraction solvent is important for QuEChERS. Acetonitrile, which is popular for extraction of quinolones from food matrices (Chen et al. 2014, Garrido Frenich et al. 2010, Li et al. 2012, Lombardo-Agüí et al. 2011, 2012, 2014a, Lopes et al. 2012b, Martínez Vidal et al. 2010, Rocha et al. 2015, Stubbings et al. 2009, Wang et al. 2012), is commonly used in QuEChERS. This is due to the easy phase separation of acetonitrile from food samples by salting-out technique, as well as the polarity of acetonitrile for the extraction of a wide range of analytes. The addition of methanol into the extraction solvent has been found to enhance the recovery of quinolones (Hu et al. 2014, Lopes et al. 2012a, Lopes et al. 2012b). As “dirtier” extracts can result with the presence of greater amount of methanol (Lopes et al. 2012a), mixtures of acetonitrile and methanol should be

avoided if the target analytes can be satisifactorily recovered with acetonitrile alone (Lopes et al. 2012b). The water content of sample matrix can also influence the performance of QuEChERS, which is suitable for extracting analytes from matrices with high water contents (Lopes et al. 2012a, Rocha et al. 2015, Stubbings et al. 2009). The addition of water into the samples with low water contents, such as poultry muscles, could improve the recovery of analytes (Rocha et al. 2015, Stubbings et al. 2009), while opposite effect was observed when extracting from poultry kidneys (Rocha et al. 2015).

Because most quinolones are amphoteric, pH of the extraction medium can significantly affect the analyte recovery in QuEChERS. Although acidic solvents (pH 2-4) enhanced the extraction of quinolones from food samples (Anderson et al. 2005, Golet et al. 2002), very acidic conditions would compromise the extraction of other antimicrobials (e.g., macrolides and sulfonamides) and decrease the cleanup efficiency of primary secondary amine (PSA) in dSPE process (Hu et al. 2014). Increased quinolone recovery could also result from formation of ion pairs between protonated structures of the quinolones and acid anions (Rocha et al. 2015). Acetic acid (1% (Capriotti et al. 2012, Garrido Frenich et al. 2010, Lopes et al. 2012b, Martínez Vidal et al. 2010, Stubbings et al. 2009) or 5% (Rocha et al. 2015), v/v) and formic acid (1% (Wang et al. 2012) or 5% (Lombardo-Agüí et al. 2011, 2012, 2014a), v/v) were generally used for pH control in QuEChERS. Modified citrate buffer in QuEChERS was found to achieve better recoveries of NOR, ENO, CIP, and tetracylines than acetate buffer in a recent study (Hu et al. 2014).

Cleanup procedure, which usually focuses on dSPE sorbent selection, is often carried out to remove the matrix effect and obtain clean extract. The purification ability of dispersive sorbents, including PSA, C_{18}, silica-based amino sorbents (NH_2), and graphitized carbon black (GCB), can vary largely. GCB could absorb structurally planar compounds and result in significant losses of

quinolones (Lombardo-Agüí et al. 2012). Both NH_2 and PSA are polar adsorbents, and PSA, with two amino-groups, has stronger polarity than NH_2. As a result, PSA exhibits high removal capacity for matrix co-extractives, including fatty acids, various sugars and pigments, and has better purification effect compared to NH_2 (Li et al. 2012). Both C_{18} (Lombardo-Agüí et al. 2011, 2012, 2014a) and PSA (Garrido Frenich et al. 2010, Hu et al. 2014, Li et al. 2012, Lopes et al. 2012b) are popular sorbents for dSPE in extraction of quinolones. A mixture of C_{18} and PSA (1:1, w/w) was also shown to perform well in the extraction of quinolones from poultry muscle and kidney samples (Rocha et al. 2015). It is worth noting that dispersive cleanup methods are highly effective, but the requirement of centrifugation poses a significant challenge for automation.

Laboratory-prepared salt mixture (4.0 g anhydrous $MgSO_4$ and 1.0 g sodium acetate) (Chen et al. 2014, Garrido Frenich et al. 2010, Lopes et al. 2012a, Martínez Vidal et al. 2010, Wang et al. 2012), as well as the commercially available Agilent SampliQ EN QuEChERS extraction kit (4 g $MgSO_4$, 1 g NaCl, 1 g sodium citrate, 0.5 g disodium citrate sesquihydrate) (Lombardo-Agüí et al. 2011, 2012), which can achieve slightly better results than the former (Lombardo-Agüí et al. 2014a), were used extensively for extraction of quinolones in QuEChERS. Both $MgSO_4$ and NaCl are important for analyte recovery, as $MgSO_4$ reduces the water content in the final extract while NaCl can reduce co-extraction of matrix components and thus result in better chromatographic peaks (Anastassiades et al. 2003a). It should be noted that heat generated from addition of $MgSO_4$ into the samples can cause degradation of some analytes and thus compromise the method repeatability and analyte recoveries, although this problem can be mitigated by proper temperature control during the separation process (Hu et al. 2014). The chelation between quinolones and Mg^{2+} can be avoided by addition of EDTA, but this would

negatively affect the clean-up results (Lopes et al. 2012b). Instead of $MgSO_4$, Na_2SO_4 could also be used as an alternative partition salt (Capriotti et al. 2012, Garrido Frenich et al. 2010).

In general, the extracts after clean-up or the supernatants after partition (QuEChERS without clean-up) are concentrated by blow down with N_2 (commonly used) (Chen et al. 2014, Garrido Frenich et al. 2010, Hu et al. 2014, Li et al. 2012, Lombardo-Agüí et al. 2011, 2012, Lopes et al. 2012a) or air (rarely used) (Lucatello et al. 2015, Rocha et al. 2015). Residues after drying are re-dissolved in a mixture of methanol/acetonitrile with acid (Chen et al. 2014, Hu et al. 2014, Stubbings et al. 2009), which are usually the mobile phase (Garrido Frenich et al. 2010, Li et al. 2012, Lopes et al. 2012a, Martínez Vidal et al. 2010) or the mobile phase components (Lombardo-Agüí et al. 2011, 2012, Lopes et al. 2012b, Rocha et al. 2015, Wang et al. 2012) used in subsequent LC separation. Only few studies skipped the evaporation step and injected the extracts directly for analysis after filtration (Lopes et al. 2012b, Martínez Vidal et al. 2010).

Unlike conventional SPE, QuEChERS is available for the pretreatment of multiple classes of antimicrobials (Hu et al. 2014, Karageorgou et al. 2013, Lopes et al. 2012b, Niell et al. 2015). QuEChERS has the advantages of simplicity and effectiveness for cleaning up of complex samples. Besides being faster and more efficient, QuEChERS procedure has been shown to have better recoveries, sensitivity, and precision for all the target quinolones compared to MIP-SPE (Lombardo-Agüí et al. 2011). Overall, QuEChERS is a promising alternative to SPE for routine extraction, and is being increasingly adopted in sample preparation for analysis of quinolones in food samples.

3. Methods for Analysis of Quinolones

After separation from the food matrices, the quinolones can be detected and quantified using a range of techniques. Instrumental, immunological, and microbiological methods are three major categories of analytical techniques for detection of quinolones. Some of these techniques even allow direct detection of quinolones in animal food products.

3.1. Instrumental Methods

The instrumental methods, which typically comprise of separation and detection, are the most common and preferred ones for routine monitoring of quinolones in food samples. The non-separative technique, flow injection analysis (FIA), has also been applied in the detection of quinolones with the unique advantages of time-saving, and easy system automation and integration (Kamel et al. 2011).

3.1.1. Separation techniques

Chromatographic methods and electrophoretic methods are the popular techniques used for separation of quinolones. LC, including high performance liquid chromatography (HPLC) (Karageorgou et al. 2013, Nebot et al. 2012) and ultra-high performance liquid chromatography (UPLC) (Junza et al. 2014, Martínez Vidal et al. 2010), which has higher sensitivity and resolution, is the most preferred technique for separation of quinolones. UPLC has shorter analysis time (several minutes vs. tens of minutes for HPLC), improved peak efficiency, better resolution, and lower solvent consumption compared to conventional HPLC. Moreover, the improved signal-to-noise ratio of UPLC enables the detection of quinolones at very low concentrations. Capillary electrophoresis (CE), which offers the advantages of fast separation, high flexibility, and reduced consumption of samples and reagents, and ease of automation, has

also been used for quinolone analysis in food samples (Ferdig et al. 2004, García-Campaña et al. 2009, Ibarra et al. 2012, Lombardo-Agüí et al. 2010a, Meng et al. 2014, Springer et al. 2014, Springer et al. 2015). For improving separation selectivity, different CE modes have been applied for separation of quinolones, such as capillary zone electrophoresis (CZE) (Rusu et al. 2014) and micellar electrokinetic capillary chromatography (MEKC) (Chen et al. 2012b, Meng et al. 2014, Rusu et al. 2014).

3.1.2. Detectors

Fluorescence detector (FLD) (Li et al. 2012, Lombardo-Agüí et al. 2014a, Mi et al. 2014, Sun et al. 2014, Urraca et al. 2014), MS (Blasco et al. 2012, Capriotti et al. 2012, Chen et al. 2014, Garrido Frenich et al. 2010, Granelli et al. 2009, Hu et al. 2014, Junza et al. 2014, Karageorgou et al. 2013, Lombardo-Agüí et al. 2012, Lopes et al. 2012a, Lopes et al. 2012b, Martínez Vidal et al. 2010, Martins et al. 2014, Nebot et al. 2012, Rocha et al. 2015, Stubbings et al. 2009, Urraca et al. 2014), ultraviolet-visible (UV-vis) (Springer et al. 2014), photodiode-array detector (PAD) (Gao et al. 2011), and laser-induced fluorescence (LIF) (Lombardo-Agüí et al. 2011) have all been used for detection of quinolones after chromatographic separation.

Quinolones in the extracts are typically determined by LC-FLD (Li et al. 2012, Lombardo-Agüí et al. 2014a, Mi et al. 2014, Sun et al. 2014, Urraca et al. 2014) and/or LC-triple quadrupole MS (LC-MS/MS) (Blasco et al. 2012, Capriotti et al. 2012, Chen et al. 2014, Garrido Frenich et al. 2010, Granelli et al. 2009, Hu et al. 2014, Junza et al. 2014, Karageorgou et al. 2013, Lombardo-Agüí et al. 2012, Lopes et al. 2012a, Lopes et al. 2012b, Martínez Vidal et al. 2010, Martins et al. 2014, Nebot et al. 2012, Rocha et al. 2015, Stubbings et al. 2009, Urraca et al. 2014). Given the high fluorescence shown by most of the quinolone compounds, detection with FLD can be highly specific and sensitive, while MS detection allows simultaneous measurements of multiple

classes of drugs, including quinolones. In particular, the matrix interference from samples is minimum for the determination of quinolones by FLD (Sun et al. 2014, Urraca et al. 2014). LC coupled with UV-vis or PAD has been used for determination of quinolones at the maximum absorption wavelength around 280 nm, although the detection limits are much poorer than those of FLD and MS (Chen et al. 2012a, Gao et al. 2011, Herrera-Herrera et al. 2013, Huang et al. 2010b, Moema et al. 2012, Tsai et al. 2009, Urraca et al. 2014, Yan et al. 2011). For CE separation, UV (Herrera-Herrera et al. 2010, Springer et al. 2014), LIF (Lombardo-Agüí et al. 2010b, Meng et al. 2014), FLD (Ferdig et al. 2004), and MS (Springer et al. 2015) can all be used for the detection of quinolones. As UV detection has limited sensitivity, significant effort on sample pre-concentration is often required. Overall, detection of quinolones by MS is much more sensitive, selective, and specific than by UV or FLD (Andreu et al. 2007). Furthermore, MS detection is fast and can simultaneously detect the related metabolic products of quinolones.

For detection of quinolones with MS, the most commonly used ionization technique is electrospary ionization (ESI) with positive-ionization mode, or ESI(+), which results in primarily the deprotonated molecular ions, $[M\text{-}H]^{+}$. In addition to ESI, a soft ionization technique, matrix-assisted laser desorption/ionization (MALDI), which was first introduced in 1988 (Karas et al. 1985), has also been used for analysis of quinolones in food and other biological samples (Prideaux et al. 2011, 2015, Shobo et al. 2015, Springer et al. 2015). Different from ESI with triple quadrupole MS, TOF mass analyzers are most often coupled with MALDI (Capocefalo et al. 2016, Springer et al. 2015). MALDI coupled with imaging mass spectrometry (IMS) is a robust and label-free technique for identifying and mapping the spatial arrangement and concentrations of analytes, their metabolites and molecular complexes directly from tissue sections (e.g., animal tissues (Prideaux et al. 2011) and plant tissues (Lee 2014)). Although

MALDI-MS is not intended for characterizing small molecules (<700 Da), techniques have been developed to allow the use of MALDI-MS for quantitative analysis of small molecules, drugs, and metabolites (Cohen et al. 2002, LeRiche et al. 2001, Shanta et al. 2012, van Kampen et al. 2006, Volmer et al. 2007). A recent study successfully analyzed quinolones in bovine milk using MALDI-TOF-MS after CE separation (Springer et al. 2015).

Tandem MS (MS/MS) is the most commonly used mass spectrometers for analysis of quinolones. Triple quadrupole (QqQ) mass analyzers operated in multiple reaction monitoring (MRM) mode are the most popular instruments. Although the excellent selectivity and sensitivity of time-scheduled MRM allows for the detection of a great number of analytes based on scanning parent ions, daughter ions, and neutral losses, these procedures only monitor a discrete list of target compounds due to the instrument's low resolution capability.

For analyzing trace analytes in complex matrices, the selectivity of QqQ MS is often insufficient. As an attractive alternative, advanced high resolution mass spectrometry (HRMS) have been employed for analyzing quinolones. Unlike quadrupole MS that monitors limited sets of pre-selected ions, time of flight (TOF) MS can simultaneously analyzing unlimited number of compounds by full-scan data. Therefore, HRMS is a much more powerful instrument and is capable of detecting additional non-targeted analytes as well as the targeted ones. Off-line MALDI-TOF-MS with CE separation (CE--MALDI-TOF-MS) and fraction collection has been used to simultaneously and unambiguously determined four quinolones in bovine milk (Springer et al. 2015). Although TOF MS can generate accurate mass data for fragment ions (0.01 Da), the process does not provide the additional selectivity that is achieved by tandem mass spectrometry (MS/MS). This is because the exact mass measurements of TOF MS depend on the ion abundances (detector saturation) and demand for relatively wide mass windows, which comprise

the selectivity of detection. To make up for the poor selectivity, TOF is often coupled to a quadrupole (Q-TOF) (Quesada et al. 2013, Turnipseed et al. 2011, Wang et al. 2012). The quadrupole in Q-TOF instrument acts as a mass filter to select the precursor ions of the target analyte between the source and the collision cell prior to the TOF analyzer, allowing it to provide accurate masses for both precursor and product ions.

Single stage Orbitrap set at 5,0000 full width at half maximum (FWHM) could also achieve selectivity comparable to MS/MS (Kaufmann et al. 2011). The resolution of Orbitrap is affected by the available measurement time, hence there is a choice between the number of data points monitored per unit of time and the resolution (10,000-100,000 FWHM). Another advantage of Orbitrap is that it can qualitatively screen degradation products or metabolites without reference substances, which is required by MS/MS. It is worth noting that more stringent sample extraction and clean-up (extensive deproteination steps) is necessary for Orbitrap as the matrix can result in significant signal suppression. Orbitrap has significantly higher resolution (10,000-100,000 FWHM) even than TOF MS (up to 12,000 FWHM), which make it possible to resolve isobaric interferences and different isomers (Kaufmann et al. 2011). Both TOF MS and LTQ-Orbitrap have been used for identifying the metabolites and thermal transformation products of quinolones incow's milk (Junza et al. 2014). The extracts after pretreatment were analyzed by TOF MS, while the metabolites and thermal transformation products were analyzed by Orbitrap to obtain the structural information by fragmenting the analytes (Junza et al. 2014).

The HRMS (TOF and Orbitrap) instruments and their flexible combinations have greatly promoted the development of mass spectrometric detectors for obtaining accuracy mass and structural information for the target analytes in complex matrix. However, such instruments are

very expensive and demand more stringent sample clean-up. At the present stage, QqQ remains the most widely used mass spectrometric detector.

Quantitation of quinolones is typically done based on the peak areas detected and the corresponding calibration curves. The precision of method, defined by the relative standard deviation (RSD), is often determined based on multiple measurement of a given standard sample. Signal suppression (Nebot et al. 2012) or enhancement (Martins et al. 2014) leading to erroneous results represents a significant drawback for ESI used in the MS analyzers. For instance, the RSD values for peak areas of ciprofloxacin and enrofloxacin decreased by approximately 30% in milk (Nebot et al. 2012). This effect can be corrected by using matrix-matched calibration curves (Dorival-García et al. 2013, Gbylik-Sikorska et al. 2015, Lombardo- Agüí et al. 2014b) and internal standards (Gbylik-Sikorska et al. 2015, Grosa et al. 2012). In addition, proper sample pretreatment, including dilution of the final extracts prior to analysis (Dorival-García et al. 2013), and washing prior to elution with appropriate solvents (Chen et al. 2010, Liu et al. 2013, Martins et al. 2014), and protein removal during cleanup (Kaufmann et al. 2011), can all help minimize the matrix interference. Parameters of the analytical method, including linearity, trueness, precision, selectivity/specificity, decision limit (CC-α), detection capability (CC-β), and ruggedness, were often established according to international standards, such as the EU Commission Decision 2002/657/EEC, which is the most common choice (Garrido Frenich et al. 2010, Granelli et al. 2009, Karageorgou et al. 2013, Kaufmann et al. 2011, Martínez Vidal et al. 2010, Martins et al. 2014, Nebot et al. 2012, Stubbings et al. 2009, Urraca et al. 2014). Validation of the method could be accomplished using internal standards or matrix-matched calibration and a recovery assay with spiked samples (Karageorgou et al. 2013, Martínez Vidal et al. 2010, Wang et al. 2012). Although the instrumental methods discussed above can meet the

need for detection of quinolones in different types of samples, the requirements of expensive instrument and well-trained personnel can limit their implementation in some settings. There is a growing need for rapid, inexpensive, and sensitive analytical strategies capable of on-site analysis and/or handling of high sample throughput.

3.2. Immunoassay- and Biosensor-based Methods

Compared to the conventional instrumental detection methods, immunoassay- and biosensor-based techniques have several unique advantages, including minimal sample pretreatment, fast analysis, low costs, capable of miniaturization, and no requirement of highly trained personnel. The working principles and key features of immunoassays and biosensors methods, and their application in analysis of quinolones in food samples are detailed in the rest of this section.

3.2.1. Immunoassay

Immunoassay is a highly selective biochemical analysis method based on the specific binding of antibodies to antigens, and can be effective and economical for screening of food samples (Fernández et al. 2011, Mi et al. 2013, 2014, Ni et al. 2014, Pinacho et al. 2012, 2014, Wen et al. 2012, Zhang et al. 2013). While LC-MS/MS can accurately detect the concentrations of quinolones, immunoassay can be used as a screening tool for detecting the residues in food samples for judgement whether they are present at concentrations above the detection limits or not (Mi et al. 2014, Zeng et al. 2016). Due to its great selectivity, immunochemical technique can significantly reduce analysis time and simplify the treatment/purification procedures compared to instrumental methods (Fernández et al. 2011, Mi et al. 2013, 2014, Ni et al. 2014, Pinacho et al. 2014, Pinacho et al. 2012, Wen et al. 2012, Zhang et al. 2013). Nonetheless, immunoassay suffers a range of limitations, such as lower specificity, cross-reactivity, and false positives. Thus, verification of the accuracy of immunoassay methods is required, which can be

done by re-testing all positive immunoassay findings and/or with confirmation with instrumental methods (Leivo et al. 2013).

3.2.1.1. Sample preparation

As shown in Table 6, solvent extraction, including single organic solvent extraction (SOSE) and two phase liquid-liquid extraction (LLE), is the most commonly used sample preparation method for immunoassay. These solvent extraction processes are simple, fast, cheap, and can meet the demand of immunoassay, although the performance may not be satisfactory when low detection levels are required (Scortichini et al. 2009). As immunoassay-based methods are non-separative, the sample preparation step should remove the matrix interferences as much as possible when screening for multiple residues.

3.2.1.2. Main procedure and labels

The typical procedure of immunoassay is illustrated on Figure 6. Analyte-antibody complex is first formed by reaction of antigen bound to the binding sites of antibodies during incubation with the samples containing the analytes. Then the number of binding sites interacted with the analytes is quantified from the measurable signals produced, which to a great extent are some kind of detectable labels. A wide range of labels, which can be radioactive, enzymatic, fluorescent, or chemiluminescent, have been assayed directly or indirectly (Gazzaz et al. 1992). So far, detection of quinolones has been achieved by enzyme-linked immunosorbent assay (ELISA) (Brás Gomes et al. 2010, Cao et al. 2009, Hu et al. 2010a, Huang et al. 2010a, Pinacho et al. 2012, Scortichini et al. 2009, Wang et al. 2016, Wen et al. 2012), fluorescence polarization immunoassay (FPIA) (Mi et al. 2013, 2014), time-resolved fluorescence immunoassay (TRFIA)

(Leivo et al. 2013, Leivo et al. 2011), and chemiluminescent enzyme immunoassay (CLEIA) (Ni et al. 2014, Tao et al. 2013, Zeng et al. 2016).

Although recent efforts have pushed the limits of ELISA and produced broad-specificity antibodies that enable detection of up to 20 quinolones (Tao et al. 2013), they still cannot recognize all the quinolone compounds. There remains a significant need for developing broad-specificity antibodies can bind all quinolones with sufficient affinity for generic immunoassays. In addition, ELISA is a heterogeneous solid-phase method and requires intricate hapten synthesis, immunoreaction equilibrium (>2 h), and free and antibody-bound analyte separation (Pinacho et al. 2012). Thus it may not meet the rising demands for screening methods that are fast, automated, and capable of high-throughout.

The heterogeneous solution phase FPIA can reach equilibrium in minutes or even seconds without requiring separation or washing, which makes it more suitable for analysis of a large number of samples than ELISA (Mi et al. 2013, 2014). Limited research has been conducted to explore its application in screening for quinolones in food samples. A non-competitive fluorescence polarization (FP) assay with molecularly imprinted polymer was used for ENR determination (Mi et al. 2014), while one-step FPIA based on a class-specific mAb for screening 16 quinolones in milk and chicken muscle samples has also been reported (Mi et al. 2013). As FPIA is limited by the matrix effect and possible cross-reactivity of the antibodies (Mi et al. 2013, 2014), more work should be done to improve the applicability of this technique in routine analysis of food samples.

Aptamers (nucleic acid-based probes), which can be easily modified and are cheaper to produce compared to antibodies, can serve as an alternative molecular recognition element in ELISA. A

direct competitive CLEIA based on several ssDNA aptamers supported on magnetic beads has been developed for quantifying ENR in milk recently (Ni et al. 2014). Although the sensitivity of the method was not better compared to some previous techniques, this approach held great promises as it does not require antibodies, eliminates the need for animals and the time required for antibody production, and can allow rapid determination of quinolones.

3.2.1.3. Technologies for improving immunoassay

Regardless of the types of immunoassays, preparation of target-specific antibodies and conjugates is of key importance. The sensitivity and selectivity of immunoassays are largely determined by the affinity and specificity of antibodies. For producing antibodies against quinolones, which are small molecules, haptens are designed. It is difficult to select specificity antibodies or antibody fragments for small haptens from libraries due to poor adsorption of these molecules on solid surfaces. A preliminary step that conjugates the hapten with a carrier protein (e.g., bovine serum albumin and ovalbumin) to mediate the adsorption of hapten onto the support can solve this problem. Unfortunately, the procedure for conjugating the hapten to a carrier protein is laborious and is complicated by potential covalent bonding of the small ligand to the solid support, such as ELISA plates. To overcome this problem, researchers have developed a rapid and sensitive ELISA assay for ciprofloxacin by replacing the plate support with paramagnetic beads, which allow binding of the free carboxylic group of ciprofloxacin to amine-derivatized beads through carbodiimide reaction (Brás Gomes et al. 2010). To date, most researchers worked on antibodies (Brás Gomes et al. 2010, Hu et al. 2010a, Huang et al. 2010a, Wen et al. 2012) and haptens for generating immunogen (Cao et al. 2009, Pinacho et al. 2012) to develop broad specificity immunoassays.

Various polyclonal antibodies (Pabs) (Cao et al. 2009, Zeng et al. 2016), monoclonal antibodies (mAbs) (Hu et al. 2010a, Huang et al. 2010a, Leivo et al. 2013, Leivo et al. 2011, Mi et al. 2013, 2014), and single chain variable fragment (ScFv) (Brás Gomes et al. 2010, Tao et al. 2013, Wang et al. 2016, Wen et al. 2012) have been used as quinolone detection reagents (Table 6). The ideal antibody is expected to have similar cross reactivity to all quinolones, which can be utilized as a broad selective receptor for developing cheap and rapid screening methods. As the structures of quinolones are different, it is difficult to produce a high homogenicity generic antibody using conventional antibody preparation technologies. The intrinsic properties (e.g., affinity and specificity) of Pabs and mAbs are fixed once they are produced. Recombinant antibody and protein engineering technologies can break down the limitation. The intrinsic properties of ScFv, a recombinant antibody, can be evolved by various mutagenesis technologies, e.g., ribosome display technology, phage display technology, and the much simpler expression via cloning variable heavy chains and variable light chains from a hybridoma cell strain and direct transforming ScFv into a host (Leivo et al. 2013, Tao et al. 2013, Toleikis et al. 2012). The binding sites of haptens and carrier proteins, as well as their binding properties, both play important roles for producing appropriate antibodies. Modification of binding characteristics has been developed for high throughput screening of quinolones by oligonucleotide-directed mutagenesis and phage display (Leivo et al. 2013). Molecular docking has also been introduced for investigating the intermolecular interactions between ScFv and competitors, which can produce ScFv mutants via site directed mutagenesis (Wang et al. 2016), random mutagenesis (Leivo et al. 2013, Leivo et al. 2011), or DNA shuffling technique (Wen et al. 2012). By using molecular docking, improved sensitivity of ScFv to quinolones and binding properties of the mutants have been achieved (Leivo et al. 2013, Leivo et al. 2011, Wen et al. 2012), Nonetheless,

a broad-specificity antibody with sufficient affinity that can bind all quinolones for generic immunoassay is still not available.

Designing an appropriate hapten is the core step for the whole process of developing a broad-specificity antibody and generating a broad specificity immunoassay. Molecular modeling is a very helpful tool for selection of quinolone haptens based on the desired specificity of antibodies (Cao et al. 2009, Pinacho et al. 2012, Wang et al. 2016, Wen et al. 2012, Zeng et al. 2016). It has been demonstrated the developed molecular model could match well with the real structure-activity relationship between the particular antibodies and quinolone haptens (Wen et al. 2012). In addition, chemical properties of quinolones can also play important roles, as the complexation between divalent cations and quinolones can largely affect the antibody affinity and the acid-base equilibria of most quinolones can strongly influence the antibody selectivity in assay media of different pH values (Pinacho et al. 2012).

3.2.2. Biosensor-based methods

Biosensor technology, which can obtain results in real time, has received increasing attention for determining various pollutants in food samples over the past decade. A biosensor is an instrument combining a biological recognition element, often called a bioreceptor (e.g., enzymes, immunosystems, antibodies, tissues, whole cells, organelles, aptamers, and nucleic acids) in direct spatial contact with a transducing device to detect chemical compounds. As a result of the interaction between the bioreceptor and the target analyte, an effect is usually produced that can be measured and recorded by the transducer. Often the matrix effect on the measurement results cannot be neglected, e.g., fat and proteins in milk can interact unspecifically with the surface-plasmon resonance (SPR) sensor surface and affect the antibody recognition event (Fernández et al. 2011, Pinacho et al. 2014). Thus, sample treatment is essential for biosensor-based methods,

and solvent extraction is the most commonly used technique (Table 7). Biosensors are typically classified based on the type of biological-recognition element or the transducing system. The most common types of transducers are electrochemical-, optical-, mass-based transducers (piezoelectric, surface acoustic), and thermal transducers. Electrochemical (Giroud et al. 2009, Kamel et al. 2011, Pinacho et al. 2014, Xie et al. 2015, Zhang et al. 2013) and optical transducer systems (Fernández et al. 2011, Huet et al. 2009, Weigel et al. 2009) have been used for analysis of quinolones in food samples.

For detection of quinolones, different electrochemical sensors, which measure changes in pH and ion concentration (potentiometirc sensor) (Kamel et al. 2011), changes of the electrochemistry properties of the electrode interface (impedimetric sensor) (Giroud et al. 2009), and current flow generated by electrochemical reaction (amperometric sensor) (Pinacho et al. 2014, Xie et al. 2015, Zhang et al. 2013), have been employed. Voltammetric detection, which belongs to amperometric sensors, was the most common choice. For electrochemical sensors, new functional materials and nanomaterials have been frequently used as the immobilization matrices for the bioreceptor with the goal of improving the response characteristics of the transducer in recent years. Instead of the traditional measurements based on the impedance characteristics of the interface, novel impedimetric immunosensors have also been developed. A poly(pyrrole-N-hydroxysuccinimide) film, functionalized by a quinolone model that mimics the ciprofloxacin structure, was electrogenerated onto the electrodes by reagentless covalent binding of the model bearing an amino group, which was used for immobilizing the immunoreaction between a layer of anti-ciprofloxacin antibody and polymer surface (Giroud et al. 2009) (Figure 6). Drastic impedimetric signal was generated in the presence of ciprofloxacin, which resulted from the displacement of immobilized antibody due to the stronger association of antibody-ciprofloxacin.

The signal was detected and characterized by electrochemical impedance spectroscopy, resulting a rather low detection limit (3 pmol/L of ciprofloxacin) (Giroud et al. 2009).

MIPs with high selectivity, high physical, chemical, and thermal stability, as well as cost effectiveness and easy preparation, have enormous potential to substitute the natural bio-recognition elements (i.e., enzymes and antibodies), which have low stability. MIPs with special molecule recognition properties of ciprofloxacin have been prepared by thermal polymerization as the receptors of a newly developed biomimetic potentiometric field monitoring device for ciprofloxacin (Kamel et al. 2011). This device had excellent analytical detection performance in terms of selectivity, sensitivity, stability, precision, accuracy, and response time.

Poly amino acids modified electrodes, prepared by electro-polymerization of β-cyclodextrin and L-arginine on carbon paste electrodes, have been used in a new electrochemical sensor for voltammetric determination of quinolones (ciprofloxacin, ofloxacin, norfloxacin, and gatifloxacin) in acidic solution (Zhang et al. 2013). The measurement was based on the electrostatic interactions between the guanidyl group of β-cyclodextrin and L-arginine with the negatively charged -COO^- group of quinolones. This sensor exhibited good repeatability, sensitivity, high stability, and requires only simple manufacturing procedures.

Amperometric magneto-immunosensor (AMIS), a magnetic modified electrochemical method with fast assay kinetics and high immunochemical reaction surface area, showed excellent performance for the detection of 7 quinolones in milk (Pinacho et al. 2014). Matrix effect caused by milk could be eliminated completely by the magnetic beads, which were biomodified with an antibody with a wide recognition profile for quinolones. The magnetic beads were easily captured by the magnetic graphite-epoxy composite (m-GEC) electrode after the

immunochemical reaction with a haptenized enzyme tracer. In the electrochemical detection process, the m-GEC electrode also functioned as a transducer, and thus required no additional sample cleanup or extraction step. With excellent electronic and robust transport properties, graphene has revolutionized the domain of nanostructured materials. Graphene modified glassy carbon electrode (GCE), prepared by dropping graphene dispersion onto GCE surface followed by air drying, has been developed for voltammetric detection of ciprofloxacin (Xie et al. 2015). This sensor showed good reproducibility, and high sensitivity and selectivity as well.

Among the optical transducers, which are label-free, SPR device has been developed and applied for screening quinolones in food products (Fernández et al. 2011, Huet et al. 2009, Weigel et al. 2009). A SPR instrument is comprised of three core elements, namely, optical system for producing and measuring SPR signal, a sensor chip that is coupled with biomolecule for specific reaction with the target analytes, and a liquid handling system (Figure 7). SPR is an oscillation phenomenon that can be induced by both electrons and photons at the interface between any two materials, and is most commonly generated by the angle-dependent way. SPR sensors can detect minor changes in refractive index resulting from the interaction between an analyte in solution and a bio-molecular-recognition element immobilized on the SPR-sensor surface. Therefore, mass changes that occur due to binding of analyte molecules at the sensor surface are measured as changes in RI. Compared to the other types of biosensors, SPR does not need labels.

To date, SPR assays for quinolones have been rarely reported. A SPR based biosensor assay using Optical SPR Biosensor System Biacore Q was developed for determination of 13 quinolones in fish, eggs, and poultry muscles (Huet et al. 2009). The samples were extracted with acetonitrile followed by a series of treatment prior to analysis. The analytical performance of this method, with respect to detection capability, specificity/selectivity, detection limit,

repeatability, ruggedness, and stability, was satisfactory. The performance of this SPR biosensor in routine and statutory analysis for quinolone residues in food matrices was further compared with that of LC-MS/MS and microbiological method (Weigel et al. 2009). The results demonstrated that SPR biosensor assay could deliver results on the same day with high sensitivity (10-50 μg/kg) at costs between those of the microbiological assay and LC-MS/MS. Although a variety of SPR devices are commercially available nowadays, inexpensive and portable device is the trend of future development. In this context, *SPReeta* Evaluation Kit SPR3 with three-channel gold chips, which were activated with a mixed self-assembled monolayer and functionalized with a quinolone haptenized protein, has been developed for selective detection of 3 quinolones in milk in the presence of other antimicrobials (Fernández et al. 2011). This biosensor method showed a good limit of detection (2±0.2 μg/L enrofloxacin) in milk samples (Fernández et al. 2011).

Together, both immunoassays and biosensors have the obvious advantages of simplicity, quick response, and low cost, yet their sensitivity, precision, and reliability still need to be improved for application in routine analysis. It is expected that immunoassay- and biosensor-based methods can serve as quick, simple, and economical screening alternatives to the instrumental analyses when precise measurement results are not necessary or not possible.

4. Future Research Needs

Despite the recent advances made on the analysis of quinolones in food samples, more researches are needed to improve the sensitivity, precision, and reliability of these techniques:

1. Animal food products have more complicated matrices, and the associated sample pretreatment is time-consuming and labor-intensive. Automation of the QuEChERS process would greatly reduce the burden in the analysis of such samples and help improve the accuracy of results. In addition, to improve the compatibility with MS detection, low vapor pressure salts ($MgSO_4$/Na_2SO_4 and sodium salts) should be replaced with more volatile ones, such as ammonium chloride, ammonium formate and acetate buffers, in QuEChERS for phase separation and extraction of analytes.

2. Immunoassay- and biosensor-based techniques are promising for rapid screening of quinolones in food samples. Nonetheless, further research and development efforts are needed to overcome their limitations and improve their applicability in routine monitoring. Stable tracers and correspondingly easy synthesis method should be developed for measurement of quinolones to avoid the time-consuming and complicated preparation of tracers. Validation of the available immunoassay-based kits by regulatory authorities is necessary before they can replace the classic quantitative methods in routine compliance monitoring. SPR biosensors and electrochemical sensors also hold great promises for continuous online monitoring.

3. Integration of different technologies can create diverse possibilities for analysis of quinolones in food samples with complicated matrices. Combination of the advantages of instrumental (accuracy and reliability), and those of immunoassay- and biosensor-based detection methods (low-cost and simplicity) can create hybrid methods with unique detection capability. SPR-MS combination, in which quinolones in the samples are first detected and captured, and then the specific compounds are identified, is a good example of such hybrid

methods. Development of such methods can greatly expand our analytical capability for analysis of quinolone residues in food products.

4. Chemometrics can aid existing analytical techniques and enhance their power for detection and quantitation of quinolones in complex food matrices. Application of chemometrics is based on modeling of the second/third/forth-order data of the signals arising from the analytes in the samples obtained from the detection devices with algorithms. It could help improve the selectivity and sensitivity of analytical methods, and reduce the cost and time of analysis.

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Table 1. Summary of the separation and instrumental detection methods for determining quinolone residues in food samples reported in the literature published between 2009 and now.

Samples		Preparation methods		Detection methods		LOD*	Recovery, %	Ref.
Analytes	**Matrix**	**Pretreatment**	**Extraction**	**Separation techniques**	**Detection method**			
CIP, ENR	Milk (2 mL)	Extracted (2 mL acetonitrile), vortexed (10 s)	USE-SPE	HPLC Synergi 2.5 μm Polar-RP 100Å (50 mm × 2.0 mm, 2.5 μm), H_2O/acetonitrile both containing 0.1% HCOOH at 0.2 mL/min	MS QqQ [a]- ESI(+)- MRM	6.3-7.9 μg/L	81-84	(Nebot et al. 2012)
DAN, MA	Milk (10 g)	No pretreatment	QuEChERs	UPLC Acquity UPLC BEH C18 column (100 mm × 2.1 mm,	MS QqQ- ESI(+)-	1.0-4.0 μg/k	56.8-111.6	(Martínez Vidal et al.

R, ENR, DIF				1.7 mm), methanol-0.05% HCOOH in H_2O, at 0.3 mL/min	MRM	g		2010)
ENO, OFL, NOR, FLU, CIP, ENR, OX, DAN, SARA, NA	Milk (500 µg)	No pretreatment	Modified-MSPD [b] Bond Elut Plexa sorbent **PC** [c]: methanol, H_2O **WS** [d]: H_2O within 4% v/v acetonitrile **EL** [e]: methanol/ acetonitrile **SS** [f]:150 mg	HPLC Perfectsil ODS-2 (250 mm × 4.0 mm, 5 µm), 0.1% TFA in H_2O/0.1% TFA in acetonitrile at 1.2 mL/min	MS QqQ-ESI(+)-MRM	2.4-15.0 µg/kg	60-83	(Karageorgou et al. 2013)

			$MgSO_4$, 50 mg PSA **dSPE**: 50 mg EC-C_{18}					
ENR, CIP, DIF, SAR	Milk (2.0 g) added with 0.5 mL 0.1 M H_3PO_4 at pH 10 and 2 mL H_2O	Deproteinization with 0.1 M NaH_2PO_4 (pH adjusted to 10 with 5 M NaOH)	SPE	UPLC Zorbax Eclipse XDB-C_8 column (150 mm × 4.6 mm, 5 μm), H_2O/acetonitrile both containing 0.1% HCOOH at 0.3 mL/min.	MS TOF-ESI(+)	--	--	(Junza et al. 2014)
CIP, NOR,	Milk (15 mL), pH	Deproteinization with 2 mL 3 M	Pipette-tip SPE **PC**:	CE Fused-silica capillary column	UV 280 nm	7.5-11.6 μg/	84-106	(Springer et al.

OFL	6.0	HCl	methanol, H_2O **EL**: methanol with 2% HCOOH.	(70 cm, 50 mm i.d.), BGE [g]: 20 mM $NH_4H_2PO_4$/2 mM CTAB		L		2014)
EN O, PEF, NO R, ENR	Milk (2.0 mL)	Added with 2.0 mL 50 g/L NaCl and 60 μL H_3PO_4, ultrasonic ated, heated, ultrasonic ated, centrifug ed.	IL-based HLLME [h]	HPLC Zorbax Eclipse XDB-C_{18} column (150 mm × 4.6 mm, 3.5 μm), 2.90 mM $[C_2MIM][BF4]$, 9.70 mM ammonium acetate/acetic acid (pH 2.7) at 0.5 mL/min.	PDA 270/2 80 nm	4.00 - 15.8 μg/ L	100.5 - 118.6	(Gao et al. 2011)
OR	Milk (4.0	Deprotein ization	SOSE [i]	HPLC	FLD	--	80.3-	(Mi et al.

B	mL), pH 6.0	with saturated $(NH_4)_2SO_4$	**EC** [j]: CH_2Cl_2	Symmetry C_{18} column (250 mm ×4.6 mm).	λ_{exc} [k] = 280 nm λ_{em} [l] = 450 nm		91.0	2014)
OFL, ENR, LOM, CIP, NOR	Honey (5.0 g)	--	SPE	HPLC Weltch Ultimate C_{18} column (250 mm × 4.6 mm, 5.0 μm), acetonitrile/H_3PO_4/H_2O (pH adjusted to 2.5 with trimethylamine) at 1.0 mL/min.	UV 275 nm	0.003-0.007 μg/kg	Milk: 80.2-91.4; honey: 83.5-95.9	(Meng et al. 2014)
CIN, CIP, DAN,	Milk and honey (10 g)	Homogenized	QuEChERs	UPLC BEH C_{18} column (100 mm × 2.1 mm, 1.7 mm),	MS Q-TOF-ESI(+	--	Honey: 3.1-68.8;	(Wang et al. 2012)

DIF, ENO, ENR, FLU, MAR, NA, NOR, OFL, OA, SARA, SPA				acetonitrile/0.1% HCOOH/10 mM ammonium formate at 0.4 mL/min	)		milk: 16.8-114.7	
ENR, CIP, MA	Bovine milk and porcine	Homogenized	QuEChERs	HPTLC [m] Methanol/acetonitrile (40:60, v/v)	MS Single MS, ESI	--	--	(Chen et al. 2014)

R	kidney (10 g)							
NOR, CIP, ENR, OFL, RUF	Milk (1 g)	Deproteinization with 2 mL of acetic acid (5% in acetonitrile)	SPE	HPLC	MS QqQ-ESI(+)-MRM	0.5 ng/g	--	(Tang et al. 2009)
CIP, ENR, NOR, NA, SARA, DIF, FLU	Milk (0.5 mL)	Deproteinization with 4% CH_3COOH in ethanol.	SOSE **EC**: acidified ethanol (ethanol: acetic acid, 96:4 v:v);	UPLC Symmetry C_{18} (75 mm ×4.6 mm, 3.5 μm), H_2O/acetonitrile both containing 0.1% HCOOH at 0.3 mL/min.	MS QqQ-ESI(+)-MRM	--	--	(Martins et al. 2014)
	Liver (3.0	Deproteinization	SOSE **EC**:					

, OA, DAN, ENR	g)	with 0.1% HCOOH in acetonitrile.	methanol: water 70:30 v:v with HCOOH 0.1%, HCOOH 0.1% in acetonitrile					
CIP, DAN, OA, MAR, DIF, ENR, SARA, FLU	Honey (1.0 g), royal jelly (1.0 g), propolis (1.5 mL) added 8.0 mL of 30 mM	Homogenized (honey was warmed before spiking and vortexed)	QuEChERs-dSPE	UPLC C_{18} column (Zorbax Eclipse Plus HHRD, 50 mm × 2.1 mm, 1.8 μm), 0.02% formic acid/acetonitrile at 0.47 mL/min	MS QqQ-ESI(+)-MRM	Honey: 0.2-1.6 μg/kg; royal jelly: 0.2-2.5 μg/kg;	Honey: 61.2-99.8; royal jelly: 56.7-96.5; propolis: 39.7-69.2.	(Lombardo-Agüí et al. 2012)

	NaH_2PO_4 buffer, pH 7.0					propolis: 0.7-4.1 µg/kg.		
OFL, NOR, CIP, ENR	Honey (1.0 g in 10 mL deionized water), pH 6.0	--	MSPE Magnetic PDMS/MWCNTs-OH particles; **PC**: methanol, H_2O; **EL**: methanol with 0.1 M HCl.	Capillary LC Monolithic silica-ODS column (350 mm × 0.2 mm), 50 mM H_3PO_4/methanol/ acetonitrile at 0.03 mL/min.	UV-vis 280 nm	0.24 - 0.48 µg/L	84.0-106	(Xu et al. 2012)
CIP, DAN,	Muscle, honey	Homogenized with 40 mL of	SPE	UPLC Kinetex Core-Shell, C_{18} (150 mm × 2.1	MS TOF-	1 µg/kg	69.7-91.4	(Kaufmann et al.

DIF, ENO, ENR, FLE, FLU, LOM, MAR, NA, NOR, OFL, OA, PA, SARA, SPA	, kidney, liver and fish (3.0 g), pH 6.5	acetonitrile and 35 mL of extraction solution, centrifuged		mm, 2.6 μm), H_2O/acetonitrile both containing HCOOH at 0.4 mL/min	ESI			2011)

CIP, DAN, DIF, ENR, FLU, MAR, NA, NOR, OFL, OA, PIP, SARA	Poultry muscle and kidney (2.0 g)	Homogenized	Modified-QuEChERs-dSPE	HPLC H_2O/acetonitrile both containing 0.1% HCOOH.	MS QqQ-ESI(+)-MRM	--	81.7-101.6	(Rocha et al. 2015)
OA, NA,	Swine muscl	Homogenized with	DLLME:	HPLC	PAD	5.6-23.8	87.5-	(Tsai et al.

FLU, DAN, PA, ENR, SARA	e (5.0 g)	5.0 mL acetonitrile and 5 µL $HClO_4$, centrifuged after addition of 2.0 g $MgSO_4$ and 1.0 g NaCl	**EC**: CH_2Cl_2; **DS**: acetonitrile;	Cosmosil 5 C_{18}-AR-II column (250 mm ×4.6 mm, 5 µm), acetonitrile/0.05 M NaH_2PO_4 (pH 2.5) both with 3.7 mM SDS at 1 mL/min.	330nm	µg/kg	112.6	2009)
			DMSPE: dispersive silica-based PSA sorbent; **DS** [n]: acetonitrile, CH_2Cl_2, H_2O.			8.3-26.3 µg/kg	84.5-24.5	
DIF, ENR, DAN, CIP	Porcine and bovine muscles (3.0 g)	Homogenized, added with 200 µL of 0.1 M EDTA	SOSE **EC**: 70% methanol, centrifuged.	HPLC Genesis C_{18} (50 mm × 2.1 mm, 4 µm), 0.2% HCOOH/0.1 mM oxalic acid/acetonitrile at 0.3 mL/min	MS QqQ-ESI(+)-MRM	3-12 µg/kg	70-76	(Granelli et al. 2009)

SARA, OFL, FLU, NOR, CIP, OA, NA, LOM, ENO	Egg, poultry, fish (2 g for each),	Homogenized	SOSE **EC**: acetonitrile, vortexed before shaking, centrifugation, evaporated to dryness, reconstituted in 1 mL PBS pH 7.4, added with hexane and vortexed, washed again after removal of hexane layer.	Biosensors Optical surface plasmon resonance (SPR)		Egg: 1 ng/g; poultry: 0.5 ng/g; fish: 1.5 ng/g.	--	(Huet et al. 2009)
PA,	Egg	--	LLE	HPLC	MS	--	92-	(Blasc

MAR, OFL, NOR, CIP, ENR, DAN, DIF, SARA, OX, FLU	(1 g)		**EC:** acetonitrile-dichloromethane	Xterra MS C18 LC column (100 mm × 2.1 mm, 3.5 μm), 0.1% HCOOH in methanol-0.1% HCOOH in water at 0.4 mL/min	QqQ-ESI-MRM		106	o et al. 2012)
	Egg (2 g)	Homogenized with 20 mL of 50 mM NaH_2PO_4 at pH 7.4, centrifuged, filtered.	MIPSPE					
CIP, ENR, NOR, NO	Fish protein (Carp) (2.5 g)	Homogenized, deproteinization with acidic acetonitri	Modified-QuEChERs-dSPE	HPLC Chromatorex C_{18} (150 mm × 4.6 mm, 5 μm), 0.05 M citric acid adjusted to pH 3.5 with	FLD λ_{exc} = 280 nm λ_{em} = 365/4	5-8 μg/kg	76-99	(Li et al. 2012)

X		le		TFA/acetonitrile at 1.0 mL/min	50 nm			
DAN, ENR, FLU, MAR, OA, SARA	Fish muscle (Gilthead seabream) (5 g)	--	Modified-QuEChERs	UPLC Acquity UHPLC BEH C18 (100 mm × 2.1 mm, 1.7 μm), 0.1% HCOOH in acetonitrile-0.1% HCOOH in H_2O at 0.3 mL/min	MS QqQ-ESI(+)-MRM	3.0-7.5 μg/kg	66-128	(Lopes et al. 2012a)
MAR, CIP, DAN, ENR, SAR	Fish muscle (Bass) (2.0 g), pH 7	Deproteinization with 5% formic acid in acetonitrile	QuEChERs-dSPE	UPLC Poroshell 120 EC-C18 (50 mm × 2.1 mm, 2.7 μm), 1% HCOOH/acetonitrile at 0.5 mL/min	FLD λ_{exc} = 294/278/325 nm λ_{em} = 514/476/36	4.7-0.1 μg/kg	72-108	(Lombardo-Agüí et al. 2014a)

A, DIF, OA, FLU					6 nm			
ENO, NOR, CIP, PEF, OFL, LOM, FLE, ENR, GAT	Fish (200 g)	Minced and homogenized with dimethylsulfoxide and acetonitrile	DMI-MSPD **PC**: acetonitrile, H_2O; **WS:** methanol, H_2O; **EC**: acetonitrile, TCA.	HPLC Agilent ZORBAX SB-C_{18} column (250 mm × 4.6 mm, 5 μm), H_2O/HCOOH/methanol/acetonitrile at 1.0 mL/min.	FLD λ_{exc} = 290 nm λ_{em} = 480 nm	0.06 - 0.22 μg/kg	64.4-99.2	(Sun et al. 2014)
OA	Chicken	--	QuEChERs-	UPLC	MS	6.4 μg/k	75.7-	(Lopes et al.

	meat (5.0 g)		dSPE	Acquity BEH C_{18} column (100 mm × 2.1 mm, 1.7 μm), H_2O/acetonitrile both containing 0.1% HCOOH at 0.3 mL/min.	QqQ-ESI(+)-MRM	g	118.3	2012b)
NOR, DIF, ENR, OA, CIP, SARA, FLU, NA, MAR,	Chicken breasts (5.0 g)	Chopped and mixed.	QuEChERs-dSPE	HPLC Synergi Fusion-RP column (100 mm × 2 mm, 2.5 μm), 0.1% (V/V) HCOOH in H_2O-HCOOH in methanol	MS QqQ-ESI(+)-MRM	--	--	(Stubbings et al. 2009)

DAN, OFL, LOM								
NOR, CIP, DAN, ENR, SAR, DIF	Chicken liver (5.0 g)	Pureed, homogenized with 5.0 mL of 25 mM H_3PO_4/acetonitrile (30:70), centrifuged.	DLLME **EC**: $CHCl_3$; **DS:** acetonitrile.	HPLC Waters XTerra MS C_{18} column (3.0 mm ×150 mm, 3.5 µm), acetonitrile/0.1% HCOOH at 0.35 mL/min.	PAD 278/280/300 nm	13-19 µg/kg	83-102	(Moema et al. 2012)
NOR, CIP, LOM,	Chicken muscle (0.5 g), pH	Deproteinization with acetonitrile/H_2O	MISPE **SO** ^{o}: MIP cartridges; **PC**: methanol,	HPLC AQUATM C18 (polar endcapped) column (250 mm × 4.6 mm, 5 µm) at 1-	FLD λ_{exc} = 280 nm λ_{em} =	2.8-12.2 µg/kg	72-102	(Urraca et al. 2014)

DAN, ENR, SARA	7.5.	with 25 mM phosphoric acid (pH 3.0) (20:80, v/v)	HEPES buffer (0.1 M, pH 7.5); **EL**: methanol with 5% TFA.	2 mL/min.	360 nm			
				UPLC BEH C_{18} Shield column (150 mm × 1.0 mm, 1.7 µm), H_2O/acetonitrile/HCOOH at 0.13 mL/min.	MS QqQ-ESI(+)-MRM	0.2-1.7 µg/kg		
MAR, ENR, DAN, SARA	Egg (10 g for QuEChERs, 1g for SE, 0.5 g for MSPD, 2g for	Homogenized	Modified-QuEChERs	UPLC Acquity BEH C_{18} column (100 mm × 2.1 mm, 1.7µm), methanol/0.05% HCOOH in H_2O at 0.3 mL/min	MS QqQ-ESI(+)-MRM	--	2-49	(Garrido Frenich et al. 2010)
			SOSE **EC**: acetonitrile, 0.5 M citric acid, 0.1 M Na_2EDTA; clean-up through an OASIS			0.2-5 µg/kg	84-91	

	SPE)		HLB cartridge. MSPD					
			MSPD blended with 2.0 g of C_{18} to get yellow material that was packed into 12 mL SPE cartridges (2.0 g of Florisil); **EL**: methanol, acetonitrile, 35% ammonia solution in			--	0-2	

			methanol. SPE			-- --	49- 79	
DAN, ENR	Egg (1.0 g)	Homogenized	Modified-QuEChERs	HPLC Deactivated silica C_{18} column (150 mm × 2.1 mm, 3 µm), H_2O containing 0.1% (v/v) HCOOH-acetonitrile containing 0.1% (v/v) HCOOH at 0.2 mL/min	MS QqQ-ESI(+)-MRM	0.9-1.0 µg/kg	58-69	(Capriotti et al. 2012)
OFL, PEF, NOR, CIP, ENR	Egg (10 g)	Deproteinization with 3.0 mL of water and 2.0 mL of lead	PT-MISPE **PC**: methanol, H_2O; **EL**: acetonitrile/ CH_3COOH	HPLC C_{18} column (250 mm × 4.6 mm, 5 µm), TBAB/acetonitrile/ TFA at 1.0 mL/min.	UV-vis 280 nm	0.53 - 1.07 µg/kg	89.1-102.5	(Liu et al. 2013)

		acetate solution, centrifuged.	(95:5, v/v).					
ENR, DIF, SARA, CIP, NOR, ENO	Vegetables (10 g)	Homogenized	Modified-QuEChERs-dSPE	HPLC Zorbax SB-Aq column (150 mm × 2.1 mm, 3.5 μm), acetonitrile/0.1% HCOOH in H_2O at 0.2 mL/min	MS QqQ-ESI(+)-MRM	0.005-0.5 μg/kg	60.0-98.0	(Hu et al. 2014)

Notes:

* For easy comparison, values of limit of detection (LOD) were converted to comparable units (μg/kg or μg/L). The LODs were calculated according to the EURACHEM Guidance (Vázquez et al. 2012), the International Conference on Harmonization (Rodríguez et al. 2011), or based on a signal-to-noise ratio of 3 for the individual compound (Esponda et al. 2009, Huang et al. 2010b, López-Serna et al. 2010, Lombardo-Agüí et al. 2010b, Lombardo-Agüí et al. 2014b, Prieto et al. 2011);

a -- QqQ: Triple quadrupole; b -- MSPD: Matrix solid-phase dispersion; c -- PC: Previously conditioned with; d -- WS: Washing solution;e -- EL: Eluent;

f -- SS: Salt for separation; g -- BGE: Background electrolyte; h -- IL-based HLLME: ionic liquid-based homogeneous liquid-liquid microextraction; i -- SOSE: Single organic solvent extraction; j -- EC: Extraction solvent; k -- λ_{exc}: Excitation wavelength; l -- λ_{em}: Emission wavelength; m -- HPTLC: High-performance thin-layer chromatography; n -- DS: Dispersive solvent; o -- SO: Sorbent.

Table 2. Summary of the advantages and limitations of different preparation methods (except offline SPE) for extracting quinolones in liquid samples.

Method		Advantages	Limitations
Modified-LLE (SALLE [a]) (Dorival-García et al. 2015, Lombardo-Agüí et al. 2014b)		• Cleanup and preconcentration in one single step • Rapid, simple and economic	• Diluted samples (resulting in very low or no preconcentration) • Non-exhaustive clean-up • Precision depends on operational quality
Modified-liquid-liquid microextraction	DLLME [b] coupled with ultrasound (Vázquez et al. 2012, Yan et al. 2011), which uses ionic liquids as the extraction solvent or adding NaCl	• Sensitive • Simple • Economic	• Poor sensitivities and high detection limits (μg/L) (Herrera-Herrera et al. 2013)

		into samples to obtain low detection levels and salting-out effect (Vázquez et al. 2012)		
		SILLME [c] (Du et al. 2014) based on the system of ACN/$MgSO_4$	• Cleanup and preconcentration in one single step • Quick, easy, cheap, effective, rugged, and safe	• Rarely used now
Modified SPE	Offline SPE	PT-SPE (Springer et al. 2014)	• Less sorbent • Reduce solvent consumption in washing and elution steps • Shorten the operation time of	• Low selectivity

			SPE • Increase sample throughout	
		PT-MISPE (Liu et al. 2013)	• Special selectivity • Easy operation, and accessible • Device without expensive SPE apparatus	• Synthesis of the packing material
	Online SPE	Semi-automatic (Prieto et al. 2011)	• Simple operation • Reduced sample and solvent volumes • Increased sensitivities and low detection limits (ng/L) • High recoveries	• Time-consuming for assembling of apparatus (mainly with two pumps and SPE column) (García et al. 2012, Prieto et al. 2011, Rodríguez et al. 2011) • Expensive for commercially available instrument (López-Serna et al. 2010)
		Fully automatic (Rodríguez et al. 2011)		

Solid-phase microextraction (SPME)	Traditional SPME		• Simple operation • Lower sample volume compared to offline SPE	• Poor sensitivity and reproducibility • Relatively high cost • Fiber fragility of traditional SPME • Non-exhaustive extraction
	Improved SPME	SPME-MD [d] (Esponda et al. 2009)	• Higher efficiency than traditional SPME	
		EE-SPME [e] (Liu et al. 2012)		
		SPME with novel fibers (MIP-coated fiber SPME (Mirzajani	• Capable for complex matrices • Fiber with good reproducibility (>10 times) and long lifetime	• Suitable for a few quinolones

		et al. 2016))		
		In-tube magnetic SPME (Manbohi et al. 2015)	• Rapid and easy automation and analysis • Possibility of fully sorbent collection after analysis • Wide linear range	• Only applied for urine and water samples
		SBSE [f] (Huang et al. 2010b)	• Higher extraction efficiency and better reproducibility than traditional SPME and LLME	• Limited applicable coatings • Coating abrasion of the laboratory-made stir bar • Difficulty in automation
QuEChERS [g] (Anastassiades et al. 2003b)			• Simplicity and effectiveness for cleaning up complex samples • High flexibility	• Significant challenge for automation

Notes:

a -- SALLE: salting-out assisted liquid-liquid extraction; b -- DLLME: dispersive liquid-liquid microextraction; c -- SILLME: salting-out induced liquid-liquid microextraction; d -- SPME-MD: SPME with micellar desorption; e -- EE-SPME: electrochemically enhanced SPME; f -- SBSE: Stir bar sorptive extraction; g -- QuEChERS: quick, easy, cheap, effective, rugged, and safe.

Table 3. Summary of SPE sorbents that have been used for extraction and concentration of quinolones in food products.

Mechanism (as depicted on Figure 4)		**Sorbents**	**Characteristic**	**Operating pH**	**Quinolones analyzed**	**Recovery, %**	**Ref.**
Van der Waals	Hydrophobic interaction (a1)	Isolute C_{18}	• Strong non-polar (hydrophobic) phase • Octadecyl (end-capped) functionalized silica • Manufactured using trifunctional silane • End-capped to reduce silanol interaction	3	PIP, ENO, NOR, CIP, OFL, ENR, LOM, MOX, CIN, NA, OA, FLU, PA	≥80	(Dorival-García et al. 2013)

		DSC-C_{18}	• Polymerically bonded octadecyl	No adjustment	OFL, NOR	35-39	(Zhou et al. 2012)
		Chromabond-C_{18} Hydra	• Octadecyl-modified silica			42-48	
	π-π interaction (a2)	Strata SDB-L	• Styrene-divinylbenzene polymer			35-38	
		Strata-X	• Modified poly(styrene-divinylbenzene)	7	OFL, NOR, LOM	92.0-104.4	(Lombardo-Agüí et al. 2010b)
		Chromabond-Easy	• Polystyrene-divinylbenzene resin	No adjustment	OFL, NOR	20-24	(Zhou et al. 2012)

	Molecular interaction (a3)	MIPs	• Molecularly imprinted polymers	7.5	CIP, NOR, ENR, DAN, LEV, SARA, OA, FLU	62-102	(Rodríguez et al. 2011)
		Magnetic MIPs	•Surface-functionalized magnetic particles with polydimethylsiloxane and multi-walled carbon nanotubes	6	OFL, NOR, CIP, ENR	81.5-94.1	(Xu et al. 2012)
Polar/dipole-dipole attraction or hydrogen bonding (b)		DSC-Si	• Unbonded acid washed silica sorbent	No adjustment	OFL, NOR	5-16	(Zhou et al. 2012)
		Chromabo	• Modified silica			35-40	

	nd-Drug					
Electrostatic (anion exchange-c1) & (a)	DSC-SCX	• Aliphatic sulfonic acid modified silica			5-20	
Electrostatic (cation exchange c2) & (b)	DSC-SAX	• Quaternary amine modified silica			13-16	
(a1) & (c1)	Chromabond-Easy	• Polystyrene-divinylbenzene resin			20-24	
	Strata-X-CW	• Styrene-divinylbenzene copolymer • Wider pka range and more flexibility elution conditions than strong cation exchange column	7	OFL, NOR, LOM	45-55	(Lombardo-Agüí et al. 2010b)
	WCX	• N-vinyl pyrrolidone-co-	acid	CIP, DIF, ENR,	80-90	(He et al.

		divinyl benzene -COOH		FLE, NOR, MOX, OFL		2015)
	Oasis MCX	• Mixed-mode cation exchange sorbent • Poly(styrene-divinylbenzene) • Have high selectivity and sensitivity to the weak alkaline compound	2.5-3	OFL, CIP	78-99	(Grosa et al. 2012)
	MPC	• Octyl-phase and benzenesulfonate mixture	3	PIP, ENO, NOR, CIP, OFL, ENR, LOM,	40-78	(Dorival-García et al. 2013)
a1 & b	Oasis HLB	• Oasis hydrophilic-				

		liphophilic balance • Poly(divinylbenzene-co-N-vinylpyrrolidone) • Specific surface area of Oasis HLB are two to three times than silica gel		MOX, CIN, NA, OA, FLU, PA		
			No adjustment	OFL, CIP	80	(Grosa et al. 2012)
			No adjustment	OFL, NOR	58-65	(Zhou et al. 2012)
			7	OFL, NOR, LOM	70.6-84.9	(Lombardo-Agüí et al. 2010b)

Table 4. Summary of the parameters of SPE methods for extracting quinolones in food products.

Adsorbent	Preconditioning	Flow rate extraction (mL/min)	Washing	Elution	Reconstituted	Ref.
OASIS HLB	1 mL MeOH + 1 mL Milli-Q water	--	2 mL phosphoric acid buffer (0.025 M, pH 3)/MeOH 95:5(v/v) + 2 mL H2O	2 mL MeOH/ammonia 95:5 (v/v)	1 mL sample dilution buffer for egg;a 2 mL for muscle/feed samples	(Scortichini et al. 2009)
Strata-X	4 mL MeOH + 4 mL	1	--	2 × 3 mL	200 mL 0.1%	(Nebot et

	Milli-Q water			MeOH	COOH in MeOH	al. 2012)
Oasis HLB	1 mL MeOH + 1 mL H2O + 1 mL 0.1M H3PO4 at pH 10	--	3 mL H2O	2 mL MeOH	200 µL H2O	(Junza et al. 2014)
HLB	5 mL MeOH + 5 mL H2O	--	5 mL H2O	5 mL MeOH	1 mL H2O	(Meng et al. 2014)
Evolute ABN	3 mL ACN + 3 mL H2O	--	3 mL H2O	2 mL ACN	H2O	(Kaufmann et al. 2011)
OASIS HLB	1 mL MeOH + 2 mL ACN + 2 × 2 mL H2O	--	6 mL n-hexane	3 mL MeOH + 3 mL ACN + 3 mL 0.04% (v/v) ammonia solution in MeOH	1 mL MeOH: 0.05% HCOOH = 50:50 (v/v).	(Garrido Frenich et al. 2010)
C18	2 mL MeOH + 2 mL H2O	--	2 mL H2O	2 mL 1 M aqueous	2 mL H2O	(Tang et al. 2009)

				ammonia (25% in MeOH)		
MIP	1 mL MeOH + 2 mL 50 mM NaH2PO4 at pH 7.4	0.5	3 mL of Milli-Q water + 1mL ACN	3 mL [2% ammonium hydroxide + MeOH/ H2O = 75:25, (v/v)]	100 μL MeOH	(Blasco et al. 2012)
MI-MAA/APTS b	3 mL MeOH + 2 mL H2O	--	2 mL H2O	4.0 mL ACN--ammonia solution (95:5, v/v)	0.5 mL 0.02 M TBAB-acetonitrile-TFA (90:10:0.06, v/v/v)	(Yang et al. 2014)
Magnetic PDMS/MWCNTs-OH c	Adsorbent activated with MeOH + H2O; added to liquid samples; sonicated for 5 min; separated rapidly from the solutions using a magnet			1 mL MeOH containing 12% HCl (0.1 M) twice under sonication for	1 mL deionized water	(Xu et al. 2012)

		5 min		

Notes:

a -- sample dilution buffer, provided by the ELISA kit (Euro-Diagnostica B.V.); b -- MI-MAA/APTS: molecularly imprinted organic--inorganic hybrid polymer; c -- magnetic PDMS/MWCNTs-OH: magnetic polydimethylsiloxane and multi-walled carbon nanotubes.

Table 5. Summary of the parameters of QuEChERS methods for extracting quinolones in food products.

Extraction		Clean-up		Ref.
Extraction solvent	**Salts**	**Sorbents in d-SPE**	**Recomposition media**	
1% of HCOOH in ACN +10 mL of 0.1 M Na_2EDTA solution	4 g $MgSO_4$, 1 g sodium acetate	--	1 mL MeOH:0.05% HCOOH (50:50, v/v)	(Martínez Vidal et al. 2010)
0 mL 5% HCOOH in ACN	Agilent SampliQ EN QuEChERS extraction kit (4 g $MgSO_4$, 1 g NaCl, 1 g sodium citrate, 0.5 g disodium citrate sesquihydrate)	C_{18} and $MgSO_4$	1 mL 10 mM citric acid solution	(Lombardo-Agüí et al. 2011)
10 mL ACN/HCOOH (99:1, v:v)	4 g $MgSO_4$, 1 g sodium acetate	--	0.5 mL acetonitrile + 0.1 mM	(Wang et al. 2012)

			ammonium acetate	
10 mL ACN, 10 mL H_2O; 200 mg Na_2EDTA	4.0 g anhydrous $MgSO_4$, 1.0 g sodium acetate.		2 mL MeOH:H_2O (1:1, v/v)	(Chen et al. 2014)
10 mL 5% HCOOH in ACN	Agilent SampliQ EN QuEChERS extraction kit (4 g $MgSO_4$, 1 g NaCl, 1 g sodium citrate, 0.5 g disodium citrate sesquihydrate)	C_{18} and $MgSO_4$	1 mL of H_2O/ACN/HCOOH (88/10/2, v/v)	(Lombardo-Agüí et al. 2012)
10 mL ACN H_2O/ (20:80 v/v), acidified with 5% acetic acid	4.0 g Na_2SO_4, 1.0 g sodium acetate	C_{18}, PSA 1:1 w/w	2 mL MeOH:H_2O (20/80, v/v) with 0.1% HCOOH (v/v)	(Rocha et al. 2015)
90% (v/v) acidic ACN	--	PSA	--	(Li et al. 2012)

2 mL H_2O, 10 mL ACN: MeOH (75:25, v/v)	4 g $MgSO_4$, 1 g sodium acetate	--	1 mL ACN:H_2O (10/90, v/v) with 0.1% HCOOH (v/v)	(Lopes et al. 2012a)
30 mM NaH_2PO_4 (pH 7), 5% formic acid in ACN	Agilent SampliQ EN QuEChERS extraction kit (4 g $MgSO_4$, 1 g NaCl, 1 g sodium citrate, 0.5 g disodium citrate sesquihydrate)	C_{18} and $MgSO_4$	1 mL H_2O/ACN/HCOOH (88/10/2, v/v/v)	(Lombardo-Agüí et al. 2014a)
5.0 mL H_2O, 10.0 mL 1% CH_3COOH in ACN /H_2O (80:20, v/v)	2.0 g disodium citrate, 1.0 g sodium citrate dihydrate, 4.0 g anhydrous $MgSO_4$	PSA	500 µL solution of 0.1% HCOOH in ACN: H_2O (50:50, v/v)	(Lopes et al. 2012b)
7 mL H_2O, 15 mL 1% CH_3COOH in ACN	6.0 g anhydrous $MgSO_4$, 1.5 g anhydrous sodium	--	1 mL ACN: H_2O (90:10, v:v)	(Stubbings et al. 2009)

	citrate dehydrate			
10 mL of 1% of acetic acid in ACN, 10 mL 0.1 M Na_2EDTA	1.0 g sodium acetate, 4.0 g anhydrous $MgSO_4$	--	1 mL solution of MeOH and 0.05% HCOOH, (50:50, v/v)	(Garrido Frenich et al. 2010)
4.0 mL of $MeOH/H_2O/CH_3COOH$ (80:20:1, v/v/v)	0.5 g CH_3COONa, 2.0 g Na_2SO_4 anhydrous; vortexed, centrifuged	--	--	(Capriotti et al. 2012)
10 mL ACN/MeOH (85:15. v:v), citric buffer solution	4.0 g anhydrous $MgSO_4$, 1.0 g NaCl	PSA	1 mL MeOH:0.1% HCOOH (20:80, v/v)	(Hu et al. 2014)

Table 6. Summary of the parameters of immunoassay methods for determining quinolones in food products.

Determination				Samples		Preparation		LOD	Recovery, %	Ref.
Antibody	**Hapten**	**Binding sites of haptens and proteins**	**Type according to lables**	**Analytes**	**Matrix**	**Pretreatment**	**Extraction method (extraction solvent)**			
scFvC4A9H1 [a]	--	Two ring of piperazinyl ring, C-1, C-3, C-7	ELISA	CIP, DAN, DIF, ENO, ENR, FLE, LOM, MAR, NOR, OFL, ORB,	--	--	--	--	--	(Wen et al. 2012)

				PAZ, PEF, PRU						
scFvC4A9 H1_mut2				SAR, DIF, TRO						
18-IA-HCH	Hapten 17,18	C-1	ELISA	CIP, ENR, DAN, DIF, SARA, NOR, OFL, FLU, MAR, OX	--	--	--	--	--	(Pinacho et al. 2012)
V_L scFvs	CIP	--	ELIS	CIP	--	--	--	9.3	--	(Brás

			A					nM		Gomes et al. 2010)
IC9 mAbs[b]	CIP	--	ci-ELISA[c]	CIP, ENR	Fishery products	--	LLE 30 mL 1 M HCl-acetonitrile (4/500, v/v) + 25 mL n-hexane.	10 ng/g	80.6-94.6	(Hu et al. 2010a)
RabMAbs[d]	CIP	--	ci-ELISA	CIP	Milk	Remove floated fat	LLE 200 μL PBS + 400 μL MeOH	0.095 ng/mL	63.0-84.6	(Huang et al. 2010a)

Pabs [e]	MAR, BEN, PEF, NOR	C-1, C-7, C-8	ci-ELISA	PIP, ENR, NOR, CIP, LOM, OFL, SPA, DAN, SARA, PEF, ENO, LEV, BAL, DIF, BEN, MAR, FRE, CAD, GAT, MOX,	--	--	--	--	--	(Cao et al. 2009)

				GRE, GEM, TRO, PRU, PAZ, FLU, OA						
ScFv	SAR	Two ring of piperazinylring, C-3, C-4, piperazine ring N-4	ELISA	SAR, DIF, CIP, ENR, NOR, PEF, LOM, ENO, AMI, DAN, OFL, MAR	Milk	--	SOSE 10 mL 0.1 M EDTA-Mcllvaine buffer	0.3-8.0 ng/mL	62.0-89.3	(Wang et al. 2016)

scFvC4A9H1_mut2	NOR	--	icCLEIA [f]	CIP, ENR, NOR, PEF, DAN, LEV, OFL, AMI, ENO, ORB, FLE, SPA, MAR, LOM, FLU, PAZ, PRU, SARA, DIF, TRO	Fish (2 g), Shrimp (2 g)	--	SOSE 8 mL ethanol/acetic acid (99:1,v/v)	0.0 8-27.2 μg/kg	--	(Tao et al. 2013)

6H7 mAbs	--	--	TRFIA [g]	FLU, NOR, CIP, DAN, ENR, MAR, SARA, DIF	--	--	--	--	--	(Leivo et al. 2011)
mH3D7 mAbs	--	C-1	TRFIA	DIF, SAR, CIP, DAN, ENR, NOR, FLU, MAR	Milk	Without preparation		0.2-68 μg/L		(Leivo et al. 2013)

mAbs	LOM	--	FPIA[h]	ORB	Milk (4 mL)	Deproteinized saturated $(NH_4)_2SO_4$ solution	3.9 ng/mL	74.3-112	(Mi et al. 2014)
C4A9H1 mAbs	CIP	Piperazine NH	FPIA	CIP, ENR, FLU, DAN, MAR	Milk (2 mL)	Deproteinized 1.5% trichloroacetic acid	16.1-182.6 ng/mL	77.8-116	(Mi et al. 2013)
					Chicken muscle (2 g)	Homogenized	LLE 8 mL PBS (0.02 M, pH 7.0) + 8 mL dichloromethane	40.4-628.8 ng/g	

aptamers	--	--	CLEIA [i]	ENR	Milk	Sterilization	2.3 ng/mL	89.7-108.6	(Ni et al. 2014)
Rabbits Pabs	PAZ	C-7	icCLEIA	PAZ, GAR, NOR, LOM, PEF, CLI, PIP, RUF, CIP, ENR, GAT, DAN, MAR, NA, OA, DIF, MOX, SAR,	Milk	Fat removed	0.1 - 33.8 ng/mL	84.6-106.9	(Zeng et al. 2016)

TOS,

PRU

Notes:

a -- scFvC4A9H1: a single chain variable fragment (scFv) generated from the murine hybridoma cells C49H1; b -- mAbs: monoclonal antibodies;

c -- ci-ELISA: competitive indirect enzyme-linked immunosorbent assay; d -- RabMAbs: rabbit monoclonal antibodies; e -- Pabs: polyclonal antibodies;

f -- icCLEIA: indirect competitive chemiluminescence enzyme immunoassay; g -- TRFIA: time-resolved fluorescence immunoassay; h -- FPIA: fluorescence polarization immunoassay; i -- CLEIA: direct competitive chemiluminescent enzyme immunoassay.

Table 7. Summary of the parameters of biosensor-based methods for determining quinolones in food products.

Determination				Samples		Preparation		LOD	Ref.
Classification	**Principle**	**Recognition element**	**Device fabrication**	**Analytes**	**Matrix**	**pretreatment**	**Extraction method**		
Electrochemical	Direct	Antibody	Impedimetric sensor	CIP	--	--	--	3 pmol/L	(Giroud et al. 2009)
Electrochemical	Direct	MIP	Potentiometirc sensor Poly(pyrrole-N-hydroxysuccinimide) film modified electrodes	CIP	--	--	--	32-46.3 µg/mL	(Kamel et al. 2011)

Electrochemical	Indirect competitive	Magnetic beads biomodified with an antibody	Amperometric magneto-immunosensor Haptenized enzyme and a magnetic graphite-epoxy composite electrode	CIP, ENR, DAN, DIF, MAR, FLU, OA	milk	Without preparation		0.009 µg/L	(Pinacho et al. 2014)
Electrochemical	Direct	Graphene	Amperometric sensor Graphene modified glassy carbon	CIP	--	--	--	0.02 µmol/L	(Xie et al. 2015)

			electrode					
Electrochemical	Inhibition	L-arginine	Amperometric sensor Polymerization β-cyclodextrin and L-arginine (L-arg) modified carbon paste electrode	CIP, OFL, NOR, GAT				(Zhang et al. 2013)
Optical	Indirect inhibition	Pabs	SPR biosensor Quinolone haptenized protein biofunction	ENR, CIP, NOR	milk	Fat removal by centrifugation + dilution with Milli-Q water	2 ± 0.2 µg/L	(Fernández et al. 2011)

			alized SPR*eeta* integrated sensor chip						
Optical	Inhibition	Pabs	SPR biosensor Core-quinolone derivative functionalized sensor chip	SARA, NA, OFL, FLU, NOR,CIP,OA,LOM,ENO	Poultry meat (2 g), egg (2 g), fish (2 g)	Homogenized	LLE 8 mL acetonitrile + 1 mL hexane	Poultry meat: 0.13 ng/g; Egg: 0.29 ng/g; Fish: 0.3	(Huet et al. 2009)

								1 ng/g	
Optical	Inhibition	Pabs	SPR biosensor Quinolone derivative functionalized carboxymethylated CM5 sensor chip	CIP, DAN, DIF, ENO, ENR, FLU, LOM, MAR, NOR, OFL, OA, SARA	Poultry muscle (2 g), egg (2 g)	--	LLE 8 mL acetonitrile + hexane	1-50 µg/kg	(Weigel et al. 2009)
					Fish (2 g)	Scaled filleted, homogenized			

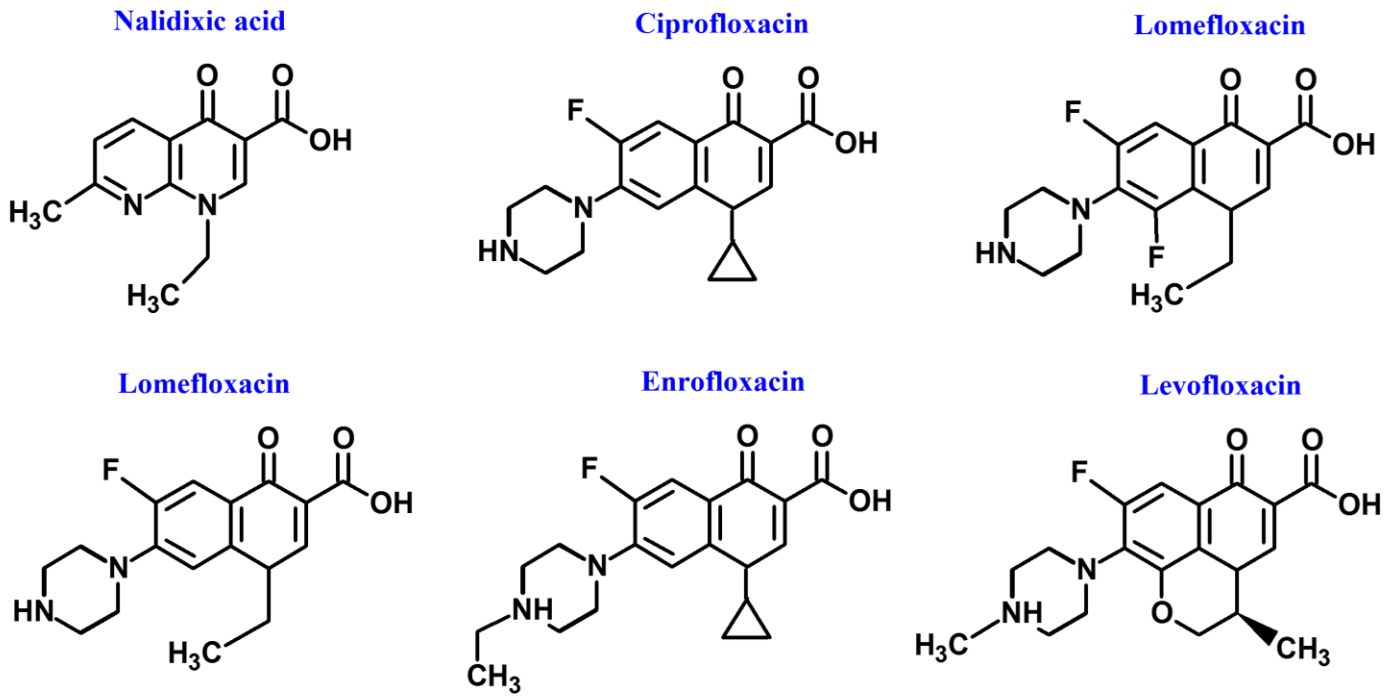

Figure 1. Structures of the first quinolone compound (nalidixic acid) and some of the most commonly used quinolone antimicrobials.

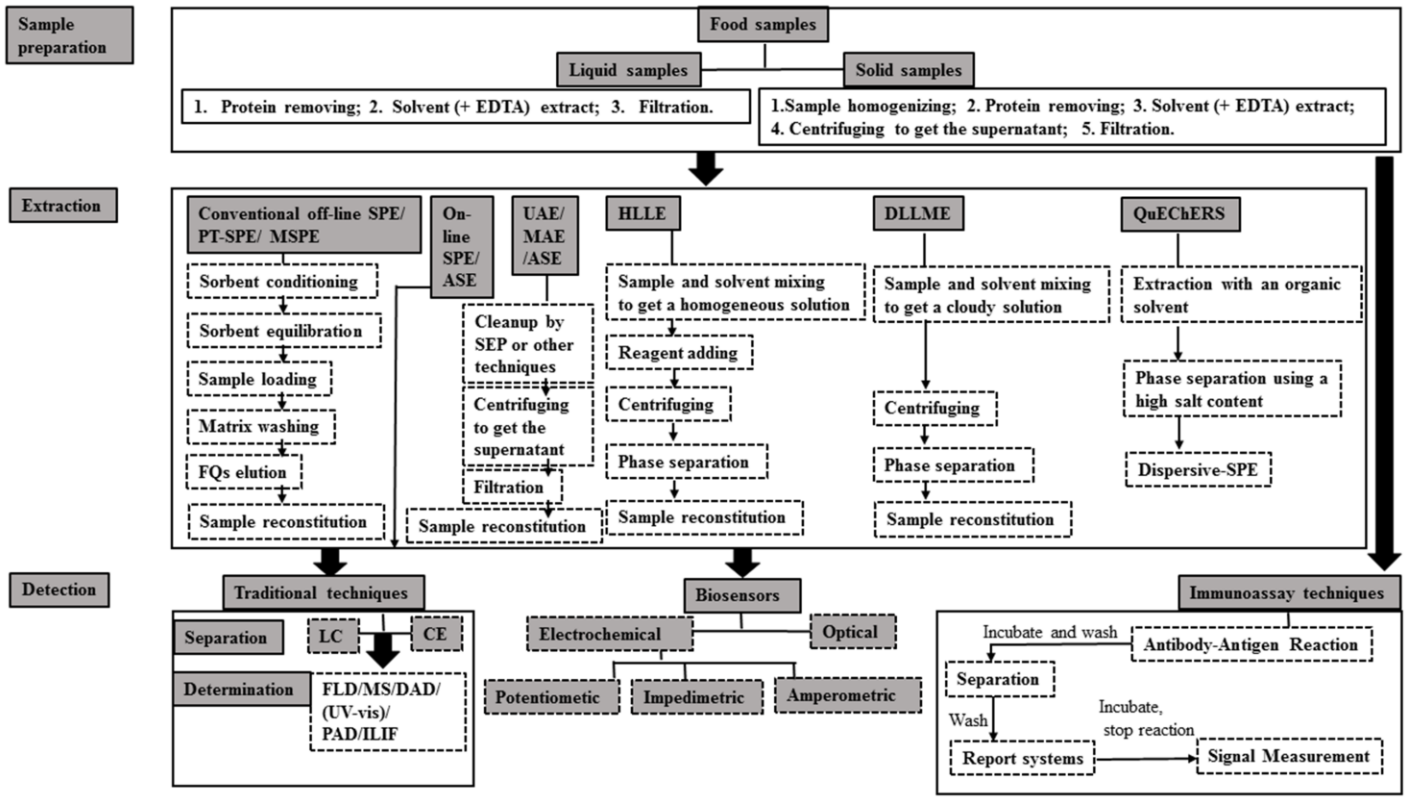

Figure 2. Typical procedures involved in the isolation and analysis of quinolones in food samples, including sample preparation, extraction, and determination. EDTA is added during the sample preparation to prevent chelation between quinolones and metal cations.

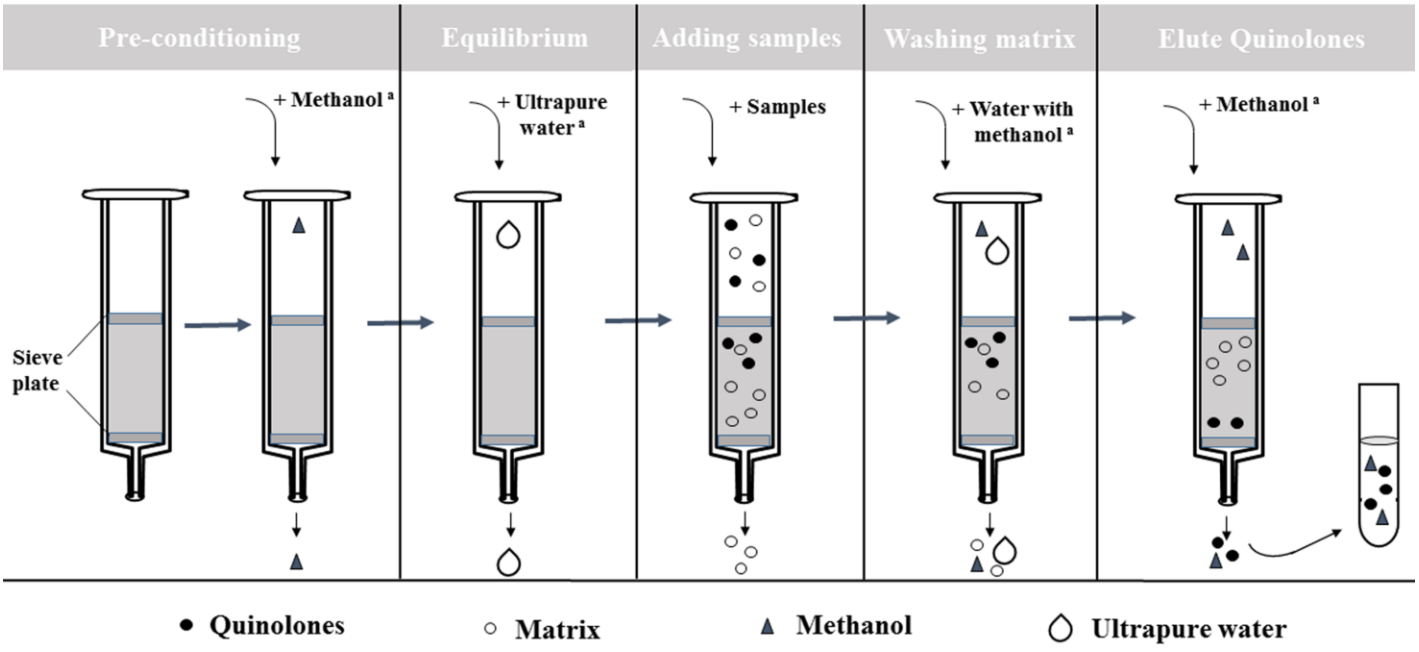

Figure 3. Flow chart of typical SPE procedure for extraction of quinolones from liquid samples.

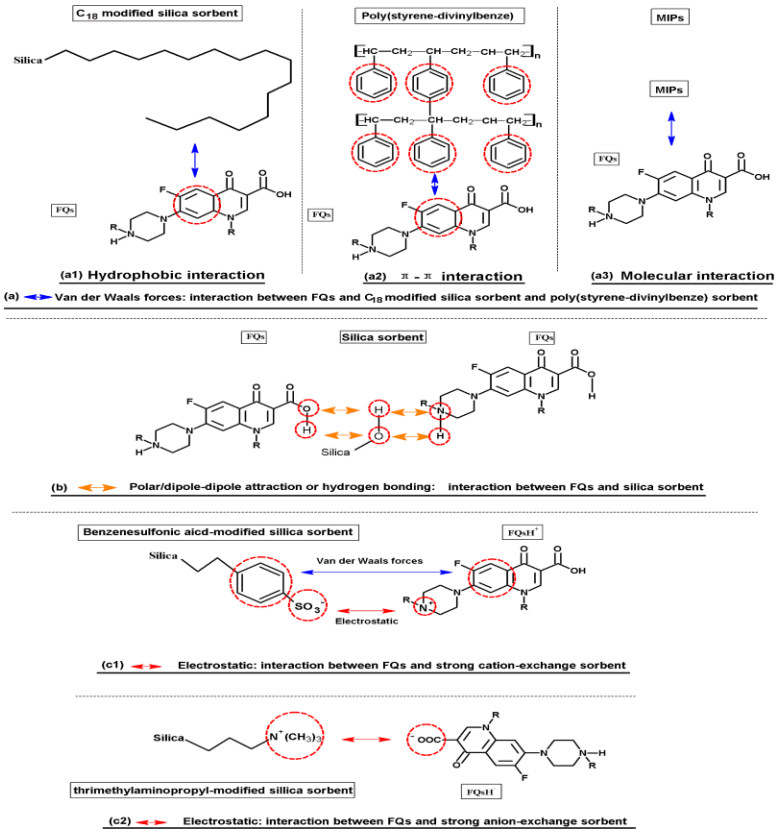

Figure 4. Summary of the major interactions between SPE sorbents and quinolones.

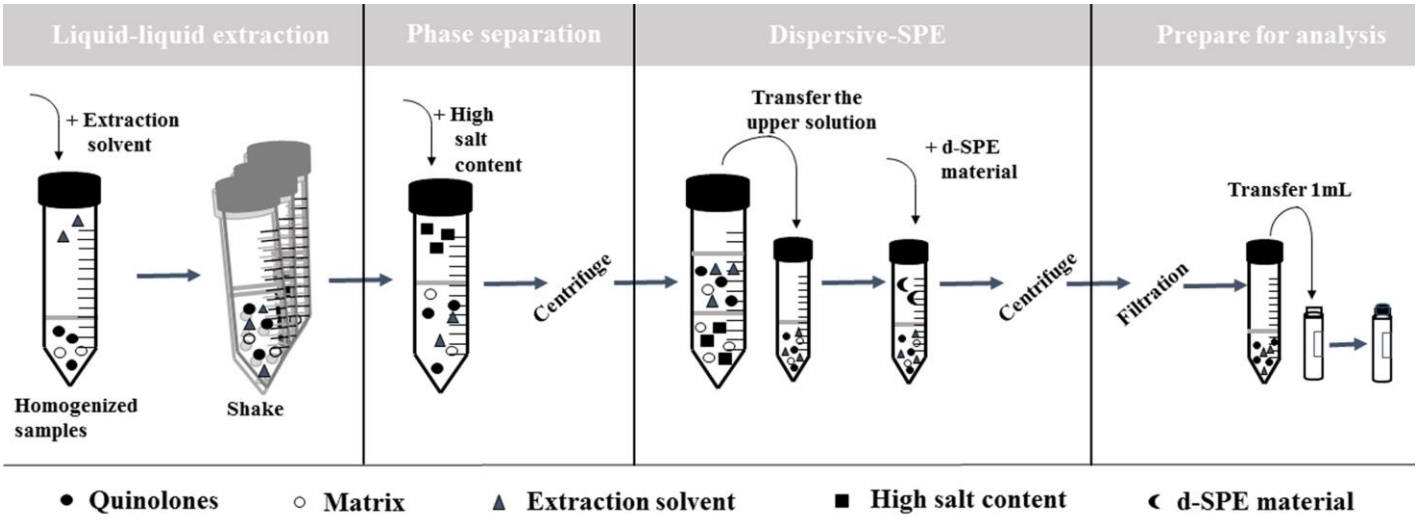

Figure 5. Flow chart of typical QuEChER procedure for extraction of quinolones in food samples.

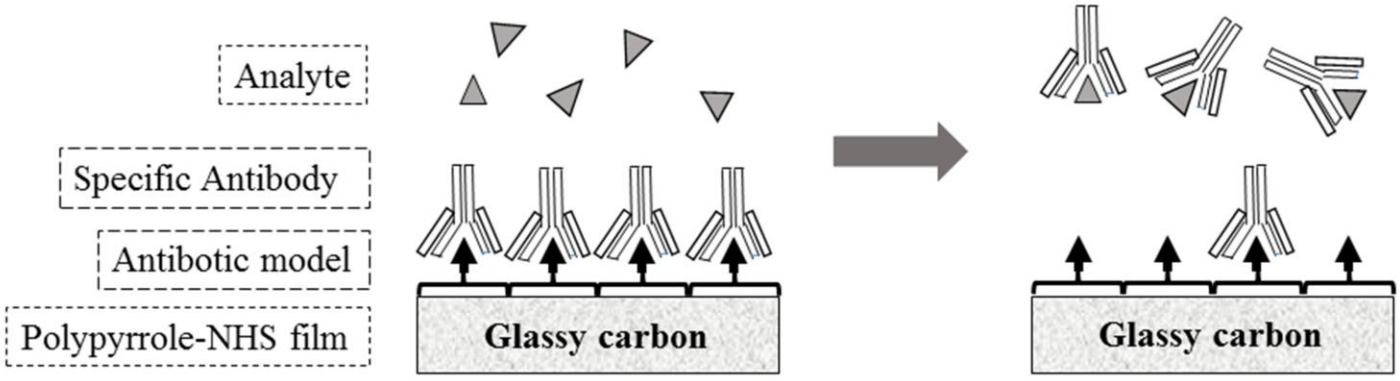

Figure 6. Working principle of an impedimetric immunosensor for ciprofloxacin based on anti-ciprofloxacin antibody displacement (after Giroud et al. 2009).

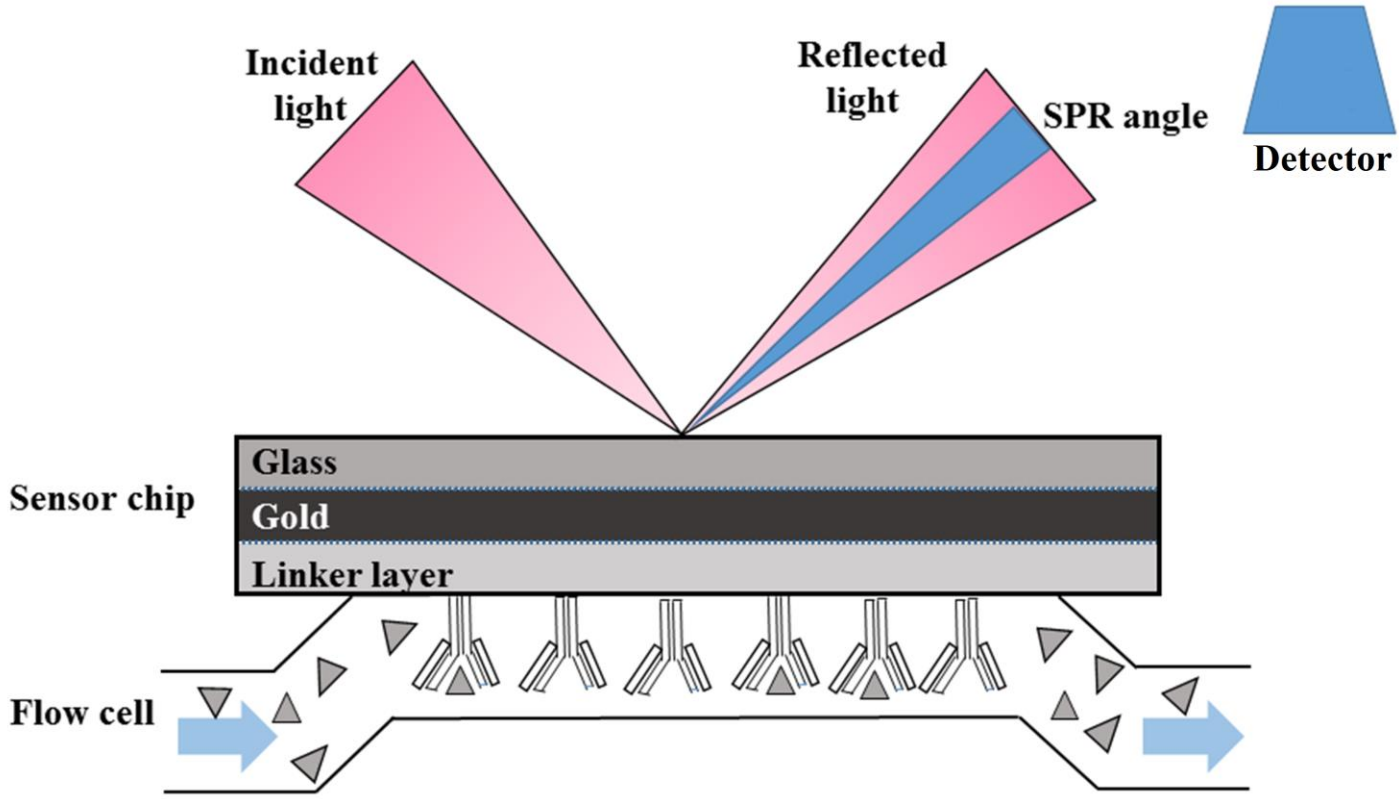

Figure 7. Working principle of SPR detection for analyte (represented by the filled triangle).

