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Review

On the Extraction of Antibiotics from Shrimps Prior to Chromatographic Analysis

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Abstract: The widespread use of antibiotics in veterinary practice and aquaculture has led to the increase of antimicrobial resistance in food-borne pathogens that may be transferred to humans. Global concern is reflected in the regulations from different agencies that have set maximum permitted residue limits on antibiotics in different food matrices of animal origin. Sensitive and selective methods are required to monitor residue levels in aquaculture species for routine regulatory analysis. Since sample preparation is the most important step, several extraction methods have been developed. In this review, we aim to summarize the trends in extraction of several antibiotics classes from shrimps and give a comparison of performance characteristics in the different approaches.

Keywords: sample preparation; extraction; aquaculture; shrimps; chromatography; antibiotics

1. Introduction

According to FAO (CWP Handbook of Fishery Statistical Standards, Section J: AQUACULTURE), "aquaculture is the farming of aquatic organisms: fish, mollusks, crustaceans, aquatic plants, crocodiles, alligators, turtles, and amphibians. Farming implies some form of intervention in the rearing process to enhance production, such as regular stocking, feeding, protection from predators, *etc.*" [1].

Since 1960, aquaculture practice and production has increased as a result of the improved conditions in the aquaculture facilities. Such improvements include better water quality, infection control, high nutrition feeds and improved aquatic species, through newly developed hybridization techniques, particular species breeding and the use of molecular genetics [2]. According to FAO 2005, in the time span from 1990 to 2005, aquaculture production each year has tripled from 16.8 million tons to 52.9 million tons. By 2015, it was also predicted that aquaculture would constitute 39% of the seafood production in weight worldwide, dramatically increasing from 4% in 1970 and 28% in 2000. Eleven of the fifteen elite aquaculture producing countries are located in Asia, with 94% of the total worldwide production, while China on its own has 71% of the total production [3].

Shrimp aquaculture is one of the most important aquacultures and makes a considerable contribution to the national economies, both in developed and developing countries. According to the "Global Study of Shrimp Fisheries" from FAO, the biggest domestic product percentage of shrimp farming belongs to Madagascar (1%), excluding the traditional shrimp fishing. The gross domestic values for other developing countries range between $2.72 million–$558 million US. Shrimp is the most profitable exported product in Cambodia, Indonesia, Kuwait, Madagascar, Mexico, Nigeria, and Trinidad and Tobago, and to a lesser extent Australia and Norway. Shrimp consumption, on the other hand, is high in most developed countries, such as Australia and Norway, with the United States presenting the highest consumption and, as a result, being the greatest shrimp market worldwide [4].

The increased aquaculture practice has resulted in increased levels of infections among the species. Usually the farming is done in cages, where high populations are confined to a limited space, and infection outbreaks are common despite good hygiene levels. Bacteria, parasites, viruses and fungi can infect the confined animals, with bacteria being the main source of infections [5].

Antibiotics are used in aquaculture in order to control the infection outbreaks. They are natural, semisynthetic or synthetic compounds and their antibacterial effect resides on their ability to eliminate the bacteria or hinder their growth. Antibiotics used for human disease treatment, such as penicillins, macrolides, sulfonamides, tetracyclines and quinolones/fluoroquinolones, are often used in aquaculture. Specifically, oxytetracycline, florfenicol, sarafloxacin, enrofloxacin, chlortetracycline, ciprofloxacin, norfloxacin, oxolinic acid, perfloxacin, sulfamethazine, gentamicin, and tiamulin are commonly used in aquaculture infections. Besides the use of antibiotics as bacterial infection treatment, sulfonamides, β-lactams and macrolides can be used as growth-promoting or infection-preventing agents. They are used in sub-therapeutic doses in animal feed or veterinary drugs [6–9].

The extensive use of antibiotics, however, may lead to residues in edible animal tissues and cause allergic or toxic effects to sensitive groups or the development of persistent microorganisms. It poses a risk to human health through the migration of antibiotics from aquaculture products to the human organism. As a result, authorities in many countries have published regulations on the antibiotic usage and residues in aquaculture and aquaculture products to minimize the risk to human health associated with consumption of their residue [9].

These regulations are strict in Europe, North America and Japan, where only few antibiotics are approved and maximum residue levels (MRLs) are introduced. However, the majority of aquaculture production and export takes place in countries where few or no regulations exist [6,9].

To comply with the EU regulation, state laboratories have to put into practice methods for both screening and confirming the presence in seafood.

Until every aquaculture country complies with regulations, controls are essential when importing aquaculture products. Sensitive analytical methods have been developed in order to control the product compliance to the regulations and ensure that the residue levels are lower than the MRLs. Sample preparation is the most important step during the development and the application of such analytical methods.

A significant number of multi-residue or single analytical methods have been reported in the literature for the determination of antibiotics in shrimps.

In general, the most common sample preparation techniques are solid phase extraction (SPE), using appropriate columns for each class examined, and solid-liquid extraction (SLE). However, liquid-liquid extraction (LLE) has been also used in some cases. In addition to this, recently developed materials, such as molecular imprinted polymers, have also been applied in some studies. The distribution of sample preparation techniques for the extraction of each class of antibiotics from shrimps is illustrated in the pie charts of Figure 1.

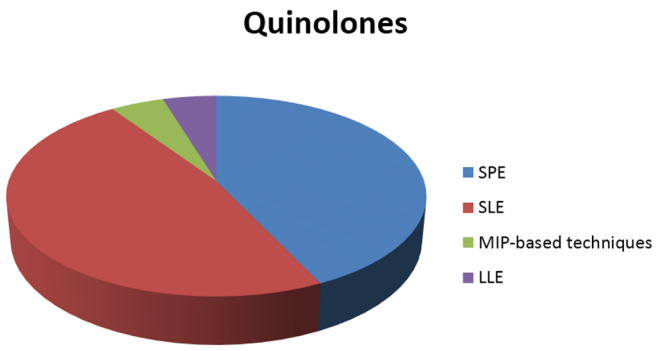


Figure 1. *Cont.*

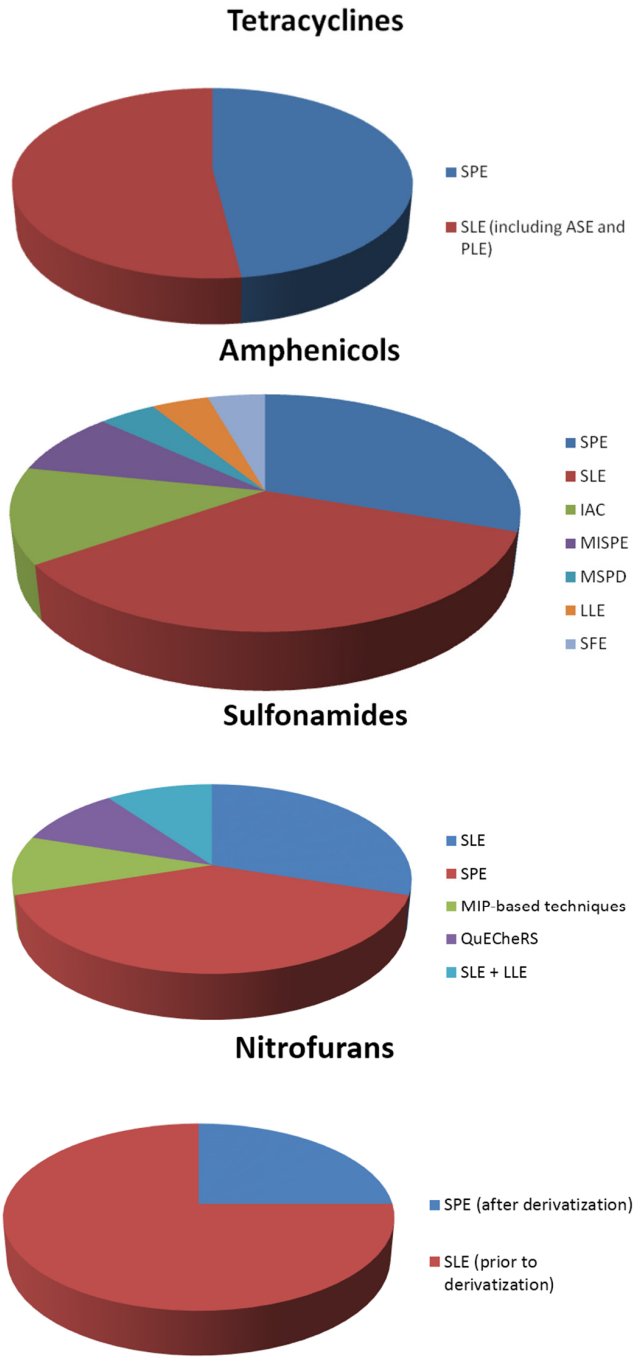


Figure 1. Sample preparation techniques used in the extraction of antibiotics from shrimps.

In this review, emphasis is put on extraction methods with regard to the isolation and purification steps. Results of published methods are summarized in the text and presented comparatively in tables.

2. Antibiotics

The most effective and useful antibacterial agents inhibit or prevent the development of the cell wall, the protein synthesis or the DNA replication and transcription. Less effective and clinically useful are those agents that act on the cell membrane or inhibit a metabolic path of the cell. Penicillins, cephalosporins and β-lactams inhibit the cell synthesis, chloramphenicol, tetracyclins and macrolides inhibit the protein synthesis, and quinolones, nitrofurans and sulfonamides inhibit the DNA synthesis [10].

Quinolones are synthetic antibiotics with a broad-spectrum antibacterial effect. This antibiotic group includes plain quinolones, such as oxolinic acid and nalidixic acid, and fluorinated quinolones, known as fluoroquinolones, such as ciprofloxacin, flumequine and sarafloxacin [5].

Quinolones have a dual heterocyclic aromatic ring structure as shown in Figure 2, with the first ring having a nitrogen atom at position 1, a carboxyl group at position 3 and a carbonyl group at position 4, and the second ring having a carbon atom at position 8. Fluoroquinolones result from the addition of a fluorine atom at position 6 of the second ring. Substitution at position 1 and 7 results in new enhanced fluoroquinolones [11–13].

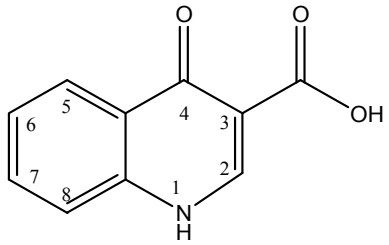
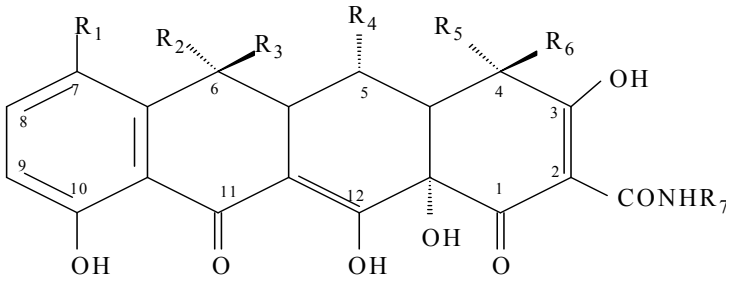


Figure 2. General chemical structure of quinolones.

The maximum residue limit in muscle tissue according to the Commission Regulation (EU) No. 37/2010 for danofloxacin, enrofloxacin-ciprofloxacin and oxolinic acid is 100 μg/kg [14].

Tetracyclines are broad-spectrum antibiotics, and their group includes tetracycline, oxytetracycline, chlortetracycline, demeclocycline, lymecycline, doxycycline, minocycline and tigecycline [15].

Tetracyclines were discovered in 1945 and were the first broad-spectrum antibiotics. The first generation of tetracyclines includes chlortetracycline and tetracycline, which were introduced for clinical use in 1948 and 1953, respectively [16,17]. Tetracycline antibiotics have a linearly arranged naphthalene ring structure (Figure 3), with a nitrogen-containing functional group region (2N region) and an oxygen-containing functional group region (C3-C4 region) [16].



Compound		R_1	R_2	R_3	R_4	R_5	R_6	R_7
TC	Tetracycline	H	CH_3	OH	H	$N(CH_3)_2$	H	H
OTC	Oxytetracycline	H	CH_3	OH	OH	$N(CH_3)_2$	H	H
CTC	Chlortetracycline	Cl	CH_3	OH	H	$N(CH_3)_2$	H	H

Figure 3. General chemical structure of tetracyclines.

The maximum residue limit in muscle tissue according to the Commission Regulation (EU) No. 37/2010 [14] for chlortetracycline, oxytetracycline and tetracycline is 100 μg/kg, while only oxytetracycline hydrochloride and oxytetracycline dihydrate are approved for use in aquaculture from the U.S. Food and Drug Administration (FDA) [18].

Amphenicols are a broad-spectrum antibiotic group that includes chloramphenicol and its metabolites, thiamphenicol and florfenicol. Florfenicol also has its own metabolite, florfenicol amine [5].

Chloramphenicol is the oldest and the most known member of this antibiotic group. It was originally isolated from cultures of Streptomyces venezuelae and was first used for clinical purposes in 1947. It is effective against many bacteria strains, but its toxicity and unwanted effects limited its use over the years [19,20].

The structure of chloramphenicol is shown in Figure 4.

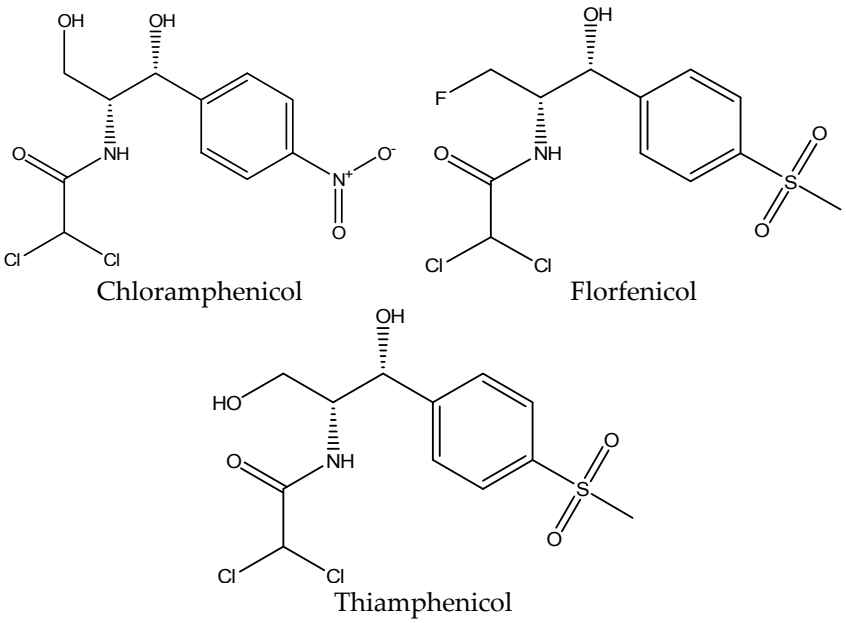


Figure 4. Chemical structure of chloramphenicol, florfenicol and thiamphenicol.

The maximum residue limit in muscle tissue according to the Commission Regulation (EU) No. 37/2010 [14] for florfenicol and florfenicol amine is 100 μg/kg; for thiamphenicol, it is 50 μg/kg, and chloramphenicol is completely prohibited. Florfenicol is only approved for use in aquaculture from the U.S. Food and Drug Administration (FDA) [18].

Macrolides are a category of semi-synthetic medium-spectrum with a macrolyclic lactone nucleus of 14–16 atoms to which different sugars are attached, forming the different types of the macrolide antibiotics. The category's most common antibiotic is erythromycin with a cladinose at C3 and desosamine at C5 (Figure 5).

Macrolides were discovered in natural products in 1950. Especially erythromycin was discovered in 1952, and it is still the most widely used macrolide drug in medicine, while at the end of the 1980s, two more semisynthetic derivatives of erythromycin were discovered.

The antibacterial activity of macrolides is due to their binding to the subunit 50S in the bacterial ribosome; as a result, it prevents the bacterial protein synthesis [21].

The MRL set by the Committee for veterinary medicinal products is 200 μg/kg in muscles, liver and kidneys of animal origin, 40 μg/kg in milk, and 150 μg/kg in eggs for the macrolide drugs [14].

Sulfonamides are derivatives of para-aminobenzenesulfonamide and their structure is similar to the structure of para-aminobenzoic acid (PABA), a molecule which takes part in the biosynthesis of dihydrofolic and folic acids by microorganisms (Figure 6). The basic structure of their molecule consists of an unsubstituted amine ($–NH_2$) on a benzene ring at C4 position and a sulfonamide group para to the amine (Figure 5). Sulfonamides are separated into four groups: (1) short—or medium acting sulfonamides; (2) long-acting sulfonamides; (3) topical sulfonamides and (4) sulfonamide derivatives for inflammatory bowel disease [22,23].

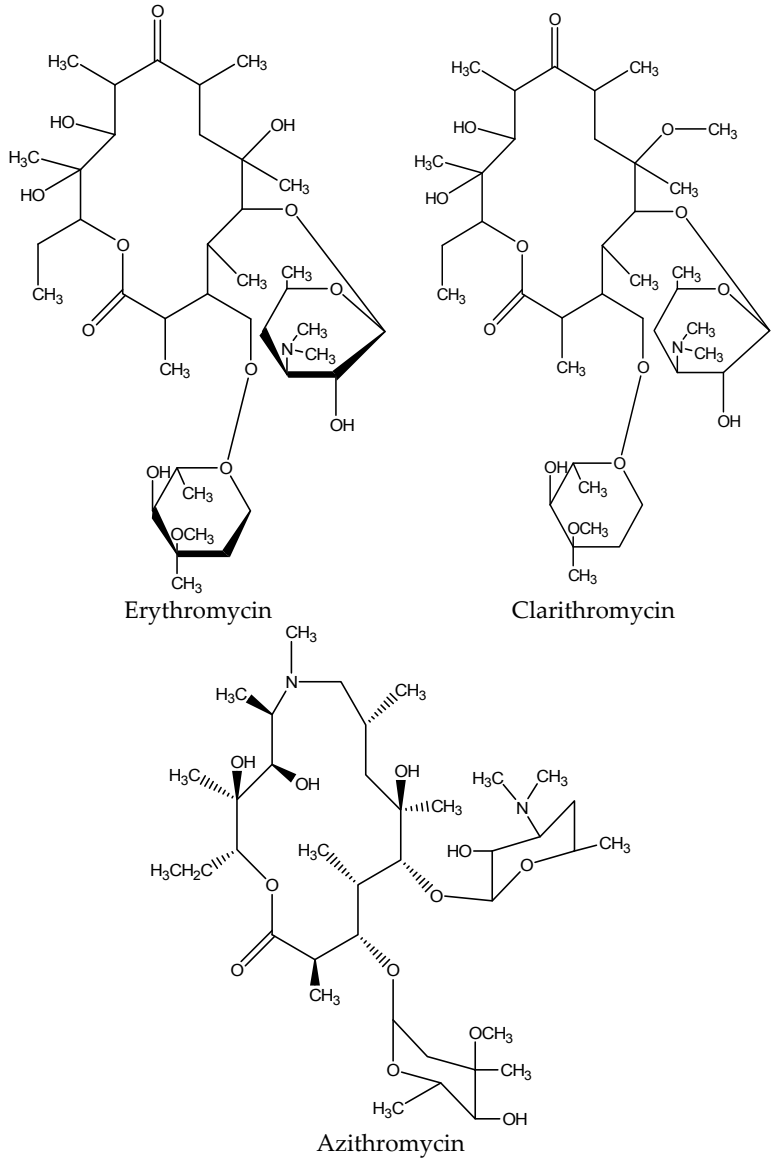


Figure 5. Chemical structure of common macrolides.

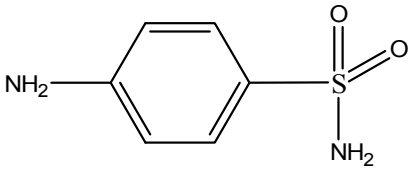


Figure 6. General chemical structure of sulfonamides.

The MRL set by the Committee for veterinary medicinal products is 100 μg/kg for the parent drug or the residues of sulfonamides in milk, fish and other seafood [14].

Most common nitrofurans are furazolidone, furaltadone, nitrofurazone and nitrofurantoin and their metabolites, 3-amino-2-oxazolidinone (AOZ), 3-amino-5-morpholinomethyl-2-oxazolidinone (AMOZ), semicarbazide (SEM) and 1-aminohydantoin (AHD), respectively. Due to the binding nitrofurans form, it is not easy to determine the parent nitrofuran, but it is possible to determine its metabolite in tissue samples. The chemical structure of nitrofurans is shown in Figure 7 [24].

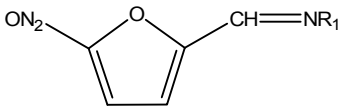


Figure 7. Chemical structure of Nitrofurans.

Nitrofurans are used as broad-spectrum antibiotics in veterinary practice, as a treatment to gastrointestinal infections [25] or against *Salmonella* sp., *Mycoplasma* sp. and some protozoa [26]. Since 1993, they have been banned in most of the countries in the world, but they are still used in some others. No MRL is set by the Committee for veterinary medicinal because nitrofurans and their metabolites are banned in EU [27].

3. Trends in the Extraction of Antibiotics from Shrimps

Shrimp tissue contains high amounts of protein. It also contains unsaturated fatty acids, such as the necessary eicosapentaenoic and docosahexaenoic acids, and minerals, such as calcium. The tissue composition depends on the feed given to the shrimps [28].

As mentioned above, a significant number of multi-residue or single analytical methods have been reported in the literature for the determination of antibiotics in shrimps.

To begin with, quinolones are mostly determined in shrimps after using SPE or SLE as the sample preparation technique. Furthermore, LLE and MIP-based techniques are equally applied in some of the studies. The same phenomenon appears in the determination of the class of tetracyclines, where SPE and SLE, including accelerated solvent extraction (ASE) and pressurized liquid extraction (PLE), are almost equally and most frequently used in the analysis of shrimps.

The class of amphenicols is determined by using a wide variety of sample preparation techniques. SLE is once again the primary preferable technique, followed by SPE. A different approach of the extraction is achieved with the use of immunoaffinity columns (IAC) for the determination of amphenicols in shrimps. Molecular imprinted—SPE (MISPE) are also used in a smaller number of studies. In addition to these, there were some cases where matrix solid phase dispersion (MSPD), LLE and supercritical fluid extraction (SFE) is performed in shrimp samples.

For the class of sulfonamides, SPE is the sample preparation of choice, followed by SLE. In addition, there are some studies in which a combination of SLE and LLE is used for the extraction of sulfonamide drugs from shrimp samples. Furthermore, MISPE and QuECheRS are applied for the determination of sulfonamides.

The determination of nitrofurans is achieved by determining the derivatives of the drugs. Derivatization takes place before or after the sample preparation. Derivatization is preformed after sample preparation using SLE, or prior to SPE.

In the following paragraphs, analytical methodologies for the extraction of antibiotics from shrimp tissue are presented and classified according to the category of antibiotics.

3.1. Extraction of Quinolones

Enrofloxacin and ciprofloxacin were extracted using 10 mL of acetonitrile. The extract was evaporated to dryness at 37 °C, and the residue was re-dissolved with an ammonium acetate buffer to a final volume of 2 mL. A SPE cleanup step was applied with a SDB-RPS cartridge (polyStyrene Divinylbenzene-Reverse Phase sorbent) preconditioned twice with 1 mL of ethanol, 1 mL of water and 1 mL of the ammonium acetate buffer, sequentially. Target compounds were eluted with 4 mL methanol and ammonium hydroxide solution 1 M (75:25, *v*/*v*). The eluates were evaporated to dryness at 37 °C, and the residue was re-dissolved in 300 μL of formic acid solution (pH = 2.5). The extraction procedure yielded recoveries between 94.0%–106.0%, 97.0%–103.0% for ENR and CIP, respectively. Analysis was carried out by an LC-MS/MS system, separation was achieved by a Polaris C18A 3 μm (150 × 2.0 mm) with a Chromsep guard column SS (10 × 2.0 mm), and the mobile phase consisted of

an acetonitrile and formic acid solution (pH = 2.5) delivered in gradient conditions. The LOD was 4 μg/kg and 3 μg/kg for ENR and CIP, respectively [29].

Ciprofloxacin, danofloxacin, enrofloxacin and sarafloxacin were extracted from shrimp samples using 16 mL of acidic acetonitrile and the addition of dichloromethane (to a final volume of 25 mL). A SPE cleanup step with a Strata C18 E was preconditioned with 2 mL of acetonitrile. The antibiotics were eluted from the SPE cartridges with 2 × 2 mL of acetonitrile. The eluates were evaporated to dryness under a nitrogen stream at 45 °C, and the residue was re-dissolved in 200 μL of acetonitrile and 800 μL of deionized water. The extraction procedure yielded recoveries between 63.0%–117.0%, 71.0%–87.0%, 72.0%–92.0%, 95.0%–125.0% for CIP, DAN, ENR and SAR, respectively. Analysis was carried out by a UPLC-MS system, separation was achieved by a HSS T3 C_{18} column (1.8 mm, 2.1 × 50 mm) (Waters, Milford, MA, USA), and the mobile consisted of 4 mM NH_4OH/50 mM formic acid buffer in either 10% MeCN or 90% MeCN (gradient elution). The LOD values were 0.13, 0.14, 0.19, 0.14 ng/g for for CIP, DAN, ENR and SAR, respectively. This method allows a single analyst to prepare 25 samples each day [30].

Ofloxacin, norfloxacin, ciprofloxacin and lomefloxacin were extracted from the spiked samples with 30 mL of a 1% acetic acid ethanol solution. A cleanup step using SPE was applied. SPE cartridge was washed with 10 mL of methanol, water, methanol in order, and the quinolones were eluted with 10 mL of 25% ammonia methanol. The eluate was evaporated to dryness under a nitrogen stream at 35 °C, and the residues were re-dissolved in mobile phase. The extraction procedure for a peeled prawn sample without shell yielded recoveries between 88.3%–99.8%, 95.9%–109.4%, 91.2%–107.0%, 88.9%–103.4% for OFL, NOR, CIP and LOME, respectively. Analysis was carried out by a HPLC system coupled with a chemiluminescence detector, and separation was achieved by a XDB-C_8, 150 mm × 4.6 mm i.d., 5 μm column. The LOD was 0.43, 0.36, 0.40 and 2.4 ng/mL for OFL, NOR, CIP and LOME, respectively. This study established a novel HPLC chemiluminescence detection method for quinolone determination, which was based on the Ce(IV)–$Ru(bpy)_3^{2+}$–HNO_3 system [31].

Enrofloxacin and ciprofloxacin were extracted from the spiked samples with 5 mL of methanol:acetic acid (98:2, *v*/*v*), the extracts were evaporated (to a final volume of 2 mL) under a nitrogen stream at 50 °C, and the residue was re-dissolved in 10 mL water:acetic acid (98:2, *v*/*v*). The SPE cleanup step involved a Sep-Pak C_{18} (500 mg, 6 mL) cartridge preconditioned and equilibrated with 6 mL of methanol and 6 mL of Milli-Q water sequentially. The quinolones were eluted with 6 mL of methanol:(1 M) phosphoric acid (9:1, *v*/*v*) and 4 mL of methanol, the eluate was evaporated to dryness under nitrogen stream at 50 °C, and the dry residue was re-dissolved in 1 mL of Tris buffer solution (pH 9.1). The extraction yielded 88.43%, 80.41% average recoveries for ENR and CIP, respectively. Analysis was carried out by a HPLC system coupled with a fluorescence detector, separation was achieved by a PLRP-S column (5 μm, 4.6 × 150 mm) with a RP18-E guard column (5 μm, 4 × 40 mm) (Polymer Laboratories Inc., Church Stretton, UK), and the mobile phase consisted of orthophosphoric acid, acetonitrile and tetrahydrofuran (gradient elution). The LOD was 0.015, 0.025 μg/g for ENR and CIP, respectively [32].

Nine fluoroquinolones and 3 acidic quinolones were extracted from the spiked samples with 20 mL of AcCN/MeOH (1:1 *v*/*v*), a SPE cleanup step with a Fe^{3+} immunoaffinity cartridge followed, and the quinolones were eluted with 0.5 mL of a McIlvaine-EDTA-NaCl buffer. The extraction procedure yielded inter-day recoveries between 73.7%–89.7% for the fluoroquinolones and 75.7%–87.6% for the acidic quinolones. Analysis was carried out by a HPLC system coupled with a spectrofluorometric detector, separation was achieved by an Atlantis dC_{18} IS column (4.6 × 20 mm, 3 mm), and the mobile phase consisted of (15:85:0.1 *v*/*v*) MeOH-water-formic acid for the fluoroquinolones and (35:65:0.1 *v*/*v*) MeOH-water-formic acid for the acidic quinolones (isocratic elution). The LOQ ranged between 1.5–50.0 mg/kg for the fluoroquinolones and 1.5–3.0 mg/kg for the acidic quinolones [33].

Flumequine, nalidixic acid and oxolonic acid were extracted from the spiked samples with 5 mL of acetonitrile. Two mL of 0.1 mol/L an ammonia solution and 2 mL *n*-hexane were added to the extracts in order to remove the colored and fatty components. The extracts were evaporated under a nitrogen

stream at 45 °C and 6 mL of hydrochloric acid 0.1 mol/L, and 6 mL of ethyl acetate were added. The ethyl acetate extract was evaporated to dryness at 40 °C, and the residue was re-dissolved in 300 μL of methanol. The extraction procedure yielded recoveries between 73.3%–84.5%, 80.4%–90.4%, 79.2%–88.3% for OXO, NAL and FLU, respectively. Analysis was carried out by a HPLC system coupled with a fluorescence detector, separation was achieved by a C_{18}-Nucleosil HD column (4 mm × 250 mm, 5 μm), and the mobile phase consisted of 0.01 mol/L oxalic acid (pH 2.3) and acetonitrile (65/35, *v*/*v*) (isocratic elution). The CC_β was 610.9 μg/kg, 13 μg/kg, and 117.3 μg/kg for FLU, NAL and OXO, respectively. This method gave good results concerning the complexity of the matrix and allows evaluation of the shrimp samples being compliant to the current European legislation [34].

Oxolinic acid, flumequine and nalidix acid were extracted from the spiked samples with 12 mL of ethyl acetate (re-extracted with another 12 mL) and the addition of 2 g anhydrous sodium sulfate, the extract was evaporated to dryness, and the residue was re-dissolved in 2 mL of a 0.2% formic acid aqueous solution. The extraction procedure yielded 92.6%, 79.3%, 79.8% average recoveries for OXO, FLU and NAL, respectively. Analysis was carried out by an LC system coupled with a fluorescence detector, separation was achieved by an Agilent Zorbax Eclipse XDB C_8 column (4.6 mm × 150 mm, 5 μm), and the mobile phase consisted of 60% oxalic acid (0.01 M), 30% acetonitrile and 10% methanol (*v*/*v*/*v*) (isocratic elution). MDL was 3, 2.7 and 2.3 ng/g for OXO, NAL and FLU, respectively. The simple extraction scheme provided LC-MS compound confirmation with increased sample throughout, over previews GC-MS methods and selectivity for the above antibiotics [35].

Flumequine, oxolinic acid and nalidix acid were extracted from the spiked samples with 5 mL of 1% acetic acid, 10 mL of acetonitrile and the addition of 2 g sodium chloride. The extract were evaporated to dryness under nitrogen stream at 55 °C and re-dissolved in 2.5 mL of reconstitution solution containing 40 ng/mL of piromidic and 100 mg/mL of EDTA in acetonitrile/water (1:1, *v*/*v*). The extraction procedure yielded recoveries between 79.0%–88.0%, 91.0%–95.0%, 100.0%–101.0% for FLU, OXO and NAL, respectively. The analysis was carried out by a LDTD source coupled to a triple quadrupole mass spectrometer. The MDL was 1.7, 2.6, 4.4 ng/g for FLU, OXO and NAL, respectively. This method was found to meet many of the drug residue analysis requirements in shrimp tissue samples, using a single solvent extraction step, resulting in decreased sample analysis and increased sample throughput [36].

OXO and FLU were extracted by mixing the spiked samples with 400 μL of supramolecular solvent. The extraction procedure yielded recoveries between 100%–102%, 100%–101.4% for FLU and OXO, respectively. Analysis was carried out by an LC system coupled with a fluorescence detector, separation was achieved by a Kromasil C_{18} column (5 μm, 150 mm × 4.6 mm), and the mobile phase consisted of 55% oxalic acid (0.01 M) and 45% acetonitrile/methanol (75:25, *v*/*v*) delivered isocratically. The CC_β was 109 g/kg, and 622 g/kg for OXO and FLU, respectively. This method proved to be reliable, fast and low-cost. It demonstrates high extraction efficiency regardless of the matrix composition, and a simple one-step analyte extraction with neither cleanup nor evaporation was needed [37].

Shrimp samples were mixed with trichloroacetic acid aqueous solution (15%, *w*/*v*), and the resulting extracts were spiked with ciprofloxacin. Yeast@MIPs or yeast@NIPs were dispersed in the extracts, collected, and washed with a 10-mL methanol-acetic acid solution (59:1 *v*/*v*). The resulting extracts were dried under nitrogen stream at 298 K, and the residues were re-dissolved in 0.4 mL methanol. The extraction procedure yielded a 86.4% recovery. Analysis was carried out by HPLC system coupled with ultraviolet detector, separation was achieved by a C_{18} (150 × 4.6 mm^2) column, and the mobile phase consisted of methanol-water (24:76, *v*/*v*) (isocratic elution). The surface imprinted yeast@MIPs developed for this paper exhibited high adsorption capacity, high selectivity, rapid binding ability for CIP, and could be used at least five times without losing their adsorption capacity. Moreover, they were successfully used in real sample analysis for CIP in shrimps yielding good recoveries [38].

An overview of the extraction methodologies for the determination of quinolones in shrimps is presented in Table 1.

3.2. Extraction of Tetracyclines

Tetracycline, oxytetracycline and chlorotetracycline were extracted from the spiked samples with 10 mL of succinic acid and an addition of 1–1.5 g sodium chloride and tissue disruptor. A SPE cleanup step with OASIS hydrophobic-lipophilic-balanced (HLB) SPE columns (6 mL, 200 mg, Waters Corp, Milford, MA, USA) were conditioned with 4 mL of methanol, water and succinic acid sequentially. The tetracyclines were eluted with 2 mL of methanol, the eluates were evaporated to dryness under nitrogen stream at 60 °C, and the residues were re-dissolved in 2 mL of 0.1% formic acid. The extraction procedure yielded 82.9%, 93.2%, 76.8% average recoveries for TC, OTC, and CTC, respectively. Analysis was carried out by an LC-MS/MS system, separation was achieved by a MacMod HydroBond PS C_8, 100 mm × 2.1 mm, column, and the mobile phase consisted of 75%, 0.1% formic acid, 18% acetonitrile and 7% methanol (isocratic elution). The average LOQ was 50 ng/g for all analytes. The developed method is ideal for routine analysis, avoids the use of complex buffers and provides a simple and fast extraction procedure [39].

Oxytetracycline, tetracycline, chlorotetracycline and doxycycline were extracted from shrimp samples with 12.5 mL of Na_2EDTA-McIlvaine buffer at pH 4. A SPE cleanup step with the C-18E cartridge (500 mg, 6 mL) (Phenomenex, Torrance, CA, USA) was activated with 10 mL of methanol and 10 mL of Milli-Q water sequentially. The tetracyclines were eluted with 10 mL of methanol, the solvent was removed under room temperature, and the residues were passed through 0.45 µm PTFE filter. The extraction procedure yielded recoveries between 83.3%–96.5%, 88.4%–96.9%, 86.0%–93.3%, 90.6%–102.0% for OTC, TC, CTC and DC, respectively. Analysis was carried out by an LC system coupled with an electrochemical detector with a nickel-implanted boron-doped diamond thin film electrode (Ni-DIA), separation was achieved by a ODS-3 Inertsil C_{18} (5 µM 4.6 mm × 250 mm) column, and the mobile phase consisted of 0.01 M phosphate buffer (pH 2.5)-acetonitrile (80:20, *v*/*v*) delivered isocratically. The LOD ranged between 0.1–0.5 g/mL for all analytes. This paper demonstrates the first use of Ni-DIA electrodes for the electroanalysis of tetracyclines, with excellent performance for the oxidative detection of tetracyclines, exhibiting well-defined voltammograms, high sensitivity and significant advantages over the BDD and glassy carbon electrode [40].

Oxytetracycline, tetracycline, chlorotetracycline and doxycycline were extracted from the shrimp samples with HPLC grade methanol. The extract was evaporated to dryness, and the residue was re-dissolved in mobile phase. The extraction procedure yielded recoveries between 91.0%–98.0%, 81.0%–99.0%, 84.0%–101.0%, 80.0%–85.0% for TC, OTC, CTC and DC, respectively. Analysis was carried out by an LC-MS/MS system, separation was achieved by a reverse phase Zorbax Eclipse Plus C_{18} (5 µm particle size, 4.6 × 100 mm) column, and the mobile phase consisted of 0.1% formic acid in water and 0.1% formic acid in methanol under gradient elution. The LOD was 11, 12, 20, 23 ng/g for TC, OTC, CTC and DC, respectively [41].

Seven tetracyclines were extracted from the spiked samples with a Dionex accelerated solvent extractor 200 (Dionex, Sunnyvale, CA, USA), which provides the use of solvents at temperatures up to 80 °C and pressures up to 85 bar, and methanol and 1 mmol/L trichloroacetic acid at pH 4.0 as solvents. The spiked samples were mixed with 5 g of Na_2EDTA-washed sand and packed in an extraction cell at pH 4.0. The extraction procedure yielded 75.6%–103.5% average recovery for all analytes. Analysis was carried out by a HPLC system coupled with a dual λ absorbance detector, separation was achieved by a ZORBAX SB-C_{18} (150 mm × 4.6 mm I.D., 5 µm) (Agilent Technology, Santa Clara, CA, USA) column, and the mobile phase consisted of methanol, acetonitrile and 0.01 M oxalic acid (gradient elution). The CC_β ranged between 7.8–108.1 µg/kg. This method provided fast sample extraction with pressurized liquid extraction, compared to conventional liquid-liquid extractions, with reduced solvent use [42].

An overview of the extraction methodologies for the determination of tetracyclines in shrimps is presented in Table 2.

Table 1. Overview of extraction methodologies for the determination of quinolones in shrimps.

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[29]	ENR and CIP	fish and prawn	Homogenized prawn tissue (1 g), spiked (100 µL IS, 3 µg/mL), extraction (10 mL ACN, vortex (1 min), shaker (15 min), centrifuged (10 min, 3700 *g*). Supernatant evaporated (dryness, 37 °C), add ammonium acetate buffer, vortex (15 s), sonicated (15 min). Purification (SPE cartridges, SDB-RPS), conditioned (successively 2 × 1 mL MeOH, 2 × 1 mL water and 2 × 1 mL ammonium acetate buffer), sample loaded, cartridge dried (centrifugation, 5 min, 3700 *g*), eluted (4 mL elution solution). Evaporation to dryness, 37 °C, reconstituted (300 µL formic acid), vortex (15 s), filtration (0.2 µm).	LC-MS/MS	LOD (µg/kg): ENR: 4, CIP: 3 LOQ (µg/kg): ENR: 14, CIP: 10 CC_α (µg/kg): ENR and CIP: 111	ENR: 94.0–106.0, CIP: 97.0–103.0
[30]	CIP, DAN, ENR and SAR	salmon, shrimp and tilapia	Tissue (4 g), mixed with acidic ACN (16 mL), CH_2Cl_2 added (to 25 mL), rotated (10 min), centrifuged (10 min, 2000 rpm), supernatant (10 mL) removed, evaporated (45 °C, N_2, to 2 mL). SPE column preconditioned (2 mL ACN), samples rinsed (2 × 2 mL ACN), passed through column, add 1 mL ACN. Eluent collected, evaporated (dryness, 45 °C, N_2), residue reconstituted (vortexing, 200 µL ACN, deionized water 800 µL), hexane (1 mL) added, vortexed, centrifuged (1000 rpm, 5 min), aqueous layer filtered (0.2 µm syringe filter).	UPLC-MS/MS	LOD (ng/g): CIP: 0.13, DAN: 0.14, ENR: 0.19, SAR: 0.14 LOQ (ng/g): CIP: 0.4, DAN: 0.43, ENR: 0.56, SAR: 0.41	CIP: 63.0–117.0, DAN: 71.0–87.0, ENR: 72.0–92.0, SAR: 95.0–125.0
[31]	OFL, NOR, CIP and LOME	prawn	Sample (5 g) dissolved (30 mL, 1% acetic acid ethanol solution), homogenized, centrifuged (4500 rpm, 5 min). Sample poured into SPE cartridge, adsorbed quinolones washed (10 mL MeOH, water, MeOH in order, 2.0 mL/min), quinolones absorbed eluted (10 mL, 25% ammonia MeOH, 1.5 mL/min). Eluent evaporated (N_2, 35 °C), dissolved (mobile phase), filtered (0.45 µm filter).	HPLC-CL	LOD (ng/mL): OFL: 0.43, NOR: 0.36, CIP: 0.40, LOME: 2.4 LOQ (ng/mL): -	OFL: 90.3–101.4, NOR: 89.5–107.8, NOR: 88.0–107.2, LOME: 94.4–106.0 (prawn sample with shell) OFL: 88.3–99.8, NOR: 95.9–109.4, NOR: 91.2–107.0, LOME: 88.9–103.4 (peeled prawn sample without shell)
[32]	ENR and CIP	prawns	Prawn muscle (1 g) extracted (5 mL MeOH: CH_3COOH, 98:2 *v*/*v*), vortexed (2 min), sonication (10 min), centrifuged (1968 *g*, 10 min), pellet tissue extracted, evaporated (to 2 mL, 50 °C, N_2), filtration, water: CH_3COOH (10 mL, 98:2 *v*/*v*) added. Sample applied to SPE cartridge (C_{18}, 500 mg, 6 mL), washed (6 mL water: phosphoric acid 1 M, 3:2 *v*/*v*), cartridges preconditioned and equilibrated (6 mL MeOH and 6 mL Milli-Q water), eluted (6 mL MeOH: phosphoric acid 1 M, 9:1 *v*/*v* and 4 mL MeOH). Eluate evaporated (dryness, N_2, 50 °C), residue re-dissolved (1 mL Tris buffer, pH 9.1), filtered (syringe filter 0.45 µm, nylon).	HPLC-FLD	LOD (µg/g): ENR: 0.015, CIP: 0.025 LOQ (µg/g): -	ENR: 88.43 (ave.), CIP: 80.41 (ave.)

Table 1. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[33]	9 FQ: MARB, OFL, NOR, CIP, ENR, DAN, ORB, DIF and SAR and 3 AQ OXO, NAL and FLU	muscle (cattle, swine and chicken), liver (chicken), raw fish (shrimp and salmon), egg (chicken), and processed food (ham, sausage and fish sausage)	Sample (2 g), ACN/MeOH (20 mL, 1:1) added, homogenized (20 s), centrifuged (2500 g, 5 min), supernatant diluted (×2 with MeOH). Diluted extract (1 mL) added to the Fe^{3+} IMAC cartridge, allowed to pass, cartridge washed (1 mL MeOH and water), eluted (0.5 mL McIlvaine-EDTA-NaCl buffer).	LC-FLD	LOQ (mg/kg): DAN: 0.8, SAR: 6.5, ORB, DIF, OXO, FLU: 1.5, NOR, OFL, CIP, ENR: 2.5, NAL: 3, MARB: 50	MARB: 88.2–89.5, OFL: 76.6–87.5, NOR: 85.4–86.4, CIP: 86.1–91.8, ENR: 88.2–90.0, DAN: 98.7–103.5, ORB: 87.3–88.7, DIF: 86.8–92.3, SAR: 81.1–81.8, OXO: 81.6–84.2, NAL: 87.7–94.9, FLU: 83.1–85.3
[34]	FLU, NAL and OXO	shrimps	Samples spiked (100 µL IS), extraction (5 mL ACN), homogenized, centrifuged (10 min, 4000× *g*, 20 °C), supernatants transferred, re-extraction. ACN extracts combined, ammonia solution (2 mL, 0.1 mol/L) and n-hexane (2 mL) added, vortexed, centrifuged, *n*-hexane supernatant removed, procedure subsequently repeated (without ammonia). ACN extract evaporated (water-bath, 45 °C, vacuum), HCl (6 mL 0.1 mol/L) and ethyl acetate (6 mL) added, vortexed, centrifuged, extraction twice replicated. Acetate supernatants combined, water-bath, 45 °C, vacuum, evaporation to dryness, 40 °C, N_2), dissolved (300 µL MeOH, ultrasonic bath).	HPLC-FLD	LOD (µg/kg): FLU: -, NAL: 6.9, OXO: - CC_α (µg/kg) FLU: 559.7, NAL: 10.3, OXO: 110.1 CC_β (µg/kg) FLU: 610.9, NAL: 13, OXO: 117.3	OXO: 73.3–84.5, NAL: 80.4–90.4, FLU: 79.2–88.3
[35]	OXO, FLU and NAL	shrimp	Sample (2.0 g), fortification, vortexed (10 s), equilibrated (15 min), ethyl acetate (12 mL) and anhydrous sodium sulfate (2 g) added, shaken (1 min), centrifuged (1500 rpm, 10 min, 4 °C), supernatant transferred, evaporated (50–55 °C, N_2), sample re-extracted (additional 12 mL ethyl acetate, as above). Supernatant added to original, evaporated (dryness or until oily residue), residue re-dissolved (2 mL, 0.2% formic acid), vortex (30 s), hexane (2 mL) added, mixed, centrifuged (5 min, 2600 rpm, 4 °C), hexane layer discarded (aspiration), aqueous liquid filtered (0.45 µm glass microfiber syringe filter).	LC-FLD, LC-MS/MS	LC-FL: MDL (ng/g): OXO: 3, FLU: 2.7, NAL: 2.3 LOQ (ng/g): OXO: 9, FLU: 8.1, NAL: 6.9	OXO: 88.0–97.7 (ave. 92.6), FLU: 77.1–80.7 (ave. 79.3), NAL: 78.6–81.7 (ave. 79.8)
[36]	FLU, OXO and NAL	catfish, shrimp, and salmon	Sample (2.5 g) fortified, equilibrated (15 min), vortex-mixed (30 s, 5 mL 1% acetic acid), ACN (10 mL) and NaCl (2 g) added, shaken (5 min, 2500 rpm), centrifuged (10,000 rpm, 5 min, 4 °C), organic layer, transferred, evaporated (55 °C, dryness, N_2,5 psi first 5 min, then 30–35 min at 12–15 psi). Reconstitution solution (2.5 mL) added to dried extracts, sonicated (1 min), vortex-mixed (30 s), centrifuged (10 min, 17,250 *g*, 4 °C), supernatants passed through filters (0.2 µm nylon syringe). Aliquots of each sample (3 mL) spotted into individual wells (96-well LazWell microtiter plate), evaporate (dryness, room temperature).	LDTD-MS/MS	MDL (ng/g): FLU: 1.7, OXO: 2.6, NAL: 4.4 LOQ (ng/g): FLU: 7.9, OXO: 17.3, NAL: 7.0	FLU: 79.0–88.0 (ave.), OXO: 91.0–95.0 (ave.), NAL: 100.0–101.0 (ave.)

Table 1. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[37]	FLU and OXO	fish and shellfish (salmon, sea trout, sea bass, gilt-head bream, megrim and prawns)	Sample (200 mg) and supramolecular solvent (400 µL) mixed, micro PTFE-coated bar introduced, vortex-shaken (2500 rpm, 15 min), thermostated (15 °C), centrifuged (15,000 rpm, 15 min).	LC-FLD	CC_α (g/kg): OXO: 104, FLU: 611 CC_β (g/kg): OXO: 109, FLU: 622 (salmon)	FLU: 100.0–102.0, OXO: 100.0–101.4
[38]	CIP	shrimp	Sample (5 g) homogenated, dispersed in trichloroacetic acid aqueous solution (15%, *w*/*v*), stirred (2 h, 398 K), centrifugation and filtration, extraction solution collected and spiked. yeast@MIPs or yeast@NIPs (5 mg) dispersed in spiked samples (10 mL), incubated (6 h, 298 K). yeast@MIPs or yeast@NIPs collected (centrifugal filtration), washed (10 mL MeOH-acetic acid solution, 59:1 *v*/*v*), extracts dried (N_2, 298 K), residues redissolved (0.4 mL MeOH).	HPLC	-	86.4
[43]	MQCA and QCA	porcine, chicken (muscles and livers), fish and shrimp (muscles)	Samples deproteinated (5% metaphosphoric acid in 10% MeOH), LLE, cleanup (solid phase extraction, mixed mode anion-exchange columns).	LC-MS/MS	LOQ (µg/kg): MQCA and QCA: 0.1	MQCA and QCA: 62.4–118.0
[44]	DES-CIP, NOR, CIP, DAN, ENR, ORB, SAR, and DIF	shrimp	Shrimp tissue extracted (ammoniacal ACN), extract defatted, evaporated, dissolution (basic phosphate buffer).	LC-FLD-MS	LOD (ng/g): - LOQ (ng/g): 0.1–1	75.0–92.0
[45]	8 FQ: (NOR, OFL, DAN, CIP, DES-CIP, ENR, SAR and DIF) and 4 AQ (OXO, FLU, NAL	salmon, trout, and shrimp	Drugs extracted with mixture of ethanol and 1% acetic acid, diluted (aqueous HCl), defatted (hexane), cation-exchange solid phase extraction.	LC-MS/MS	LOD (ng/g): QNs: 0.1, FQNs: 0.4	57.0–96.0
[46]	CIP, DAN, DIF, ENR, FLU, MARB, NAL, NOR, OFL, ORB, OXO and SAR	muscle, liver, chicken eggs, milk, prawn and rainbow trout	Sample extracted (ACN-water, 95:5), 1/5 of filtered extract diluted (water, keep ACN ratio at *ca.* 60%), passed through C_{18} mini-column, eluate evaporated (dryness), residues dissolved (MeOH-water, 30:70, *v*/*v*)	HPLC-FLD	LOD (µg/g): - LOQ (µg/g): 0.005	CIP: 75.7, DAN: 96.5, DIF: 77.9, ENR: 97.3, FLU: 75.7, MARB: 80.7, NAL: 71.0, NOR: 74.4, OFL: 96.1, ORB: 74.3, OXO: 70.2, SAR: 72.3
[47]	6 FQ	fish, shrimp and crab	Sample extraction (acid ACN), defatted (*n*-hexane, water removed (Na_2SO_4).	UPLC-MS/MS	LOD (µg/kg): 0.1 (all) LOQ (µg/kg): 0.2 (all)	76.9–95.9

Table 1. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[48]	12 FQ (MARB, NOR, ENR, CIP, DES-CIP, LOME, DAN, SAR, DIF, OFL, ORB and ENO) and 6 AQ (OXO, NAL, FLU, CIN, piromidic acid and pipemidic acid)	milk, chicken, pork, fish and shrimp	Extraction with ACN-1% HCOOH, diluted (10% ACN), defatted (hexane).	LC-MS/MS	CC_α (ng/g): 0.18–0.68 CC_β (ng/g): 0.24–0.96 (all)	-
[49]	MARB, NOR, CIP, LOME, DAN, ENR, SAR, DIF, OXO, NAL and FLU	chicken, pork, fish and shrimp	Extraction with 0.3% metaphosphoric acid and ACN (1:1, *v*/*v*), cleanup (HLB cartridge).	HPLC-FLD	LOD (ng/g): - LOQ (ng/g): 5.0–28.0	71.7–105.3
[50]	MARB, CIP, NOR, LOME, DAN, ENR, SAR, DIF, OXO and FLU	swine, chicken, and shrimp tissues	Samples (⩽2.0 g) and small volume of organic reagent (⩽4.6 mL) of a nonchlorinated solvent.	HPLC-FLD	LOQ (ng/g): - LOQ (ng/g): 0.3–1 (all)	72.8–106.8

Table 2. Overview of extraction methodologies for the determination of tetracyclines in shrimps.

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[39]	TC, OTC, and CTC	shrimp and whole milk	Shrimp extracted (1–1.5 g sodium chloride, 10 mL succinic acid, tissue disruptor, blending 20–30 s), tissue disruptor rinsed (2 × 3 mL succinic acid), centrifuged (5 min, 4000 rpm, 4 °C), supernatant decanted (25 mL depth filter, into centrifuge tube with 1–1.5 g alumina and 5 mL, 0.01 M oxalic acid), re-extracted (10 mL succinic acid), blending (tissue disruptor), centrifuged (5 min, 4000 rpm, 4 °C), supernatant decanted (depth filter), filter washed (4 mL water), extracts shaken (10 s), centrifuged (5 min, 4000 rpm, 4 °C).(HLB) SPE columns (6 mL, 200 mg) conditioned (sequentially 4 mL MeOH, 4 mL water and 4 mL succinic acid, 4 mL succinic acid above column bed), extracts applied (flow rate 45 drops/min), column washed (4 mL water), dried (5 min, full vacuum), eluted (2.0 mL MeOH), extracts evaporated (dryness, 60 °C, N_2, 15 min), ACN (1 mL) added , residue dissolved (2.0 mL, 0.1% HCOOH), vortexed.	LC-UV, LC-MS/MS	LOD (ng/g): - LOQ (ng/g): 50 (all, ave.)	OTC: 82.9 (ave.), TC: 93.2 (ave), CTC: 76.8 (ave)
[40]	OTC, TC, CTC and DC	shrimp	Sample (2.50 g), Na_2EDTA-McIlvaine buffer (12.5 mL, pH 4) added, blended (30 s), shaken (10 min), centrifuged (30 min, 3500 rps). Supernatant loaded into SPE cartridge, activated (10 mL MeOH and 10 mL Milli-Q water), washed (10 mL Milli-Q water), eluted (10 mL MeOH), solvent removed at room temp., residues filtered (0.45 µm PTFE filter).	Ni-DIA electrode, HPLC/Ni-implanted electrode, HPLC/Ni-DIA electrode	Ni-DIA electrode: LOD (g/mL):OTC: 0.1, TC: 0.1, CTC: 0.5, DC: 0.5, LOQ (g/mL): -	Ni-implanted electrode: OTC: 84.8–102.5, TC:85.9–97.0, CTC: 91.48–97.9, DC: 88.4–103.7 Ni-DIA electrode OTC: 83.3–96.5, TC: 88.4–96.9, CTC: 86.0–93.3, DC: 90.6–102.0
[41]	TC, OTC, CTC and DC	prawns	Sample, homogenized, HPLC grade MeOH added, centrifuged (15 min, 3000 rpm), supernatant evaporated (dryness), dissolved (mobile phase, 0.1% formic acid in MeOH), filtered (0.22 µm membrane filter).	LC-MS/MS	LOD (ng/g): TC: 11, OTC: 12, CTC: 20, DC: 13 LOQ (ng/g): TC: 19, OTC: 20, CTC: 20, DC: 20	TC: 91.0–98.0, OTC: 81.0–99.0, CTC: 84.0–101.0, DC: 80.0–85.0
[42]	OTC, TC, CTC, MNC, MTC, DMC and DC	egg, fish and shrimp	Extraction with Dionex accelerated solvent extractor 200 using MeOH and 1 mmol/L TCA at 80 °C/85 bar/pH 4.0. Sample (5 g) mixed (5 g Na_2EDTA-washed sand), packed in extraction cell (circular glass microfiber filters, 1.98 cm, above and below the packing). Resulting extracts diluted, evaporated (dryness, 40 °C, N_2), residue dissolved (1 mL mobile phase), vortexed, filtered (0.22 µm nylon Millipore chromatographic filter).	HPLC	CC_α (µg/kg): MNC: 5.5, OTC: 101.8, TC: 102.2, DMC: 6.5, CTC: 106.8, MTC: 8.8, DC: 13.0 CC_β (µg/kg): MNC:7.8, OTC:104.2, TC: 104.4, DMC:8.6, CTC:108.1, MTC: 10.5, DC: 15.3	OTC: 80.5–101.8, TC: 81.5–85.4, CTC: 78.7–85.7, DC: 83.4–89.1, DMC: 82.1–85.3, MNC: 80.4–99.7, MTC: 81.4–86.2

3.3. Extraction of Amphenicols

Chloramphenicol was extracted from shrimps using 4 mL of a phosphate extraction solution. An aliquot of 4.5 mL of ethyl acetate was added in the supernatants, the organic layer was evaporated to dryness under mild nitrogen stream at 45 °C, and the residue was re-dissolved in 300 μL of methanol/water (50:50 *v*/*v*). The extraction procedure yielded recoveries between 98.3%–100.0%. Analysis was carried out by an LC-MS/MS system, separation was achieved by a C_{18} reverse-phase analytical column (100 mm × 2.1 mm, 4 μm) connected to a C_{18} pre-column (1 cm × 4 mm, 4 μm), and the mobile phase consisted of water and methanol (gradient elution). The LOD was 0.03 ng/g. The extraction procedure used in this study proved to be simple and fast, with no cleanup step needed and there was no matrix interference [51].

Chloramphenicol was extracted from shrimps with 7 mL of ethyl acetate and the addition of 1 g sodium sulfate anhydrous. The extracts were evaporated to dryness under nitrogen stream at 40 °C, and the residues were re-dissolved in 1 mL of acetonitrile. Analysis was carried out by an LC-MS/MS system, separation was achieved by a X-Terra (2.1 × 150 mm, 3.5 μm) column, and the mobile phase consisted of methanol and water containing 0.1% NH_4OH delivered using a gradient elution program. The CC_β was 0.04 μg/kg [52].

Chloramphenicol was extracted from the spiked samples with 5 mL of ethyl acetate, and after some evaporate/re-dissolve steps the final ethyl acetate extract was evaporated to dryness under nitrogen stream at 45 °C. The residue was re-dissolved in 0.5 mL of hexane:CCl_4 (1:1 *v*/*v*) and mixed with 0.7 mL of HPLC-grade acetonitrile-water (1:1 *v*/*v*), and the upper clear phase was used for the analysis. The extraction procedure yielded recoveries between 95.88%–96.96%. Analysis was carried out by an LC-ESI-MS/MS system, separation was achieved by a C_{18} reverse phase Unisil HPLC column (150 × 4 mm i.d., 5 μm) (Gasukuro Kogyo, Inc., Tokyo, Japan), and the mobile phase consisted of water 90% plus acetonitrile 10% and water 10% plus acetonitrile 90% (isocratic elution). The CC_β was 0.098 mg/kg [53].

Chloramphenicol was extracted from the spiked samples with 5 mL of acetonitrile. An aliquot of 5 mL of chloroform was added to the extracts; after vortexing and centrifugation, the chloroform layer was discarded. The acetonitrile extracts were evaporated to dryness under nitrogen stream, and the residues were re-dissolved in 1 mL of mobile phase. The extraction procedure yielded recoveries between 85.5%–115.6%. Analysis was carried out by an LC-MS/MS system, separation was achieved by a Luna 5 μm C_{18} (150 × 4.6 mm) column, and the mobile phase consisted of water and acetonitrile delivered under gradient conditions. The LOD was 0.02 mg/kg. This method performed a simple and rapid liquid–liquid extraction without using any other cleanup step such as SPE [54].

Chloramphenicol was extracted from the spiked samples with 20 mL of acetonitrile/4% NaCl in water solution (1:1, *v*/*v*), the extract was de-fatted with 2 × 10 mL of *n*-hexane, and 7 mL of water-saturated ethyl acetate was added to the remainder. The ethyl acetate extracts were evaporated to dryness and re-dissolved in 3 mL of water/acetonitrile (95:5, *v*/*v*). A SPE cleanup step with a C_{18} (500 mg/3 mL) cartridge preconditioned with 10 mL of methanol and 10 mL of water/acetonitrile (95:5, *v*/*v*) followed, and the CAP was eluted with 3 mL of water/acetonitrile (45:55, *v*/*v*). 4 mL of water-saturated ethyl acetate was added to the eluate, the extracts were evaporated to dryness under nitrogen stream, and the residue was re-dissolved in 1 mL of acetone/toluene (20:80, *v*/*v*). A second SPE step with a Silica cartridge preconditioned with 6 mL of acetone/toluene (20:80, *v*/*v*) followed. CAP was eluted with 6 mL of acetone/toluene (70:30, *v*/*v*). The eluent was evaporated to dryness, and 50 μL of derivatization mixture *N*,*O*-bis(trimethylsilyl)acetamide (BSA)/*n*-heptane (1:1, *v*/*v*) was added to the residue. The extraction procedure yielded 95.0% average recovery. Analysis was carried out by a GC-MS system, and separation was achieved by a 30 m × 0.2, 5 μm I.D. column, 0.25 mm ZB5 column. The CC_β was 0.087 mg/kg [55].

Chloramphenicol and Chloramphenicol glucuronide were extracted from the spiked samples with 7 mL of acetonitrile and a SPE cleanup step with a Chem-Elut cartridge followed. Analytes were eluted twice with 15 mL and 15 mL of dichloromethane, the eluate was evaporated to dryness

under a nitrogen stream at 45–50 °C, and the residue was re-suspended with 5 mL of hexane:ethyl acetate (50:50 *v*:*v*). A second SPE cleanup step followed with a Bond Elut-NH_2 cartridge. Analytes were eluted with 3 mL of ethyl acetate:methanol (50:50 *v*:*v*), the eluate was evaporated to dryness under nitrogen stream at 45–50 °C, and the residue was re-dissolved in 300 µL of HPLC grade water. Analysis was carried out by an LC-MS/MS system, separation was achieved by a Nucleodur 5 µm C-18 (EC), 125 × 2.0 mm column, and the mobile phase consisted of 55% 10 mM ammonium acetate and 45% methanol delivered isocratically. The CC_β was 0.17 µg/kg [56].

Chloramphenicol was extracted from spiked samples with 40 mL of a 0.05-mol/L phosphate buffer (pH 7.0), and 3 mL of 15% trichloroacetic acid in water were added to the extracts in order to precipitate the proteins. The extract was loaded into MISPE cartridges, the eluates were evaporated to dryness under nitrogen stream, and the residue was re-dissolved in mobile phase. The extraction procedure yielded recoveries between 84.9%–89.0%. Analysis was carried out by a HPLC system coupled with a UV detector, separation was achieved by a Beckman C_{18} column cartridge (4.6 mm × 250 mm, 5 µm), and the mobile phase consisted of methanol and water (40:60, *v*/*v*) delivered isocratically. The developed MISPE method provides simple cleanup and preconcentration of CAP with high efficiency, which can increase the sensitivity of conventional chromatographic methods. Additionally, MISPE can be used for enrichment, purification and determination of trace CAP from complex food matrices [57].

Chloramphenicol, thiamphenicol, florfenicol and florfenicol amine spiked samples were blended with 2 g of C_{18} material (dispersion adsorbent). The mixture was transferred to a glass column with degreased cotton packed at the bottom and at the top of the sample mixture, and the column was tightly compressed. The analytes were eluted with 5 mL of ethyl acetate-ACN-25% ammonium hydroxide (10/88/2, *v*/*v*/*v*), the eluate was dried under nitrogen stream at 50 °C, and the residue was reconstituted with 1 mL of 5% MeOH in a 0.1% formic acid-5 mmol/L ammonium acetate solution. The extraction procedure yielded recoveries between 84.0%–98.8%. Analysis was carried out by an LC-MS/MS system, separation was achieved by a Hypersil C_{18} column (150 mm × 2.1 µm, 5 µm), and the mobile phase consisted of 0.1% formic acid solvent (including 5 mmol/L ammonium acetate) and methanol delivered using gradient elution. The CC_β was 0.05, 0.11, 0.13, 0.04 µg/kg for florfenicol, florfenicol amine, thiamphenicol and CAP, respectively [58].

Chloramphenicol, florfenicol and thiamphenicol shrimp samples were mixed with 0.5 g of sea sand and 1 g of anhydrous sodium sulfate using a glass mortar. The dry mixture was placed into a SFE chamber that was closed and attached to the SFE system. The extract was evaporated to dryness under nitrogen stream, and the residue was re-dissolved with ethyl acetate for GC-MS analysis. The extraction procedure yielded 92.0%, 87.0%, 85.0% recovery for chloramphenicol, florfenicol and thiamphenicol, respectively. The analytes were collected by *in situ* silylation with Sylon BFT, analysis was carried out by a GC-MS system, and separation was achieved by a TR-5MS (30 m × 0.25 mm i.d. × 0.25 µm film thickness (Thermo Electron, Waltham, MA, USA). The LOD was 8.7, 15.8, 17.4 pg/g for chloramphenicol, florfenicol and thiamphenicol, respectively [59].

Chloramphenicol was extracted from the shrimp samples with ethyl acetate, the extract was evaporated and the dry residue was re-dissolved in 15 mL of salting out solution. In order to remove the fatty components, n-hexane was also added. A second extraction with ethyl acetate followed, the extract was evaporated, and the dry residue was re-dissolved in 5 mL of ACN-water (10:90, *v*/*v*). A cleanup step with sol-gel filter column on-line coupled to an immunoaffinity column containing anti-CAP antibodies followed, and CAP was eluted with 10 mL of ACN-water (40:60, *v*/*v*). For better analyte concentration, the eluate was extracted twice with 3 mL of ethyl acetate and the addition of 2 g sodium sulfate. The extract was evaporated to dryness under nitrogen stream, and the residue was re-dissolved in 1 mL of ACN-water (10:90, *v*/*v*). The extraction procedure yielded 68.0% recovery. Analysis was carried out by a HPLC system coupled with a UV detector, separation was achieved by a Spherisorb S ODS1, 250 × 4.6 mm I.D., 5 µm, column, and the mobile phase consisted of 10 mM sodium acetate pH 5.4 and ACN using gradient elution. The LOD was LOD 1.8 ng/g. The immunoaffinity

columns developed in this study could efficiently remove the shrimp matrix interferences and could be repeatedly used without a decrease in their cleanup efficiency [60].

Ultrasound-assisted matrix solid phase dispersion (MSPD) was applied for the extraction of Chloramphenicol, thiamphenicol and florfenicol. Preconditioned SPE sorbent was mixed with the spiked sample, the mixture was replaced in the SPE cartridge, and the antibiotics were eluted with 1 mL of acetonitrile and then with 1 mL of methanol. The extract was evaporated to dryness under nitrogen stream at 40 °C, and the residue was re-dissolved in 400 μL of lamotrigine aqueous solution 10 ng/mL. The extraction procedure yielded recoveries between 81.3%–114.5%, 72.0%–103.3%, 89.1%–120.6% for thiamphenicol, florfenicol and CAP, respectively. Analysis was carried out by a HPLC system coupled with a diode array detector, separation was achieved by a LiChroCART-LiChrospher® 100 RP-18 (5 μm, 250 × 4 mm) (Merck, Darmstadt, Germany) column, and the mobile phase consisted of ammonium acetate (0.05M) and ACN (70:30 *v*/*v*, isocratic elution). The LOQ was 20 μg/kg for all analytes [61].

An overview of the extraction methodologies for the determination of amphenicols in shrimps is presented in Table 3.

3.4. Extraction of Sulfonamides

Sulfadiazine, sulfamerazine, sulfameter, sulfamethazine, sulfamethoxazole and sulfadimethoxine were extracted using MIP-based SPE and determined with HLPC-UV. Extraction was performed on the shrimp samples with an aquatic solution of acetic acid followed by vortexing, sonication and centrifugation. The supernatant was loaded into the MISPE/NISPE cartridges. The cartridges were washed with acetonitrile in water and elution took place with MeOH/acetic acid, and the eluate was evaporated to dryness under nitrogen flow. The residue was dissolved in acetonitrile in water, filtered and analyzed. Solvent A in the mobile phase was acetic acid/water and solvent B was acetonitrile. Gradient analysis was performed at a flow rate of 1 mL· min^{-1}, and the UV detector was set at 270 nm. The recoveries obtained ranged from 85.5% to 106.1%, while LOD was among 8.4 to 10.9 μg/kg, and LOQ was among 22.4 to 27.7 μg/kg [62].

Fourteen sulfonamides were determined in shrimp samples. Extraction was performed with acetonitrile followed by a sonication step and a centrifugation step. The supernatant was kept, and the same process of extraction was followed once more. C_{18} powder was added into the 2 supernatants after being put together, the solution was homogenized and centrifuged. The supernatant of this step was evaporated to dryness under nitrogen flow. The residue was dissolved with potassium dihydrogen phosphate and filtered before HLPC injection. The mobile phase consisted of potassium dihydrogen (A) and methanol (B). A Capcellpak C_{18} column was used, flow rate was set at 1 mL· min^{-1}, and the detection was performed at 270 nm. The recoveries ranged from 51.8% to 89.7%. The LOD for SAs was among 3 and 6 μg/kg, and the LOQ among 9 and 18 μg/kg [63].

Fourteen sulfonamides, sulfanilamine, sulfadiazine, sulfathiazole, sulfapyridine, sulfamerazine, sulfamethazine, sulfamethizole, sulfamethoxypyridazine, sulfachloropyridazine, sulfadimethoxine and sulfadoxine, sulfamethoxazole, sulfamethoxine, and sulfaquinoxaline residues were determined in shrimps. The samples were homogenized and a mixture of acetic acid-methanol-acetonitrile and acetonitrile were added to them. After centrifugation, the supernatant was transferred to a separatory funnel with DI water and DEG. Methylene chloride was added to the funnel, and separation was performed; the bottom layer was collected and evaporated to a final volume of 2–3 mL with a rotary evaporator. The solution was applied to a SCX SPE cartridge, and the sulfonamides were eluted with acetone-ammonium acetate mix. The eluate was evaporated to a final volume of 2 mL, prior to LC analysis. The analytical column used for the separation was a Symmetry C_{18}, 3.5 μm, 150 mm × 4.6 mm I.D. The mobile phase consisted of aqueous acetic acid-methanol-acetonitrile (A) and acetonitrile (B). Post-column derivatization took place with fluorescamine solution. The fluorescent detection was performed at 400 nm excitation wavelength and 495 nm emission wavelength. The mean recoveries for the spiked shrimp samples at three levels ranged from 67.3% to 90.5% [64].

Seven sulfonamides (sulfaguanidine, sulfadiazine, sulfamethazine, sulfamonomethixine, sulfamethoxazole, sulfadimethoxine and sulfaquinoxaline) were determined in shrimp samples with a monolithic column coupled with boron-doped diamond amperometric detection. Extraction was performed to the samples with Na_2EDTA-Mcllvaine's buffer solution, and the mixture was sonicated and centrifuged. The supernatant was applied to an Oasis SPE cartridge and elution was performed with methanol. The eluate was evaporated under nitrogen flow, and the residue was dissolved with the mobile phase and filtered, prior to HPLC-EC analysis. Separation was achieved with the use of a monolithic column. The mobile phase consisted of phosphate buffer, acetonitrile and ethanol. The LOD value was found between 1.2 ng/mL and 3.4 ng/mL, and the LOQ value was found between 4.1 ng/mL and 11.3 ng/mL [65].

Eight sulfonamides (sulfachloropyridazine, sulfadiazine, sulfamerazine, sulfamethazine, sulfamethizole, sulfmethoxazole, sulfanilamine and sulfathiazole) were determined in shrimp samples using LC-MS/MS analysis. The shrimp samples were spiked, the extraction of sulfonamides was achieved with acetonitrile in acidic conditions, and EDTA was added to the extract, prior to SPE step. An Oasis HLB SPE cartridge was loaded with the extract, the drugs were eluted with methanol, and then the solution was evaporated to a final volume of 4 mL. The analysis was carried out using a triple quadrupole LC-MS/MS with positive electrospray ionization and MRM mode. A reverse-phased C_{18} column was used for the separation of the drugs, and the mobile phase consisted of HPLC-grade water with formic acid and ammonium formate (A) and a mixture 1:1 (*v*:*v*) of methanol-acetonitrile [66].

Eight sulfonamides (sulfadiazine, sulfamerazine, sulfaguanidine, sulfisoxazole, sufladimethoxine, sulfamonomethoxine, sulfadoxine and sulfamethoxazole) were determined in shrimp samples with UPLC analysis using a graphene/polyaniline modified screen-printed carbon electrode. The samples were extracted with a Na_2EDTA-Mckkvaine buffer solution. The mixture was vortexed, sonicated and centrifuged. The supernatant was applied to a Microcolumn Vertipak^{TM} for the SPE procedure, the sulfonamides were eluted with methanol, and the extract was filtered before UPLC injection. The mobile phase consisted of phosphate solution: acetonitrile: ethanol, and the potential used was +1.4 V *vs.* Ag/AgCl. The LOD was found between 1.162 ng/mL and 2.900 ng/mL, and the LOQ was found between 3.336 ng/mL and 20.425 ng/mL [67]

An overview of the extraction methodologies for the determination of sulfonamides in shrimps is presented in Table 4.

3.5. Extraction of Macrolides

Nine macrolides (erythromycin, tylosin, josamycin, spiromicyn, neospiromycin, tlmicosin, gamithromycin, tildipirosin and oleandomycin) were determined in shrimp samples with LC-MS/MS analysis. Extraction was performed to homogenized samples using bearing balls, water and acetonitrile. The mix was centrifuged, the supernatant was kept to another tube, and extraction was performed again to the sample with acetonitrile and phosphate buffer. The complete supernatant was centrifuged and then applied to a Bond-Elut C_{18} SPE cartridge. Elution was achieved with methanolic ammonium acetate, and hexane was added to remove the fat. Hexane was removed by aspiration, and the solution was evaporated under nitrogen flow to a final volume of less than 1 mL. Methanolic ammonium acetate and methanol was added to the solution to a final volume of 1 mL, and the mix was centrifuged. A quantity of it was filtered and remained overnight before LC-MS/MS analysis. The analytical column used for the separation of the macrolides was a Kinetex 2.6 μm XB-C_{18} 2.1 mm I.D. × 100 mm and a SecurityGuard Ultra C_{18} 2.1 mm guard. The mobile phase consisted of an aqueous solution of formic acid and acetonitrile, and the detection was performed with a triple quadrupole MS/MS combined with an electrospray ionization source in the positive mode. The LOD was 0.5 μg/kg, and recoveries were found between 47% and 99% [68].

Six macrolides (erythromycin, elandomycin, azithromycin, clarithromycin, tilmicocin and roxithromycin) were determined in shrimp samples using HPLC-UV analysis, after sample preparation with magnetic MIP-based SPE. The samples were spiked and remained overnight. NaOH and acetonitrile were added the next day, and the mix was vortexed and centrifuged. MSPE was performed to the supernatant with MMIPs, which were magnetically separated from the solution. Elution of the macrolides from the MMIPs was achieved with a mixture of methanol and KH_2PO_4. The eluate was evaporated to dryness under nitrogen flow, and the residue was dissolved with a mixture of acetonitrile and KH_2PO_4. The separation of the macrolides was achieved with a SunFireTM C_{18} column (250 mm × 4.6 mm I.D., 5 μm, Waters). The mobile phase consisted of acetonitrile (A) and KH_2PO_4 (B), and the detection was performed at 210 nm. The LOD was found between 0.015 μg/kg and 0.2 μg/kg, and the LOQ was found between 0.075 μg/kg and 0.5 μg/kg [69].

3.6. Extraction of Nitrofurans

Furazolidone, furaltadone, nitrofurazone and nitrofurantoin were determined in shrimp samples with UPLC-MS analysis. The four drugs were extracted from the samples by using HCl and were derivatized with 2-nitrobenzaldehyde (NBA). After remaining overnight, the samples were neutralized and centrifuged, and the supernatant was applied to preconditioned Oasis HLB cartridges. Elution was performed with ethyl acetate, and the eluate was evaporated to dryness under nitrogen flow, reconstituted in the mobile phase and filtered. The mobile phase was methanol and an aqueous solution of ammonium formate. The LOD was between 0.5–0.8 mg/kg, and LOQ was 1 mg/kg [70].

Table 3. Overview of extraction methodologies for the determination of amphenicols in shrimps.

References	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[51]	CAP	fish, shrimp, poultry, eggs, bovine and swine	Samples homogenized, IS and phosphate extraction solution (4 mL) added, ultrasonic bath (15 min), centrifugation (3000 *g*, 10 min).Supernatant transferred, 4.5 mL ethyl acetate added, vortexed (1 min), centrifuged (3000 *g*, 10 min). Organic layer transferred, evaporated (45 °C, N_2). Residue re-suspended (300 µL MeOH water, 50:50 *v*/*v*), vortexed (20 s).	LC-ESI-MS/MS	LOQ (ng/g): 0.03, LOQ (ng/g): 0.1	98.3–100.0
[52]	CAP	honey, shrimp, and poultry meat	Sample (1 g), spiked (50 µL IS, 10 ng/mL), sodium sulfate anhydrous (1 g) and ethyl acetate (7 mL) added, shaken (20 min), centrifuged (15 min, 2000 rpm). Supernatant transferred, ethyl acetate (7 mL) added to sediment, both supernatants combined, evaporated (dryness, N_2, 40 °C).ACN (1 mL) added on residues, evaporated (N_2, 40 °C), re-suspended (500 µL MeOH/H_2O, 10:90), vortexing (15 s), filtered	LC-ESI–MS/MS	CC_α (µg/kg): 0.03, CC_β (µg/kg): 0.04	-
[53]	CAP	shrimp	Homogenized shrimp meat (3.0 g), water (2 mL) added, spiked (5d-CAP IS, final concentration 0.5 mg/kg), ethyl acetate (5 mL), shaken (10 min, 100 rpm), vortexed (30 s), centrifugation (3000 *g*, 10 min). Extract evaporated (dryness, N_2, water bath, 45 °C). Residue dissolved (1 mL, 1 M ammonium acetate and 4 mL petroleum ether), vortexed (60 s), centrifuged (5 min, 3000 *g*), upper phase discarded, isooctane (2 mL) added, vortexed (30 s), centrifuged (3000 *g*, 10 min), upper phase discarded, ethyl acetate (3 mL), vortexing (60 s), centrifugation (3000 *g*, 5 min). Organic layer collected, reduced (dryness, N_2, water bath, 45 °C. Residue dissolved (0.5 mL hexane:CCl_4, 1:1 *v*/*v*), mixed (0.7 mL HPLC-grade CAN-water, 1:1 *v*/*v*), vortexed (30 s), centrifuged (4000 *g*, 6 min), upper phase filtered (0.22 µm PVDF syringe filter).	LC-ESI-MS-MS	CC_β (mg/kg): 0.057, CC_β (mg/kg): 0.098	95.88–96.96
[54]	CAP	honey, fish and prawns	Homogenized tissue (1.0 g) weighed, spiked (50 µL d^5-CAP IS, 6 ng/mL), vortexed (30 s), allowed (20 min), ACN added (5 mL), vortexed (15 s), shaken (20 min, 180 rpm), centrifuged (5 min, 4000 rpm). Supernatant transferred; chloroform added (5 mL), vortexed (15–20 s), agitation and centrifugation, centrifugation (5 min, 2000 rpm), chloroform layer discarded. ACN phase evaporated (dryness, N_2, water bath at 40–45 °C). Residue re-constituted (1 mL of mobile phase, water–ACN, 90:10 *v*/*v*).	LC-ESI-MS/MS	CC_α (mg/kg): 0.04, CC_β (mg/kg): 0.06, LOD (mg/kg): 0.02, LOQ (mg/kg): 0.06	85.5–115.6 (all)

Table 3. *Cont.*

References	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[55]	CAP	shrimp, crayfish and prawns	Freeze-dried samples (2 g), reconstituted (water, original sample 10 g, IS (d^5-CAP) added, extraction (ACN/4% NaCl, 1:1 *v*/*v*, 20 mL), homogenized, centrifuged (4000 rpm, 15 min). Supernatant separated, de-fatted (2 × 10 mL *n*-hexane), ethyl acetate (7 mL) added, vortexed, supernatant transferred, extraction repeated. Combined supernatants evaporated (dryness), re-dissolved (3 mL of water/ACN, 95:5 *v*/*v*). Re-dissolved sample applied to C_{18} cartridge (500 mg, Separtis). Cartridge preconditioned (10 mL MeOH and 10 mL water/ ACN, 95:5 *v*/*v*), sample eluted (3 mL water/ACN, 45:55 *v*/*v*), ethyl acetate (4 mL) added to eluted sample, vortexed, extraction repeated. Combined extracts evaporated (dryness, N_2), residue re-dissolved (1 mL of acetone/toluene, 20:80 *v*/*v*), applied onto a Silica cartridge (1 g). Cartridge preconditioned (6 mL of acetone/ toluene, 20:80 *v*/*v*), washed (2 ×3 mL acetone/toluene 20:80 *v*/*v*), eluted (6 mL acetone/ toluene, 70:30 *v*/*v*), extract evaporated (dryness), derivatization mixture (50 µL, BSA/n-heptane, 1:1 *v*/*v*) added, react (45 min, 60 °C).	GC/NCI/MS	CC_α (mg/kg): 0.074, CC_β (mg/kg): 0.087	95.0 (all)
[56]	CAP and CAP glucuronide	honey and prawns	Sample (3 g) homogenized, 7 mL ACN added, centrifugation (10 min, 3900 G, 4 °C). Supernatant applied to cartridge (10 mL Chem-Elut, 5 min), elution (15 mL and 10 mL CH_2Cl_2), evaporation (dryness, 45–50 °C), residue re-suspended (5 mL hexane:ethyl acetate, 50:50 *v*:*v*), extract loaded (pre-conditioned SPE cartridge, 500 mg, 3 cc). SPE cartridge washed (3 mL ethyl acetate), eluting (3 mL ethyl acetate:MeOH, 50:50 *v*/*v*), evaporation (dryness, N_2, 45–50 °C), dissolved (300 µL HPLC grade water).	Biacore Q biosensor, LC–MS/MS	Biosensor: CC_α (µg/kg): 0.04, CC_β (µg/kg): 0.17 LC-MS/MS: CC_α (µg/kg): 0.09, CC_β (µg/kg): 0.17	-
[57]	CAP	milk and shrimp	Samples (10 g), spiked, placed statically (15 min), phosphate buffer (40 mL, 0.05 mol/L, pH 7.0) added, vortexed (2 min), sonicated (15 min), centrifuged (1.4×10^3 *g*, 10 min). Supernatant transferred, to precipitate proteins TCA in water (3 mL, 15%) added, vortexed (2 min), centrifugation (1.4×10^3 *g*, 10 min), filtered (microfilters, 0.45 µm). Eluent samples from MISPE cartridges evaporated (dryness, N_2), re-dissolved (mobile phase).	HPLC-UV	-	84.9–89.0

Table 3. *Cont.*

References	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[58]	CAP, THI, FFC and FFC amine	shrimp and fish	Sample (1 g) placed into a mortar, blended (2 g, C_{18} material-dispersion adsorbent, 5 min) with a pestle, homogeneous mixture transferred in glass column (300 × 15 mm i.d.) with degreased cotton packed at the bottom/top of the sample, column tightly compressed. Extraction solvent mixture ethyl acetate-ACN-25% NH_4OH (10/88/2, *v*/*v*/*v*, 5 mL) used for elution, eluate dried (N2, 50 °C), residue reconstituted (1.0 mL 5% MeOH in 0.1% formic acid 5 mmol/L CH_3COONH_4).	LC–MS/MS	CC_α (µg/kg): FFC: 0.01, FFC amine: 0.05, THI: 0.07, CAP: 0.01 CC_β (µg/kg): FFC: 0.05, FFC amine: 0.11, THI: 0.13, CAP: 0.04	84.0–98.8
[59]	CAP, FFC and THI	shrimp	Sample (0.5 g), 500 µL working standard solution added, homogenized, dehydrated (0.5 g sea sand and 1 g anhydrous Na_2SO_4) in a glass mortar. Dry mixture placed into the SFE chamber, modifier introduced, chamber closed and attached to SFE system. Extracted substances collected *in situ* (silylation in a glass tube), tube filled with solvent containing derivatization reagent (20 mL, Sylon BFT), placed in a column oven. After extraction, solvent evaporated (dryness, N_2), residue resolved (200 µL ethyl acetate).	NCI–GC/MS	LOD (pg/g): CAP: 8.7, FFC: 15.8 and THI:17.4	CAP: 92.0, FFC: 87.0, THI: 85.0
[60]	CAP	shrimp	Sample (10 g) homogenized, extracted (×2, ethyl acetate), acetate extracts evaporated, residue dissolved (15 mL salting out solution), fatty components removed (*n*-hexane), extraction (ethyl acetate), extract evaporated, residue dissolved (5 mL ACN-water, 10:90 *v*/*v*). Solution pumped through sol-gel filter column (flow-rate 0.5 mL/min) on-line coupled to immunoaffinity column (containing 0.67 mg anti-CAP antibodies). Flushing (10 mL ACN-water, 10:90 *v*/*v*, 0.5 mL/min), filter column removed, IAC washed (10 mL ACN-water, 10:90 *v*/*v*), eluting CAP (10 mL ACN-water, 40:60 *v*/*v*, 1.0 mL/min). Eluate extracted (2 × 3 mL ethyl acetate), combined extracts dried (2 g Na_2SO_4), centrifugation (1580 *g*, 5 min), ethyl acetate phase decanted, evaporated (N_2), residue dissolved (1 mL ACN-water, 10:90 *v*/*v*).	HPLC-UV	LOD (ng/g): 1.8, LOQ (ng/g): -	68.0

Table 3. *Cont.*

References	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[61]	CAP, THI and FFC	shrimp	Matrix solid phase dispersion: SPE cartridge conditioned (2 mL MeOH and 2 mL water), frits and sorbent removed, sorbent placed in a beaker with 0.5 g homogenized shrimp (spiked with 400 µL of mixture of three antibiotics), blending, sonicated (10 min). SPE cartridges repacked (one frit at the bottom, then sorbent/spiked sample, second frit on top, compressed with glass stirring rod), cartridge washed (1 mL ultra pure water), sequential elution (1 mL ACN and then 1 mL MeOH).Evaporation (dryness, water bath, 40 °C, under stream of nitrogen), dry residue dissolved (400 µL aqueous solution of lamotrigine, 10 ng/mL), filtration (syringe filter, 0.2 µm).	HPLC	LOQ (µg/kg): 20 (all), CC_α (µg/kg): THI: 58.8, FFC: 1030.8, CAP: 59.2, CC_β (µg/kg): THI: 64.6, FFC: 1046.8, CAP: 63.8	THI: 81.3–114.5, FFC: 72.0–103.3, CAP: 89.1–120.6
[71]	CAP	shrimp tissue	Samples spiked (isotopically labeled internal standard, d^5-Cap), ethyl acetate extraction, defatted (hexane), cleanup (SPE C_{18}). Elute evaporated, derivatized with Sylon BFT.	GC/MS-MS	LOQ (ng/g): 0.3	95.0–111.0 (ave.)
[72]	CAP, THI, FFC and FFC amine	shrimp	MISPE	LC	LOD (µg/kg): CAP: 0.016, THI: 0.093, FFC: 0.102, FFC amine: 0.029, LOQ (µg/kg): -	92.4- 98.8 (all)
[73]	CAP	fish and shrimp	Samples extracted (ethyl acetate), defatted (hexane), derivatized (Sylon BFT).	GC-MS	LOD (ng/g): 0.04 (all), LOQ (ng/g): 0.1 (all)	69.9–86.3 (all)
[74]	CAP	aquatic products	Samples extracted with (ethyl acetate-NH_4OH, 98:2 *v*/*v*), cleanup (IAC).	HPLC-UV, HPLC-MS/MS	LOD (µg/kg): -, LOQ (µg/kg): 0.25 (all)	92.0–97.3 (ave.)
[75]	CAP	chicken meat, fish meat, shrimp meat and honey	Analytes extracted (ethylacetate), defatted (n-hexane, LLE).	LC-MS/MS	-	76.2
[76]	CAP	honey and prawns	Sample shaken with buffer, centrifuged, applied to IAC	LC-MS/MS	LOD (µg/kg): 0.05, LOQ (µg/kg): -	84.0%–108.0%

Table 3. *Cont.*

References	Analytes	Sample	Sample Preparation	Analytical Technique	LOD-LOQ, CC_α-CC_β	Recovery (%)
[77]	FFC and FFC amine	fish, shrimp, and swine muscle	Samples extracted, defatted (hexane), cleaned (SPE, Oasis MCX cartridges), eluate evaporated (dryness), derivatized.	GC-microcell electron capture detector	LOD (ng/g): FFC: 0.5, FFC amine: 1 (all), LOQ (ng/g): -	94.1–103.4 (ave.)
[78]	CAP, THI and FFC	shrimp	Samples extracted (basic ethyl acetate), extracts defatted (L-L partition), cleaned (C_{18} SPE cartridge).	LC-MS/MS	LOD (ng/g): CAP and THI: 0.01, FFC: 0.05, LOQ (ng/g): -	CAP: 73.9–96.0, THI: 78.6–99.5, FFC: 74.9–103.7
[79]	CAP, THI, FFC and FFC amine	shrimp muscle and pork	Samples extracted with 2% basic ethyl acetate, L-L partition, SPE.	HPLC-MS/MS	LOD (µg/kg): CAP: 0.001, THI: 0.020, FFC: 0.002, FFC amine: 0.003 (all), LOQ (µg/kg): -	78.17–99.86

Table 4. Overview of extraction methodologies for the determination of sulfonamides in shrimps.

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CC_α, CC_β	Recovery %
[62]	SDZ, SMR, SME, SMZ, SMX, SDM	Fish, Shrimp	Fish and shrimp samples (5.0 g), spiked at 3 levels, MISPE extraction, 1% acetic acid (10.0 mL), vortexed, sonicated (5 min), centrifuged (5.0×10^3 *g*, 5 min), supernatant applied to MISPE/NISPE cartridges, washed (5% ACN 1.0 mL in water—1% acetic acid), elution (3 mL MeOH/acetic acid 9/1 *v*/*v*), evaporation with N_2 at 40 °C, dissolved with 0.5 mL 28% ACN in water, filtration (0.22 µm)	HPLC-UV	LOD (µg/kg): 8.4–10.9 LOQ (µg/kg): 22.4–27.7	85.5%–106.1%
[63]	SDZ, STZ, SMZ, SMX, SMP, SCPD, SDM, SMM, SPZ, SDX, SSZ, SCP, SMT, SQX	flatfish, jacopever, sea bream, common eel, blue crab, shrimp, abalone	Sample (1 g), ACN (5 mL), homogenized (1 min), extraction × 2 -sonication (10 min), centrifugation (4500× *g*, 10 min), supernatant collected, add 100 mg C_{18}, homogenization (30 s), powder dispersed, centrifugation (4500× *g*, 10 min), evaporation with N_2 to dryness, dissolved with KH_2PO_4 (5 mM, 1 mL), filtration (0.45 µm)	HPLC-PDA Confirmation with LC-MS/MS	LOD (µg/kg): 3–6 LOQ (µg/kg): 9–18	51.8%–89.7%

Table 4. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CC_α, CC_β	Recovery %
[64]	SN, SDZ, STZ, SPD, SMR, SMZ, SMTZ, SMP, SCP, SMM, SDX, SMX, SDM, SQX	catfish, shrimp, salmon	Samples (10 g), 0.2% CH_3COOH-MeOH-ACN (10 mL, 85:10:5), homogenized (30 s, 20000 rpm), ACN (90 mL), shaker (10 min), centrifugation (10 min), ACN (30 mL) for extraction, shaker, centrifugation, CH_2Cl_2 (60 mL), shake (3 min), leave 15 min, bottom layer to flask with boiling chips, extraction repeated, concentration to 2–3 mL, CH_2Cl_2:acetone (60:40, 5 mL). SPE on SCX cartridges preconditioned (2.5 mL acetone, 2.5 mL 0.2% acetic acid, 2.5 mL acetone), elution with acetone-0.4 M CH_3COONH_4 (50:50 v/v, 5 mL), evaporation with N_2 to 2 mL.	HPLC-FLD	LOQ (ng/g): 1	67.3%–90.5%.
[65]	SG, SDZ, SMT, SMM, SMX, SDM, SQX	Shrimp	Homogenizes shrimp (2 g), Na_2EDTA-Mcllaine's buffer (10 mL), mixed, vortexed (5 min), sonicated, centrifuged (3500 rpm, 10 min), SPE with Oasis HLB (200 mg, conditioned with 5 mL Milli-Q water, 5 mL Na_2EDTA-Mcllvaine buffer solution), elution with MeOH (7 mL), evaporation with N_2, reconstituted with mobile phase (10 mL), filtered (0.45 μm).	HPLC-EC (BBD amperometric detection)	LOD (ng/mL): 1.2–3.4 LOQ (ng/mL): 4.1–11.3	(Spiked samples 1.5, 5, 10 $\mu g \cdot g^{-1}$) 81.7 to 97.5%
[67]	SDZ, SMR, SG, SSZ, SDM, SMM, SDX, SMX	Shrimp	Homogenized shrimp (2 g), Na_2EDTA—Mcllvaine buffer, vortexed (5 min), sonicated, centrifuged (3500 rpm, 10 min), SPE Microcolumn Vertipak™ HCP (conditioned with MeOH, Milli-Q water, Na_2EDTA-Mcllvaine buffer), supernatant (10 mL), supernatant (10 mL) loaded, elution with MeOH (7 mL), filtration (0.20 μm pore size).	UPLC-ECD	LOD (ng/mL): 1.162–2.900 LOQ (ng/mL): 3.336–20.425 $ng \cdot mL^{-1}$	-

Four nitrofuran metabolites, 3-amino-2-oxazolidinone (AOZ), 3-amino-5-morpholino-methyl-1,3-oxazolidinone (AMOZ), semicarbazide (SEM) and 1-aminohydatoin (AHD), were determined in shrimp tissue. The samples were washed with methanol, HCl solution was then added, and derivatization was achieved with 2-NBA. After remaining overnight in an incubator, the samples were neutralized and extracted with ethyl acetate. The extract was evaporated to dryness under nitrogen flow, and the residue was reconstituted with reconstitution solvent (water, acetonitrile, glacial acetic acid). Extraction with hexane was performed, and the final aqueous solution was filtered, prior to HPLC analysis. The mobile phase consisted of water, glacial acetic acid (A) and acetonitrile, water, glacial acetic acid (B). The UV detection was achieved at 275 nm. The recoveries for spiked samples, for the four metabolites, were found between 107% and 115% [80].

Four nitrofuran metabolites, AOZ, AMOZ, SEM and AHD, were determined in shrimp samples with LC-IDMS/MS analysis. The samples were acidified with HCl, derivatized with 2-NBA and left in an incubator overnight. After being neutralized, the samples were extracted twice with ethyl acetate and the extract was evaporated to dryness under nitrogen flow. The residue was dissolved with HPLC grade water and filtered before LC analysis. A Symmetry C_{18} (2.1 × 150 mm, 3.5 μm) analytical column and a Symmetry C_{18} guard column (2.1 × 10 mm, 3.5 μm) were used. The mobile phase consisted of acetonitrile (A) and water with aqueous solution acetic acid (B). The CCα of the derivatized metabolites was between 0.08 $\mu g \cdot kg^{-1}$ and 0.20 μg/kg. The CC_β was between 0.13 μg/kg and 0.85 μg/kg [81].

Four nitrofuran metabolites (furalizone—AOZ, furaltadone—AMOZ, nitrofurazone—SEM and nitrofurantoin—AHD) were determined in shrimp samples using LC-MS/MS analysis. The samples were firstly washed with methanol, HCl and 2 NBA were then added to them, and the samples were kept overnight in an incubator. After being neutralized with NaOH, ethyl acetate was added to the samples, and they were centrifuged. The supernatant was evaporated near to dryness, the residue was re-dissolved with methanol, and the final mixture was filtered before LC-MS/MS analysis. The CC_α was between 0.12 μg/kg and 0.23 μg/kg. The CC_β was between 0.21 μg/kg and 0.38 μg/kg, and the recoveries were found to be 88%–110% [82].

An overview of the extraction methodologies for the determination of macrolides and nitrofurans in shrimps is presented in Table 5.

3.7. Multi-Residue Methods

Thirteen sulfonamides, 3 fluoroquinolones and 3 quinolones were extracted from the spiked samples with 10 mL of acetonitrile and the addition of 0.1 mL p-toluenesulfonic acid monohydrate (*p*-TSA), 0.1 mL *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine dihydrochloride (TMPD) solution, 2 g NaCl and ceramic homogenizer pellet. The extract was evaporated to dryness under nitrogen stream at 50–55 °C, and the residue was re-dissolved in 2 mL of acetonitrile:formic acid:water (10:0.4:89.6 *v*/*v*). The extraction procedure yielded 98.0%–104.0% average recovery for all analytes. Analysis was carried out by LC-MS/MS system, separation was achieved by a YMC ODS-AQ 2 × 100 mm, 3 μm column, and the mobile phase consisted of 0.1% formic acid in water and acetonitrile delivered under gradient elution. This method does not require a SPE cleanup step because it is fast and inexpensive, and an analytical chemist can prepare and analyze 12–16 samples per working day [83].

Five different sample treatment methods were tested for the extraction of multiclass antibiotics and veterinary drugs: benzalkonium chloride, ethoxyquin, leucomalachite green, malachite green, mebendazole, sulfadiazine, sulfadimethoxine, sulfamethazine, sulfamethizole, sulfanilamide, sulfapyridine, sulfathiazole and trimethoprim. The sample preparation was as follows:

(1) Spiked samples were extracted with 10 mL of acetonitrile containing 1% acetic acid with the addition of 4 g of anhydrous magnesium sulfate and 1.75 g of sodium chloride. 250 mg of primary-secondary amine and 750 mg of anhydrous magnesium sulfate were added to 5 mL of the acetonitrile supernatant. The final extract was evaporated to near dryness, reconstituted with 20% (*v*/*v*) methanol in water to a final volume of 2 mL.

(2) Spiked samples were extracted with 6 mL of trifluoroacetic (20%, w/v), and the extract was evaporated to near dryness and reconstituted with 20% (v/v) methanol in water to a final volume of 0.5 mL.

(3) Spiked shrimp samples were mixed with 2 g of aminopropyl (Bondesil-NH_2), and the mixture was transferred to a SPE cartridge. The antibiotics were eluted twice with 5 mL of acetonitrile, and the eluates were evaporated to near dryness and reconstituted with 20% (v/v) methanol in water to a final volume of 1 mL.

(4) Spiked shrimp samples were mixed with 3 mL of sulfuric acid 0.17 M, 0.158 g of sodium tungstate and 12 mL of acetonitrile in order to precipitate the proteins. An SPE cleanup step followed, with a C_{18} cartridge preconditioned with 5 mL of methanol and 5 mL of water. The analytes were eluted with 1 mL of acetonitrile/water (30:70 v/v), 2 × 2 mL of ethyl acetate were added to the eluate, and the organic extracts were evaporated to near dryness and with 20% (v/v) methanol in water to a final volume of 1 mL.

(5) In order to precipitate the proteins, spiked shrimp samples were mixed with 100 mL of 0.2% of metaphosphoric acid in acetonitrile, the mixture was filtered through a 0.45 μm filter, and the extract was evaporated to a final volume of 30 mL. A SPE cleanup step followed with an Oasis HLB SPE cartridge, and the analytes were eluted with 5 mL of acetonitrile. The eluate was evaporated to near dryness and reconstituted with 20% (v/v) methanol in water to a final volume of 1 mL.

The QuEChERS method was preferred. The extraction procedure yielded recoveries between 33.0%–118.0% for all analytes. Analysis was carried out by an LC–TOF/MS system, separation was achieved by a RR Zorbax Eclipse XDB-C_{18} analytical column (50 mm × 4.6 mm and, 1.8 μm), and the mobile phase consisted of 0.1% formic acid and acetonitrile (gradient elution). The LOD ranged between 0.06–7.1 μg/kg for all analytes [84].

Forty-three multi-class veterinary drugs were extracted from the spiked samples with 5 mL of water and 15 mL of 1 vol. % formic acid in acetonitrile or acetonitrile. Four grams of magnesium sulfate, 1.5 g trisodium citrate dehydrate and 2 g sodium chloride were then added to the mixtures. The extract was used directly for LC-MS/MS analysis without further handling. Analysis was carried out by an LC-MS/MS system, separation was achieved by a Syncronis aQ (2.1 mm i.d. × 100 mm, 5 μm column, and the mobile phase consisted of 0.1% formic acid in 10 mmol/L ammonium acetate and acetonitrile under gradient conditions [85].

Lomefloxacin, enoxacin, sarafloxacin, enrofloxacin, sulfadiazine, sulfamethoxydiazine and sulfadimethoxypyrimidine were extracted from the spiked samples with accelerated solvent extraction and acetonitrile was the extraction solvent. The extract was evaporated to dryness under nitrogen stream at 45 °C, and the residue was re-dissolved in 1 mL of methanol. The extraction procedure yielded recoveries between 88.9%–94.8%, 88.0%–93.1%, 87.6%–95.7%, 88.0%–93.2%, 88.7%–91.0%, 86.7%–90.0%, 85.4%–88.8% for LOME, ENO, SAR, ENR, sulfadiazine, sulfamethoxydiazine and sulfadimethoxypyrimidine, respectively. Analysis was carried out by capillary zone electrophoresis system couples with a UV detector, separation was achieved by a uncoated fused silica capillary of i.d. 50 μm with total length of 48.5 cm (effective length 40 cm), capillary was filled with a borate buffer (25 mM, pH 8.8) containing methanol, and the analytes moved through the capillary by reversing the polarity (−25 V). The LOD was 0.025, 0.033, 0.025, 0.020, 0.013, 0.013, 0.013 μg/mL for LOME, ENO, SAR, ENR, sulfadiazine, sulfamethoxydiazine and sulfadimethoxypyrimidine, respectively. The accelerated solvent extraction provides rapid extraction procedures and lower solvent usage in comparison with the extraction procedures used in the literature [86].

Sulfadiazine, sulfamethazine, sulfamethazine, sulfachloropyridazine, sulfadimethoxine and sulfaquinoxaline were determined in shrimp samples after extraction with trichloroacetic acid and hydroxylamine hydrochloride. The samples were vortexed and centrifuged. Sodium succinate and NaOH were added to the supernatant, and it was then applied to Waters Oasis HLB cartridges. Elution was performed with MeOH and CH_3CN/MeOH. Into the eluate ammonium formate buffer, EDTA

and ascorbic acid were added. After evaporation under vacuum until 0.8 mL and an addition of water/acetonitrile mix up to 1 mL, the final solution was vortexed and centrifuged. Half of the final solution was used for analysis, which was performed by LC-MS/MS. Phenyl column separated the analytes prior to analysis, and APCI was used as ionization source in negative mode. The estimated recovery ranged from over 40% to over 90%. The LOD of SQX was achieved at 20 ng/g and 10 ng/g for the other sulfonamides [87].

An overview of the extraction methodologies for the multi-class antibiotics analysis in shrimps is presented in Table 6.

Table 5. Overview of extraction methodologies for the determination of macrolides and nitrofurans in shrimps.

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CCα, CCβ	Recovery %
[68]	Macrolides—(erythromycin, tylosin, josamycin, spiromicyn, neospiromycin, tilmicosin, gamithromycin, tildipirosin and oleandomycin) Lincosamides—Lincomycin, Pirlimycin, Clindamycin	Salmon, Shrimp, Tilapia	Homogenized sample (5 g), extraction with ACN (10 mL), water (1 mL), shaker (700 rpm), centrifugation (5 min, 400× *g* RCF), re-extraction with ACN, phosphate buffer (3 mL), shaker, centrifugation, the two supernatants centrifuged again (5 min, 6100× *g* RCF), SPE on Bond-Elut cartridge (pre-conditioned with water, 12% ACN), elution with methanolic CH_3COONH_4 (750 µL × 2), fat removal with water and hexane, vortexed, centrifuged (5 min, 1000× *g* RCF), evaporation with N_2 to volume < 0.75 mL, methanolic CH_3COONH_4 (50 µL), mixed, MeOH to volume 1 mL, centrifugation (15 min, 2130× *g*, 5 °C).	LC-MS/MS	LOD (µg/kg): 0.5	47%–99%
[69]	Macrolides—ERY, ELAN, AZM, CLM, TIM, RXM, Quinolones—CIP, SPFX Amphenicols—CAP, TAP	Pork, Fish, Shrimp	Spiked samples, NaOH for hydrolysis of lipids (500 µL), extraction with ACN (20 mL), vortexed (15 min), centrifuged (5 min, 7000 rpm), supernatant with MMIPs (100 mg) mixed, magnetically removed, washed with ACN:water, elution with (10 mL) MeOH/50 mM KH_2PO_4 (pH 8), evaporation to dryness, residue reconstituted with mL ACN/25 mM KH_2PO_4	UPLC-UV	LOD (µg/kg): 0.015–0.2 LOQ (µg/kg): 0.075–0.5	-
[70]	Nitrofurans—Furazolidone, furaltadone, nitrofurazone, nitrofurantoin	Shrimp	Homogenized samples (2.5 g), added HCl aqueous and 2-NBA for derivatization, incubating overnight, neutralized with di-sodium hydrogen phosphate and NaOH,centrifugation (5 min, 4000 rpm), supernatants SPE Oasis HLB (conditioning with ethyl acetate, MeOH, Milli-Q water), cartridge washed with water, elution with ethyl acetate (6 mL), evaporation to dryness, redissolved with mobile phase (1 mL), filtered (0.20 µm)	UHPLC-QqQ-MS/MS	LOD (mg/kg):0.5–0.8, LOQ (mg/kg): 1	-
[80]	Nitrofurans—nitrofuran metabolites, AOZ, AMOZ, SEM and AHD,	Shrimp	Homogenized sample (5 g), washed with MeOH (20 mL) mixing, centrifugation (10 min, 2500 rpm), washing with MeOH and water, HCl (10 mL), derivatization with 2-NBA, incubated overnight, $Na_3PO_4 \cdot 12H_2O$ solution added, neutralized with NaOH (2 M), extraction with ethyl acetate, evaporation to dryness, reconstituted with 500 µL reconstitution solvent, extracted tree times with hexane, filtration (0.45 µm)	HPLC-UV	LOD (mg/kg): 2	107%–115%

Table 5. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CCα, CCβ	Recovery %
[81]	Nitrofurans—AOZ, AMOZ, SEM and AHD	Shrimps	Sample (1 g) spiked at 2 μg/Kg, hydrolysis with HCl (5 mL), derivatization with 50 μL 2-NBA, overnight incubation, neutralizing with NaOH and phosphate buffer, extraction with ethyl acetate, evaporation to dryness, dissolution with HPLC grade water, filtration.	LC-IDMS/MS	CC_α (μg/kg): 0.08–0.20 CC_β (μg/kg):0.13–0.85	-
[82]	Nitrofurans—furalizone—AOZ, furaltadone—AMOZ, nitrofurazone—SEM and nitrofurantoin—AHD	Shrimps	Homogenized sample (1 g) washed with methanol, centrifuged (4 min 4000 rpm) repeated, HCl and 2-NBA to the sample, incubated overnight, neutralized with NaOH, ethyl acetate added (4 mL), centrifuged, extraction again, supernatant evaporation near dryness, residue dissolved with methanol, filtrated (0.45 μm) analysis, AMOZ-d^5 internal standard	LC-MS/MS	CC_α (μg/kg): 0.12–0.23, CC_β (μg/kg): 0.21–0.38	88%–110%

Table 6. Overview of extraction methodologies for the determination of multi-class antibiotics in shrimps.

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CCα, CCβ	Recovery (%)
[83]	26 veterinary drugs: 13 SAs TRI, 3 FQ, 3 AQ, 3 TPM, 2 LC dyes metabolites, 1 hormone	fish and other aquaculture products (tilapia, catfish, eel, pangasius, sablefish,swai, salmon, trout, and shrimp	Tissue (4.0 g $\pm$ 0.03 g) weighed, SMZ-^{13}C solution (0.040 mL) added, EDTA-McIlvaine buffer (2.0 mL) added, mixed (10 s). ACN (10 mL), p-TSA (0.100 mL), TMPD solution (0.100 mL), NaCl (2.0 g) and ceramic homogenizer pellet added, shaken (5 min), centrifuged (6000 rpm, 5 °C, 5 min) Organic layer transferred, ACN (10 mL) added, shaken (5 min), centrifuged. ACN layers combined, evaporated (dryness, water bath, 50–55 °C, N_2). Residue reconstituted (2.0 mL the dissolution solution), mixed (30 s), sonicator (5 min), centrifuged (10,000 rpm, 5 °C, 5 min). 0.5 mL portion filtered (0.2 µm PTFE syringe filter).	LC-MS/MS	-	98.0–104.0 (all, ave.)
[84]	BC, EQ, LMG, MG, MBZ, SDZ, SDM, SMZ, SMTZ, SN, SPD, STZ,TRO	shrimp	Five different sample treatment methodologies were tested: ACN extraction followed by cleanup by QuEChERS. Sample (10 g) homogenized, ACN containing 1% acetic acid (10 mL) added, shaken (1 min), anhydrous $MgSO_4$ (4 g) and NaCl (1.75 g) added, shaking repeated (1 min).Extract centrifuged (3700 rpm, 3 min), supernatant (5 mL) (ACN phase) transferred to centrifuge tube (with 250 mg PSA and 750 mg anhydrous $MgSO_4$), shaken (20 s), centrifuged (3700 rpm, 3 min), extract (2 mL) evaporated (near dryness, reconstituted (20% v/v MeOH in water, to a final volume of 2 mL), filtered (0.45 µm PTFE filter). 1. Extraction with TCA: Shrimp (1 g), TCA solution added (6 mL, 20%, w/v), homogenized (ultrasonic bath, 30 s), centrifuged (5 min, 3700 rpm). Supernatant (3 mL) taken, evaporated (near dryness), dissolved in MeOH in water (20% v/v, to a final volume of 0.5 mL), filtered (0.45 µm PTFE filter). 2. Matrix solid phase dispersion (MSPD) procedure: Shrimp (1 g), (2 g, Bondesil-NH_2) added, mixture transferred to SPE cartridge containing 2 g Florisil, connected to vacuum system. Elution with ACN (2 × 5 mL), final extract evaporated (near dryness), reconstituted with MeOH in water (with 20% v/v, to a final volume of 1 mL), filtered (0.45 µm PTFE filter).	LC-TOFMS	LOD (µg/kg): BC-C12: 0.6, EQ: 7.1, LMG: 0.6, MG: 0.06, MBZ: 0.1, SDZ: 4.5, SDM: 0.3, SMZ: 0.1, SMTZ: 0.8, SN: 3.5, SPD: 0.5, STZ: 2.9, TRI: 0.7	BC-C12: 53.0, EQ: 53.0, LMG: 90.0, MG: 118.0, MBZ: 118.0, SDZ: 82.0, SDM: 85.0, SMZ: 114.0, SMTZ: 33.0, SN: 115.0, SPD: 109.0, STZ: 81.0, TRI: 87.0

Table 6. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CCα, CCβ	Recovery (%)
			3. SPE-based method I: (a) Protein precipitation: Shrimp (1 g), sulfuric acid (3 mL, 0.17 M), sodium tungstate (0.158 g) and ACN (12 mL) added, mixture shaken, centrifuged. Supernatant (10 mL) filtered (0.45 µm PTFE filter). (b) SPE: Aliquot (3 mL) transferred to C_{18} cartridge preconditioned with 5 mL MeOH and 5 mL water), washing (500 µL of water 500 µL ACN/water 5:95), elution (1 mL of ACN/water, 30:70). (c) LLE: SPE eluate, ethyl acetate (2 mL) added, shaking (30 s), organic phase separated, extraction repeated (2 mL ethyl acetate), extracts combined, evaporated (near dryness), reconstituted with MeOH in water (20% v/v, to a final volume of 1 mL), filtered (0.45 µm PTFE filter). 4. SPE-based method II: Shrimp (5 g), metaphosphoric acid in ACN (100 mL, 0.2%) added, mix filtered (0.45 µm filter), evaporated (N_2 stream, until 30 mL). Extract loaded onto Oasis HLB cartridge, washed (5 mL ACN:water, 20:80 v/v), eluted (5 mL ACN), evaporated (near dryness), reconstituted with MeOH in water (20% v/v, a final volume of 1 mL), filtered (0.45 µm PTFE).			
[85]	43 multi-class veterinary drugs (sulfonamides, quinolones, coccidiostats and antiparasites)	milk, fish and shellfish (salmon, tiger shrimp, red sea bream and bastard halibut)	Sample (5 g), working standard solution (50 µL or 500 mL) added, waiting (>30 min), water (5 mL) and HCOOH in ACN (15 mL, 1 vol. %, Method A) or ACN alone (15 mL, 1 vol. %, Method B) added, homogenized, magnesium sulfate (4 g), trisodium citrate dehydrate(1.5 g) and NaCl (2 g) added, shaken (1 min), centrifuged (1800× g, 10 min), supernatant transferred, dilution extraction solvent, portion of the solution transferred to a microtube, centrifuged (16,000× g, 10 min).	LC-MS/MS	LOQ (µg/kg): 1–10 (all)	48.5–113.6 (all) (Method A) 11.1–116.5 (all) (Method B)
[86]	LOME, ENO, SAR, ENR, SDZ, SMD, SDMP	shrimp and sardine	Sample (5 g) and diatomite (1.5 g) mixed, transferred into extraction cell (ACN extraction solvent). Extraction conditions: oven temperature 60 °C, 3 min heat-up time, pressure 10.3 MPa, two static cycles, static time 5 min, flush volume 40% of extraction cell volume. Extract purged (pressurized N_2, 90 s), evaporated (dryness, N_2, 45 °C), residue dissolved (MeOH, to 1 mL), filtered (0.45 µm).	CZE	LOD (µg/mL): LOME: 0.025, ENO: 0.033, SAR: 0.025, ENR: 0.020, SDZ: 0.013, SMD: 0.013, SDMP: 0.013 LOQ (µg/mL): LOME: 0.08, ENO: 0.10, SAR: 0.08, ENR: 0.07, SDZ: 0.04, SMD: 0.04, SDMP: 0.04	LOME: 88.9–94.8, ENO: 88.0–93.1, SAR: 87.6–95.7, ENR: 88.0–93.2, SDZ: 88.7–91.0, SMD: 86.7–90.0, SDMP: 85.4–88.8

Table 6. *Cont.*

Reference	Analytes	Sample	Sample Preparation	Analytical Technique	LOD, LOQ, CCα, CCβ	Recovery (%)
[87]	SDZ, SMR, SMZ, SCP, SDM, SQX, ENR, SAR, DIF, OXO, NAL, FLU, LMV, LVG, MG, GV, OTC, TOLSa	Shrimp	blended shrimp (2 g), 100 µL standard, TCA & NH_2OH-HCl added, homogenized, vortex (10 min), centrifugation (4000 rcf, 4 °C, 15 min), supernatant into solution sodium succinate (2.5 mL) and NaOH (10N, 280 µL)—pH 3.6 ± 0.1, Oasis HLB cartridge pre-conditioned (washed 3 mL ammonium formate buffer, 3 mL Milli- Q water, dried for 2 min), elution with MeOH (2 mL) CH_3CN/MeOH 1:1 *v*/*v* (1 mL), to the elute ammonium formate buffer (20 mM, pH 3.9), EDTA (50 µL, 0.1 M), ascorbic acid (1 mg/mL in MeOH), evaporation with N_2 till 0.8 mL, aliquot of 1:1 water/AC N added to fill 1 mL, centrifugation (14000 rpm, 10 min), analysis of the middle portion (~0.8 mL)	LC-ion trap-MS	10 ng/g for SQX	40%–90%
[88]	21 veterinary drugs: SAs (SDZ, SMR, SMZ, SCP, SDM, SQX), TCs (OTC, TC, CTC), FQ (NOR, CIP, ENR, SAR, DIF, FLU, OXO,NAL) and cationic dyes (MG, GV, LMG, and LGV)	shrimp	Sample (2 g) extracted (×2, 2 different pH values), supernatant diluted (aqueous internal standard), online SPE automated sample cleanup.	HPLC-MS/MS	-	-
[89]	FQ, TCs, macrolides, lincosamides, SAs and others	livestock and fishery products	Extraction with two solutions of different polarity: highly polar compounds extracted with Na_2EDTA-McIlvaine's buffer (pH 7.0) and medium polar compounds were extracted with ACN containing 0.1% HCOOH. Cleanup with SPE polymer cartridge, first extracted solution applied to the cartridge (highly polar compounds retained), second extracted solution applied to the same cartridge, both highly and medium polar compounds eluted.	LC-MS/MS	LOQ (µg/kg): 0.1–5	-
[90]	CAP and nitrofuran metabolites	shrimp	Extraction steps: neutralization of hydrolysates, addition of ACN for extraction, salting out of organic phase from the ACN-aqueous mixture	LC-MS/MS	-	98.6–109.2 (all)
[91]	33 FQ and SAs	eels and shrimps	Sample extracted with acidified ACN, cleaned-up (hexane), concentrated (evaporator).	HPLC-MS/MS	LOD (µg/kg): 1.0, LOQ (µg/kg): 2.0	66.0–123.0
[92]	AMOZ, AOZ, AHD, SEM CAP	shrimp	single extraction procedure	LC-MS/MS	LOD (ng/g): nitrofuran metabolites: 0.5, CAP: 0.3	-

4. Conclusions

Increased aquaculture practice has resulted in increased levels of infections among species. Various classes of antibiotics including quinolones, tetracyclines, b-lactams, sulfonamides, *etc.* exhibit activity against both Gram-positive and Gram-negative bacteria; therefore, they are widely used in aquaculture to treat or prevent diseases.

However, the extended use of antibiotics in aquaculture has led to the demand for developing sensitive methods for their determination. The focus of this review has been to present the trends in microextraction techniques for the analysis of shrimps, as many different antibiotic classes are used in shrimp aquaculture worldwide, although some of them have been forbidden in other countries due to their dangerous side effects on humans.

Evidently, the analysis of antibiotics in shrimps still requires a significant amount of solvents and tedious extraction protocols due to the complex matrix; therefore, microextraction techniques are scarcely applied, indicating that there is still a lot of research to be done in this direction.

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Abbreviations

ACN	Acetonitrile
AHD	1-Aminohydatoin
AMOZ	3-Amino-5-morpholino-methyl-1,3-Oxazolidinone
AOZ	3-Amino-2-Oxazolidinone
APCI	Atmospheric Pressure Chemical Ionization
AQ	Acidic Quinolones
ASE	Accelerated Solvent Extraction
AVE	Average
AZM	Azithromycin
BC	Benzalkonium Chloride
BDD	Boron Doped Diamond
BG	Brilliant Green
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
CAP	Chloramphenicol
CCα	Decision Limit
CCβ	Detection Capability
CIN	Cinoxacin
CIP	Ciprofloxacin
CLM	Clarithromycin
CTC	Chlortetracycline
CV	Crystal Violet Cation
CWP	Coordinating Working Party
CZE	Capillary Zone Electrophoresis
d^5-Cap	d^5-Chloramphenicol
DC	Doxycycline
DES-CIP	Desethylene Ciprofloxacin
DI water	Deionized Water
DIF	Difloxacin
DMC	Demeclocycline
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediaminetetraacetic Acid

ELAN	Elandomycin
ENR	Enrofloxacin
EQ	Ethoxyquin
ERY	Erythromycin
EU	European Union
FAO	Food and Agriculture Organization
FAO	Food and Agriculture Organization of The United Nations
FFC	Florfenicol
FLU	Flumequine
FQ	Fluoroquinolones
GC	Gas Chromatography
GC/MS-MS	Gas Chromatography-Mass Spectrometry
GC/NCI/MS	Gas Chromatography-Negative Chemical Ionization-Mass Spectrometry
GV	Gentian Violet
HLB	Hydrophilic-Lipophilic Balance
HPLC	High-Performance Liquid Chromatography
HPLC-CE	High-Performance Liquid Chromatography Cation-Exchange
HPLC-CL	High-Performance Liquid Chromatography-Chemiluminescenece Detection
HPLC-FLD	High-Performance Liquid Chromatography-Fluorescence Detection
HPLC-UV	High-Performance Liquid Chromatography-Ultraviolet Detection
IAC	Immunoaffinity Column
IS	Internal Standard
LC dye metabolites	Leuco Dye Metabolites
LC-ESI-MS/MS	Liquid Chromatography-Electrospray Ionization-Mass Spectrometry
LC-FLD	Liquid Chromatography-Fluorescence Detection
LC-FLD-MS	Liquid Chromatography-Fluorescence-Mass Spectrometry
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LC-TOFMS	Liquid Chromatography-Time-Of-Flight Mass Spectrometry
LC-UV	Liquid Chromatography-Ultraviolet Detection
LCV	Leucocrystal Violet
LDTD-MS/MS	Laser Diode Thermal Desorption-Mass Spectrometry
LGV	Leucogentian Violet
L-L partition	Liquid-Liquid Partition
LLE	Liquid-Liquid Extraction
LMG	Leucomalachite Green
LOD	Limit of Detection
LOME	Lomefloxacin
LOQ	Limit of Quantification
MARB	Marbofloxacin
MBZ	Mebendazole
MCX	Mixed Mode Cation Exchange
MDL	Method Detection Limit
MeCN	Acetonitrile
MeOH	Methanol
MG	Malachite Green Cation
MIP	Molecularly Imprinted Polymer
MISPE	Molecularly Imprinted Solid Phase Extraction
MNC	Minocycline
MQCA	3-Methyl-quinoxaline-2-carboxylic Acid
MRLs	Maximum Residue Levels
MSPD	Matrix Solid Phase Dispersion

MT	Methyltestosterone
MTC	Methacycline
NAL	Nalidixic Acid
NBA	Nitrobenzaldehyde
Ni-DIA electrode	Nickel-Implanted Boron-Doped Diamond Thin Film Electrode
NIP	Non-Molecularly Imprinted Polymer
NOR	Norfloxacin
OFL	Ofloxacin
ORB	Orbifloxacin
OTC	Oxytetracycline
OXO	Oxolinic Acid
PABA	Para-Aminobenzoic Acid
PEF	Perfloxacin
PLE	Pressurized Liquid Extraction
PSA	Primary–Secondary Amine
PTFE	Polytetrafluoroethylene
p-TSA	*p*-Toluenesulfonic Acid Monohydrate
QCA	Quinoxaline-2-Carboxylic Acid
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe
RNA	Ribonucleic Acid
RXM	Roxythromycin
SAR	Sarafloxacin
SAs	Sulfonamides
SCPD	Sulfachloropyridazine
SCPZ	Sulfachloropyrazine
SDB-RPS	Polystyrenedivinylbenzene-Reverse Phase Sorbent
SDM	Sulfadimethoxine
SDM	Sufladimethoxine
SDMP	Sulfadimethoxypyrimidine
SDX	Sulfadoxine
SDX	Sulfadoxine
SDZ	Sulfadiazine
SEM	Semicarbazide
SFE	Supercritical Fluid Extraction
SG	Sulfaguanidine
SLE	Solid Liquid Extraction
SMD	Sulfamethoxydiazine
SME	Sulfameter
SMM	Sulfamonomethoxine
SMP	Sulfamethoxypyridazine
SMR	Sulfamerazine
SMT	Sulfamethazine
SMTZ	Sulfamethizole
SMX	Sulfamethoxazole
SMZ	Sulfamethazine
SMZ-13C6	Sulfamethazine-13C6
SN	Sulfanilamide
SPD	Sulfapyridine
SPE	Solid Phase Extraction
SPZ	Sulfaphenazole
SQX	Sulfaquinoxaline

SSZ	Sulfisoxazole
SSZ	Sulfisoxazole
STZ	Sulfathiazole
Sylon BFT	{*N*,*O*-Bis(Trimethylsily) Trifluoroacetamide[BSTFA]-Trimethylchlorosilane [TMCS], 99 + 1}
TC	Tetracycline
TCA	Trichloroacetic Acid
TCs	Tetracyclines
THI	Thiamphenicol
TIM	Tilmicocin
TMPD	*N*,*N*,*N*′,*N*′-Tetramethyl-*P*-Phenylenediamine dihydrochloride
TOLSa	Toltrazurisulfone
TPM	Triphenylmethane Dyes
TRI	Trimethoprim
UPLC-MS/MS	Ultra-Performance Liquid Chromatography-Mass Spectrometry
UV	Ultra Violet

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