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Microextraction techniques for antibiotics surveillance in the food chain and environment

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ABSTRACT

Antibiotics are commonly used to prevent and treat infections in human medicine, animal farming, and aquaculture. However, their excessive use can result in the development of antibiotic resistance and the presence of antibiotic residues in the food and environment. Therefore, it is essential to monitor antibiotic use and assess resistance, but the lack of standardisation and long-term quantitative data on antibiotic usage in different animal species is very challenging. Sample preparation techniques, such as solid-phase extraction (SPE) and liquid-liquid extraction (LLE), have been widely used, but they have limitations, including the need for large sample volumes, organic solvents, and complex and labourious protocols. Microextraction techniques (μExT) that align with the principles of Green Analytical Chemistry have gained attention in recent decades. Depending on the type of μExT used and the target analytes, the amounts of solvents, reagents, and samples used can be reduced by up to ten times or more. Often, the extraction time is also shortened by several orders of magnitude, labware requirements are much lower, and the analytical hardware can be simplified without compromising acceptable analytical performance. Notably, this includes the substitution of expensive LC-MS configurations with LC-UV or FLR cheaper equipment and detection systems. Greener solvents, such as ionic liquids (IL), supramolecular solvents (SUPRAS), and deep eutectic solvents (DES), have also been reported, further contributing to the development of more sustainable and environmentally friendly antibiotic extraction and analytical procedures. The AGREE tool metrics shows that substitution of conventional extraction approaches with μExT enables a greener profile for any methodology developed to analyse antibiotics in different food and environmental samples. This article provides a detailed overview of the advantages of using different μExT to monitor antibiotic usage in the food industry and environment and discusses the challenges and opportunities in this field.

1. Introduction

Antibiotics have been in development for more than 80 years since Fleming first discovered penicillin in 1928. After penicillin, it was time for the others to use natural, semi-synthetic, and synthetic antibiotics. Even so, Fleming anticipated that if misused, antibiotics could potentially lead to the development of antibiotic resistance over time. Antibiotics are relatively inexpensive and are widely used to prevent and treat infections in humans and animals. Among the wide range of antibiotics, the World Health Organization (WHO) classifies fluoroquinolones, third- and fourth-generation cephalosporins, macrolides, glycopeptides, and polymyxins, as "highest priority critically important"

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antibiotics for human medicine because of the limited availability of alternatives for the treatment of bacterial infections. These antibiotics are the preferred treatment options for serious human infections [1]. Although antibiotics are essential for treating and preventing infections in humans, they are widely used in food-producing animals and can serve as a reservoir for antibiotic-resistant bacteria [1]. They are used in subtherapeutic doses in animal feed as growth promoters, as feed to control the reproductive cycle and breeding performance in broilers, pigs, and cattle, and as prophylactic agents [2]. Consequently, large amounts of antibiotics are used annually in animal agriculture and aquaculture worldwide, and their misuse results in lasting side effects to human and environmental health. The use of antibiotics in animals may result in the formation of antibiotic residues in food items such as meat, chicken, egg, milk, honey, and fish [3]. A summary of the most commonly used antibiotics and their applications is shown in Fig. 1. Residues of these drugs can cause various toxic effects in humans, including allergies, toxicity to different organs, reproductive disorders, and carcinogenesis [3]. The use of natural fertilisers can also pose a risk to the environment owing to antibiotic contamination when applied to the soil because antibiotics can then enter aquatic and terrestrial environments and remain as persistent organic pollutants (POPs) [4]. Remarkably, different studies clearly show the lack of a harmonised approach to monitoring antibiotic use in animal species and assessing resistance using the same methodology. In addition, there is no long-term quantitative data on the amount of antibiotics used in different animal species [1].

The quantification of antibiotics and their metabolites in environmental and food samples can be challenging owing to the complexity of the samples. Often, such analysis is only possible through the targeted analysis of compounds for which reference standards are available or can be easily synthesised; therefore, it is limited to a few already known compounds. Therefore, the role of sample preparation in the analytical layout used for monitoring is crucial [5]. Effective sample preparation is essential in analytical chemistry, especially for complex matrices such as biological and environmental samples. The main challenge is to recover the target analytes in a form that allows accurate determination with high sensitivity and specificity [6].

The goal of this article is to provide an overview of the advancements that μExT has facilitated to the monitoring of antibiotic use in the food chain and environment. This is a comparative analysis between selected examples reported in the literature since 2018 and equivalent applications using conventional extraction approaches and will focus, among other factors, on the limitations of the methodologies employed, analysis costs, and their environmental impact. In addition, the challenges and prospects of this field of research are discussed. In this sense, this review aims to go beyond an exhaustive description of the methodologies available for antibiotic monitoring that can be found elsewhere [7, 8].

2. Microextraction techniques (μExT)

Conventional extraction techniques, such as Solid-Phase Extraction (SPE) and liquid-liquid extraction (LLE), have been widely employed in recent decades for sample preconcentration. However, most of these extraction approaches and their variants require large volumes of samples and organic solvents, along with labourious, long, and complex protocols. One of the most commonly used extraction techniques in analytical chemistry, SPE, uses packed extraction sorbent particles to achieve more selective extraction of analytes and cleaning of samples, thereby increasing the extraction capacity [9]. Other techniques have explored the use of unpacked sorbents (dispersive extraction techniques), such as magnetic-SPE (MSPE) [10–12], in which the sorbent and target analytes are recovered through a magnetic field, and Matrix Solid-Phase Dispersion (MSPD) [13], which is widely used for solid samples. In contrast, Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) extraction relies on a salting-out mechanism and does not require sorbents. QuEChERS was first developed by Anastassiades et al. [14] to extract pesticides from foodstuffs. This technique is carried out in two steps: the first step of salting-out extraction promotes equilibrium between the aqueous and organic phases, and the second step removes interferents and improves the extraction of target analytes using dispersive SPE (dSPE) [15].

However, in recent decades, growing concerns about the environment and planet sustainability have boosted the development and improvement of microextraction approaches capable of fulfilling the requirements of Green Analytical Chemistry (GAC). These μExT have been developed to reduce the amount of solvents, reagents, and samples used, thereby achieving a more sustainable and environmentally friendly extraction and analytical procedure. Most μExT are based on the same principles as conventional extraction techniques, primarily LLE

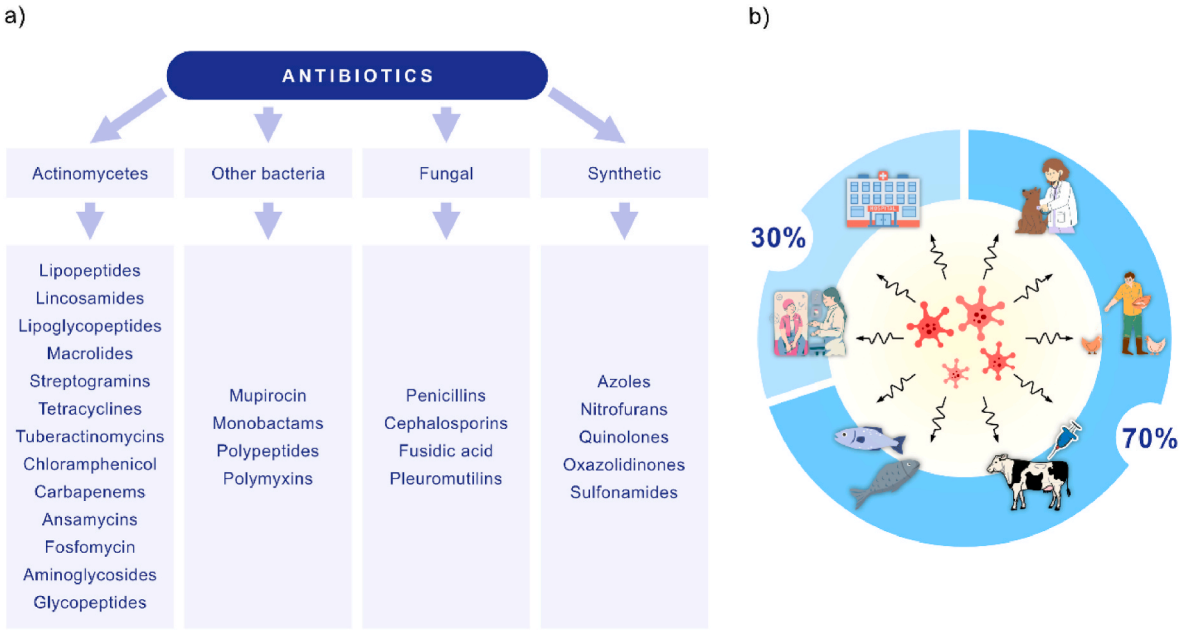

Figure 1. Main classes and antibiotics currently used (A) and their applications (B).

and SPE, but with a higher analytical performance. For instance, liquid–liquid microextraction (LLME) has been developed over conventional LLE, with the main advantage being the drastic reduction in the volume of solvent used (from mL to μL, reviewed in Ref. [16]). Depending on how the contact between the sample matrix and the extraction solvent occurs, there are three different variants of LLME: dispersive LLME (dLLME), hollow Fiber-LLME (HF-LLME), and Single Drop Microextraction (SDME) [17]. A schematic of the general dLLME procedure is shown in Fig. 2. In addition, the type of solvent used in dLLME has also evolved to reduce the toxicity and environmental impact associated with the use of conventional organic solvents. Accordingly, in recent years, ionic liquids (IL), supramolecular solvents (SUPRAS), or deep eutectic solvents (DES) have been reported as "*green*" solvents due to several ecological characteristics they possess, such as high reaction efficiency, thermal stability for reuse and ability to easily resolve organic compounds [18–20]. Natural deep eutectic solvents (NADES) obtained from natural components produced by cell metabolism are highly promising for many applications [20].

The miniaturised solventless extraction technique introduced by Pawliszyn and Arthur in 1990 [21], known as Solid-Phase Microextraction (SPME), is one of the most successful μExT. SPME is based on the adsorption of volatile analytes from an aqueous sample through a fused silica fibre, followed by thermal desorption on a gas chromatographic column (Fig. 2). With the development of this technique, several advantages have been achieved, such as a reduction in the time required for sample treatment, the amount of adsorbent used, and elimination of the use of solvents in the case of volatile analytes [21]. Other miniaturised techniques include pipette-tip SPE (PT-SPE), microextraction using a packed sorbent (MEPS and its variant μSPEed), and miniaturised MSPD. PT-SPE is based on the use of tips containing the sorbent inside using a micropipette for sample aspiration and dispensing. Unlike PT-SPE, in MEPS and μSPEed, sorbent particles are tightly packed inside a small reservoir, and the liquid sample is withdrawn using manual, semi-automated, or fully automated platforms (reviewed in Ref. [22]). Although the experimental procedures for MEPS and μSPEed are very similar, there are important differences. The most significant difference is the particle size of the sorbent (50–60 μm in MEPS, while in μSPEed, it was <3 μm, which increased the surface area of the sorbent particle, increasing the adsorption capacity) and the flow direction (a bidirectional channel in MEPS, while μSPEed is unidirectional, allowing higher pressures to be reached, also favouring the extraction yield) [22,23]. Finally, MEPS cartridges are screwed into syringes, whereas μSPEed adopts a simple plug-and-play design, which allows easy substitution and utilisation in automated platforms. Thus, μSPEed substantially improves MEPS performance and range of applications, enabling better extraction yields with higher sensitivity and selectivity [22].

3. Antibiotics microextraction from food samples

The determination of antibiotics in food samples is of great interest to control the quality of food consumed by humans and prevent toxic effects in susceptible consumers. Furthermore, it is essential to monitor the overuse of antibiotics and their role in the development of bacterial resistance in the food chain and environment. As mentioned in the previous section, μExT have been proposed as eco-friendly alternatives to conventional extraction methods. According to the literature published since 2018, antibiotics have been widely detected in samples of animal origin owing to their veterinary use. Detailed data from the studies that employed antibiotic microextraction are presented in Supplementary Table 1. Overall, dLLME was the most reported microextraction approach (~40 %), followed by SPME (~20 %), and to a lesser extent, other formats such as vortex-assisted microextraction (VAME) and liquid-phase microextraction (LPME). In addition, in some of these studies, more sustainable and greener solvents, such as IL, DES, or NADES, were used instead of conventional solvents. Among the studies involving the microextraction of antibiotics from food samples, six were selected to critically assess the improvement that microextraction elicited in the overall analytical performance of the analysis of the same antibiotics in comparison with conventional extraction. In addition to the analytical performance, the simplicity of the experimental procedures, recoveries, experimental conditions, and extraction times were addressed to verify whether the greener profiles coincided with the most recent microextraction approaches proposed in the literature for antibiotic extraction from foodstuffs. This evaluation was supported by an analytical eco-scale assessment and an analytical GREEnness calculator [24], which was grounded in the 12 principles of

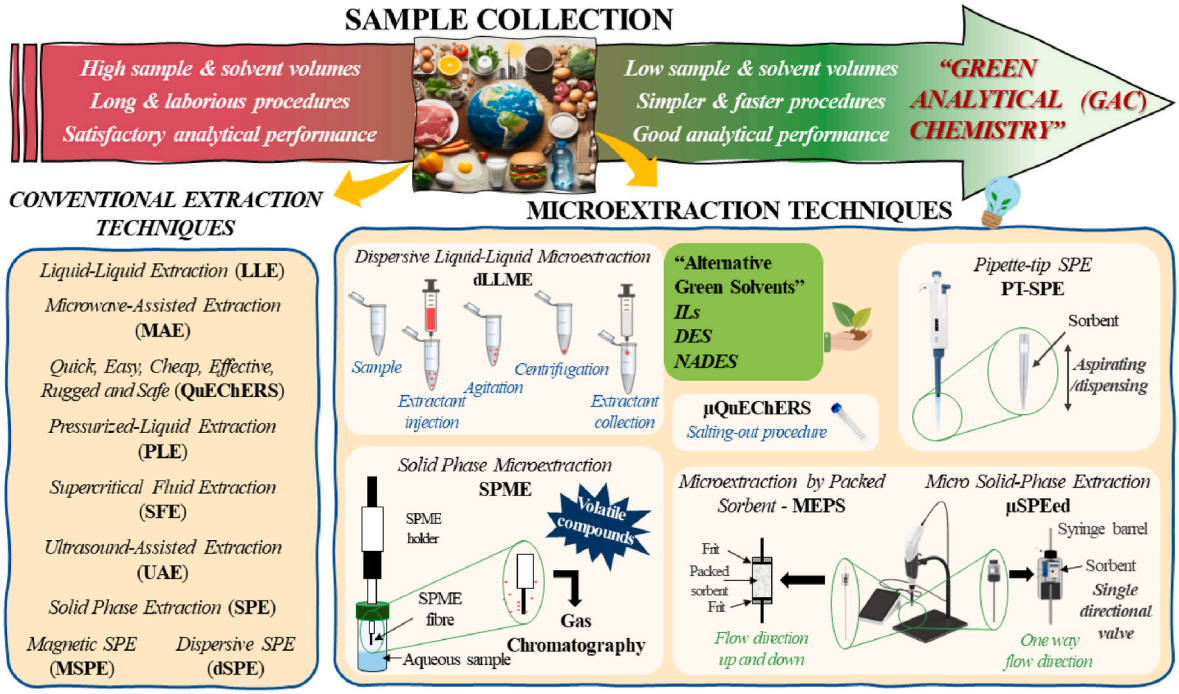

Fig. 2. Schematic representation of the commonly used μExT.

green analytical chemistry and applied to all methods listed in Table 1.

Soares Maciel et al. [25] employed a semiautomatic MEPS to extract tetracyclines from milk samples, considerably simplifying the experimental procedure in terms of time, solvents and glassware usage and user intervention by comparison with, for instance, the conventional SPE approach previously used by De Ruyck and De Ridder [26]. Using the same sample volume and similar LC-MS/MS instrumentation, the MEPS approach allowed a remarkable improvement in the analytical performance for the analysis of the same target analytes over the SPE method (Table 1). The improved efficiency and environmentally friendly nature of the extraction procedures are reinforced by the outcomes of the eco-scale assessment and AGREE tool analysis [24]. Another remarkable improvement enhanced by microextraction is the extraction of tetracyclines from honey using hollow-fibre liquid-phase microextraction (HF-LPME) [27]. This approach avoids the use of any sorbent and fewer solvents than SPE [28] while determining the same antibiotics in honey samples with good analytical performance. Again, this performance was corroborated by the green assessment tools used in this review (Table 1).

Chloramphenicol (CAP) is another antibiotic often found in honey. To improve its assessment, Campone et al. [29] and Shaaban [30] proposed methodologies employing liquid-liquid microextraction assisted by ultrasound (UA-dLLME) and Natural Deep Eutectic Solvents (NADES). Both procedures are simple and allow a significant decrease in the solvent volume (from mL to μL) and sample amounts when compared with other studies previously reported for the same purpose. For instance, Verzegnassi et al. [31] proposed an SPE extraction procedure using large solvent volumes (15 mL of sodium acetate to dissolve the sample, 4 mL of MeOH or HCl for cartridge conditioning) and twice the sample mass (2 g). As shown in Table 1, the analytical performances obtained using UA-dLLME and SPE are very similar, and are lower when NADES is used to substitute the organic solvent in the dLLME method [30]. However, it should be considered that the analytical platform used in this case was UHPLC-UV, which limits the analytical performance of the method described in comparison with the LC-MS/MS approach followed in other reports used for comparison [29,31]. Finally, it is worth mentioning that the use of NADES improved the recovery of the target analytes reported for the UA-dLLME method [29], and the greener profile of this approach was much higher than that obtained using the conventional extraction approach (Table 1).

Nasir et al. detected four sulfonamides in milk and chicken meat using a fast and simple sample pretreatment method based on a magnetic process combined with SPME (M-SPME) and HPLC-DAD analysis [32]. This methodology yielded good analytical performance with much better detection limits than those of the SPE-LC-ESI-MS approach reported by Koesukwiwat et al. [33] (Table 1). Beyond the obvious advantage of using a simpler and cheaper analytical configuration, the analysis time and solvent requirements are considerably lower in the microextraction methodology. These benefits are reflected in the substantial differences observed between the two techniques in terms of green assessment.

β-lactams, notably penicillin derivatives, are widely used to control bacterial infection in dairy cattle. Therefore, the development of methodologies for assessing their residues in foodstuffs is highly relevant. With this aim, Sahebi et al. [34] proposed a methodology involving a μSPE procedure followed by UHPLC-MS/MS to extract and analyse five β-lactam residues from milk samples. The authors customised ionic liquid-modified magnetic nanoparticles (MNPs) that were used as a recoverable dispersive sorbent, which enhanced the analytical performance by several orders of magnitude compared to the methodology proposed by Karageorgou et al. [35] using a US-assisted SPE and QuEChERS in a matrix solid-phase dispersion (MSPD) format. Once again, the experimental layout using the μSPE methodology is considerably simpler and faster than that of its SPE counterpart, despite exhibiting a less pronounced variation in terms of the evaluation of greenness.

Overall, the eco-scores of the methodologies presented in Table 1 involving microextraction are >80, indicating that these methods represent excellent or acceptable green analysis profiles [24]. The most environmentally friendly methods for antibiotic analysis are M-SPME/HPLC-DAD and μSPE-UHPLC/MS/MS, both of which employ nanoparticles for microextraction. However, these results differed according to the AGREE tool used, which may be due to the more challenging evaluation of aspects from a green-chemistry perspective. Regarding the acceptable green evaluation for conventional extractions, no method is ideal for green analysis on an ecological scale. Furthermore, in general, they have lower total scores than the μExT. A direct comparison of the methodologies employing SPE and a μSPE equivalent procedure shows an increase of more than 20 % in the greener profile because of the use of μExT instead of a conventional extraction procedure. Despite these analytical considerations, the methodologies reported were able to detect antibiotics at different levels, ranging from concentrations below the MRL to 75 μg kg^{-1} (Table 1). For example, CAP was detected in several honey samples (5 out of 66 [29] and 95 % of the samples [36]), corresponding mostly to imported honey. This clearly shows the importance of monitoring the presence of antibiotic residues in food samples, particularly when they are produced in countries where such controls may be more relaxed.

4. Application in environmental samples

The development of efficient extraction procedures for the analysis of antibiotics in environmental samples is crucial for their prompt detection and control, avoiding or mitigating the contamination of the surrounding ecosystems, and preventing the disruption of important food chains (Supplementary Table 2).

Recently, the use of DES has attracted the attention of researchers because they are considered an environmentally friendly alternative to conventional organic solvents owing to their non-flammability, negligible vapour pressure, miscibility with other solvents, and high thermal stability. LLME using DES and the additional application of magnetic forces have been reported to be effective methods for detecting fluoroquinolones (FQ) in surface water [37]. Moreover, the proposed methodology is very fast and requires only 10 μL DES [37]. Yıldırım et al. [38] proposed an automated Lab-In-Syringe (LIS) SDME method using NADES. This is a fully automated method, characterised by the use of a small amount of solvent (60 μL) [38] which has a great potential for adoption by other laboratories as soon a commercial solution may be available.

Shahriman et al. [39] chose thin-film microextraction (TFME) using p-Poly-(MMA-IL) (paper-based polymeric ionic liquid) as the coating material to overcome the disadvantages of conventional methods, such as SPE, Stir Bar Sorptive Extraction (SBSE), and SPME [40–42]. Cellulose filter paper exhibits excellent properties, low cost, and good resistance to various pH values. By using a thin flat membrane and increasing the surface-to-volume ratio, the extraction time can be reduced [39]. Table 2 provides a detailed overview of the proposed methodology.

The use of environmentally friendly μExT has a positive effect on the sensitivity and accuracy of antibiotic detection. The highest sensitivity (LOD) achieved in recent years was 1 fg/L using a solvent-free enrichment strategy based on bubbling solid-phase microextraction coupled with mass spectrometry to analyse 16 polycyclic aromatic hydrocarbons and seven antibiotics in environmental water samples [43]. Such accurate extraction techniques allow for appropriate sample preparation of complex matrices. Furthermore, such techniques are characterised by good environmental performance, low sample size, and solvent consumption, and are simpler and faster than the conventional methods. The most economical and shortest microextraction time (8 min) was recorded for LLME [37]. For SPE, additional sample preparation steps and analytical equipment are required, which increases the sample preparation process and cost of analysis. Antos et al. [42], for instance, analysed water samples taken from a river using SPE. This required a

Table 1
Selected examples of antibiotic μExT recently reported in the literature and their comparison with conventional approaches.

Antibiotic	Sample (amount)	Extraction technique/ extraction time (min)	Analytical approach/ analysis time (min)	Analytical performance		Amounts reported (μg L^{-1})	Analytical eco-scale assessment/ AGREE tool	Ref.
				LOD/LOQ (μg L^{-1})	Recovery (%)			
Tetracyclines (CTC, TC, OTC & DOX)	Milk (5 mL)	**MEPS:** Sil sorbent conditioning (8 × MeOH, 500 μL + 2 × Mcllvaine buffer + EDTA); spiked sample loading (6 × 1 mL); washing (2 × Mcllvaine buffer + EDTA, 3 × air drying); elution (6 × MeOH; N_2 drying); resuspension 100 μL H_2O/10	**HPLC-MS/MS:** BEH C_8, 40 °C, 0.35 mL min^{-1} ACN (A), 0.1 % HCOOH (B); Source 150 °C/8	0.03–0.21/ 0.05–0.69	102.1–107.7	<MRL	90–100/0.51	[25]
Tetracyclines (OTC, 4-epi-OTC, TC, 4-epi-TC, CTC, 4-epi-CTC & DC)	Milk (5 mL)	Sample precipitation (10 mL 20 % (w/v) TCA; 5 min shaking; 10 min centrifugation; supernatant filtration), **OASIS HLB SPE** column conditioning (4 mL MeOH washing, 4 mL H_2O & 4 mL TCA 20 %); 3 mL MeOH elution; N_2 drying; 1 mL elution (0.1 % formic acid + 25 % of MeOH)/20	**LC-MS/MS:** Alltima C_{18}, 25 °C, 0.25 mL min^{-1}, 0.1 % HCOOH, (v/v, A), MeOH/ACN (70/30, v/v + 0.1 % HCOOH, v/v - B), Source - 130 °C/20	5/29.4	93.5–99.0		54–100/0.36	[26]
Tetracyclines (TTC, CTC, DOX, OXY, MC)	Honey (3 mL)	Sample dilution (1:5, w/v) with 0.05 mol L^{-1} Na_2HPO_4 (pH 9.5); **HF-LPME**: 15 mL spiked sample, acceptor phase: 0.1 mol L^{-1} H_3PO_4, 1 mol L^{-1} NaCl (pH 1.0); donor phase: 0.05 mol L^{-1} Na_2HPO_4 (pH 9.5); 700 rpm agitation speed/ 45	**LC-Q-TOF/MS:** Shim-pack C_{18} column, 40 °C, 0.4 mL min^{-1} 0.1 % HCOOH (v/v – A), ACN + 0.1 % HCOOH (v/v - B); Source: 250 °C/5	0.09/0.26 μg kg^{-1}	81.2–108.2		90–100/0.65	[27]
Tetracyclines (TC, OTC, CTC, DC, MC & MTC)	Honey (3 g)	sample + 6 mL buffer (pH 4.0) + 10 min stirring; **Discovery DSC-phenyl SPE** (500 mg) cartridge: 5 mL ACN & 5 mL oxalic acid activation; 5 mL Na_2EDTA conditioning; 5 mL 10 % (v/v) MeOH/ethyl acetate elution; drying; 0.5 mL oxalic acid resuspension	**LC-PDA**/25	15–30 ng g^{-1}	92.1–96.1	n.d.	64–100/0.48	[28]
CAP	Honey (1 g)	**UA-dLLME**: spiked sample + 5 mL H_2O, 1 h stirring, 800 μL ACN + 300 μL $CHCl_3$; shaken, 2 min US bath; 5 min centrifugation; extraction solvent ($CHCl_3$) drying; reconstitution: 100 μL MeOH 30 % (v/v)	**UHPLC-MS/MS**: Kinetex C_{18}, 30 °C; 0.3 mL min^{-1} H_2O (A) + MeOH (B), source T 400 °C/7	0.0115/ 0.0364 μg kg^{-1}	52.0–60.0	n.d.–1.62 ng g^{-1}	87–100/0.48	[29]
CAP	Honey (1 g)	**dLLME with NADES**: sample + 5 mL H_2O; vortex; filter; spike + 0.4 g NaCl; vortex; 100 μL NADES (menthol:AcOH, 1:1); 1 min vortex; 10 min centrifugation; 500 μL EtOH added to the upper layer (NADES); filtration/20	**UPLC-UV:** Acquity BEH C_{18}, 40 °C, 0.5 mL min^{-1}, H_2O:EtOH (80:20, v/v)/4.5	0.20/0.60 mg kg^{-1}	98.8%–101.5		86–100/0.55	[30]
CAP	Honey (2 g)	**SPE-LL Partitioning**: Sample + 15 mL Sodium Acetate (0.1 M); **OASIS HBL SPE** cartridges; 2 mL MeOH elution; evaporation, 0.4 mL buffer resuspension + 0.6 mL ACN: DCM (4:1, v/v)/10	**LC-MS/MS**/10	0.012/ 0.021 μg kg^{-1}			57–100/0.32	[31]
Sulfonamides (SDZ, SMM, SMX, SMZ)	milk (10 mL); chicken meat (2 g)	Pretreatment: (a) 10 mL milk + 4 mL 15 % TCA; 30 s vortex; (b) 2.0 g chicken + 10 mL ACN 80 % (v/v); 2 min vortex; 5 min US; 10 min centrifugation; supernatant collection + 10 % NaCl; adjusted to pH 4; **M-SPME**: Pretreated sample + 20 mg TMCNTs; 2 min vortex; sorbent recovery (external	**HPLC-DAD:** Zorbax SB-C_{18}, 25 °C, 1.0 mL min^{-1}; 0.1 % AcOH, pH 4.0 + ACN 75 % (v/ v)/6	milk: 0.11/ 0.56 chicken: 0.43/5.0	milk:81.0–97.8 chicken:80.7–103.4	n.d.–75 μg kg^{-1}	92–100/0.6	[32]

(*continued on next page*)

Table 1 (*continued*)

Antibiotic	Sample (amount)	Extraction technique/ extraction time (min)	Analytical approach/ analysis time (min)	Analytical performance		Amounts reported (μg L^{-1})	Analytical eco-scale assessment/ AGREE tool	Ref.
				LOD/LOQ (μg L^{-1})	Recovery (%)			
		magnet); 200 μL ACN + 1 % NH_4OH; 1 min US; magnet attached to vial, injection/25-40						
Sulfonamides, tetracyclines, and pyrimethamine	Bovine milk (5 g)	20 % TCA precipitation, Mcllvaine buffer, pH 4.5 adjustment, **Oasis HLB SPE** (5 mL MeOH+5 mL H_2O, sample loading, washing (5 mL 5 % MeOH + 5 mL 5 % MeOH with 2 % acetic acid), elution (5 mL MeOH + 5 mL 95 % MeOH with 2 % NH_4OH), evaporate to dryness; 1 mL mobile phase elution; 0.45 μm filtration; injection/50	**LC-ESI-MS**/60	0.5–3	72–106		64–100/0.32	[33]
β-lactams (AMP, AMX, CLX, OXC, PEN G)	Milk (5 g)	**μSPE**: defatted and deproteinized sample, filtration; US-extraction (2.5 min) with magnetic nanoparticles (MNPs); settled MNPs + retained analytes dried (N_2 flow); analytes desorption (MeOH), drying (N_2 flow), reconstitution in the initial mobile phase, filtration; injection/45	**UPLC-MS/MS**/6.5	0.03–0.20/ 0.10–0.68 μg kg^{-1}	87–107		91–100/0.45	[34]
12 β-lactams	Milk (500 μL)	dSPE + UA MSPD (mixed sorbent **QuEChERS + OASIS HLB**): 125 mg QuEChERS salts + 500 μL milk + 500 μL standards mixture; 10 min US; sample transferred to OASIS HLB cartridge; wash (7 % acetone, 5 mL); 1 mL MeOH/2 mL ACN elution; drying (N_2 flow); reconstitution 500 μL H_2O/60	**UPLC-PDA**/37.5	6.3–15.3/ 19.2–46.5 μg kg^{-1}	85.0–115.7	n.d.	84–100/0.41	[35]

4-epi-CTC - 4-epi-chlortetracycline; 4-epi-OTC - 4-epi-oxytetracycline; 4-epi-TC - 4-epi-tetracycline; μExT - microextraction techniques; AcOH - Acetic acid; ACN - acetonitrile; AMOX - amoxicillin; AMP - ampicillin; CAP - chloramphenicol; $CHCl_3$ - chloroform; CLOX - cloxacillin; CTC - chlortetracycline; DAD - diode array detection; dLLME - dispersive liquid-liquid microextraction; DC - doxycycline; DCM – Dichloromethane; EDTA - ethylenediaminetetraacetic acid; EtOH - ethanol; HCOOH - formic acid; G-Sil - graphene supported on silica; H_2O - water; H_3PO_4 - phosphoric acid; HF-LPME - hollow-fibre liquid-phase microextraction; HP-DES - hydrophobic deep eutectic solvent; HPLC - high-performance liquid chromatography; LC-ESI-MS/MS - electrospray ionization tandem mass spectrometry; LL Partitioning - liquid-liquid partitioning; LOD - limit of detection; LOQ - limit of quantification; MC - minocycline; MeOH - methanol; MEPS - microextraction by packed sorbent; MTC - methacycline; M-SPME – magnetic solid-phase microextraction; MNPs - magnetic nanoparticles; MP - mobile phase; MS/MS - tandem mass spectrometry; N_2 - nitrogen; Na_2HPO_4 - sodium dihydrogen phosphate; NaCl - sodium chloride; NADES - natural deep eutectic solvents; n.d. – not detected; NH_4OH - ammonium hydroxide; OTC - oxytetracycline; OXA - oxacillin; PEN. G - Penicillin G; QuEChERS - Quick Easy Cheap Effective Rugged Safe; SAD - sulfanilamide; SCP - sulfachloropyridazine; SDM - sulfadimethoxine; SDZ - sulfadiazine; SFO - solidification of floating organic drop; SGN - sulfaguanidine; SME - sulfameter; SMM - sulfamonomethoxine; SMP - sulfamethoxypyridazine; SMR - sulfamerazine; SMT - sulfamethizole; SMX - sulfamethoxazole; SMZ - sulfamethazine; SPD - sulfapyridine; SPE -solid-phase extraction; SQX - sulfaquinoxaline; STZ - sulfathiazole; TCA - trichloroacetic acid; TMCNTs - thiol-functionalized magnetic carbon nanotubes; TC - tetracycline; UA-dLLME - ultrasound-assisted dispersive liquid-liquid microextraction; UPLC - ultra high-performance liquid chromatographic; US - ultrasound; UV - ultraviolet.

100 ml water sample, which is 10–100 times more than when using microextraction (based on Table 2). The consumption of organic solvents was also significantly higher (12 ml MeOH), which increased the cost of analysis per sample. However, this is still a smaller volume of sample and solvent than that required for most LLE applications, as reported by Akhter et al. [44]. In addition, the extraction time (120 min) was excessively high (Table 2). The *greenness* of the proposed methodologies was evaluated using an analytical eco-scale assessment and an Analytical GREEnness calculator based on the 12 principles of GAC [24, 45]. The total eco-scores of all the methodologies presented in Table 2 involving microextraction were >50, indicating that the reported methods had acceptable green profiles [45]. The most environmentally friendly methods are BE-CNTPSI/MS [43] and DES-LLME/HPLC-FLD [37]. The results differed according to the AGREE tool used, which may be due to the more challenging evaluation of aspects from a green-chemistry perspective. The LIS-automated SDME/HPLC-FLD procedure [38] has the advantages of an automated procedure and smaller sample volume. Regarding the results of conventional extraction, as expected, all methods presented a considerably lower green profile for both *greenness* calculators. This clearly supports the conclusion that μExT contributes to meeting the principles of GAC by simplifying the extraction process and shortening the extraction time, while improving the overall analytical performance. In the selected studies, the antibiotic concentrations ranged from <LOD to 54.41 μg L^{-1}. The intensive use of antibiotics affects living organisms and stimulates the development of antibiotic resistance [46]. For this reason, the improvement that μExT allows to the methodologies currently used to analyse antibiotics in the environment are very relevant.

Table 2
Methodologies for determination of antibiotics in the environment.

Antibiotics	Sample (amount)	Extraction technique/extraction time (min)	Analytical approach/ analysis time (min)	Analytical performance		Amounts reported (μg L^{-1})	Analytical eco-scale assessment/ AGREE tool	Ref.
				LOD/LOQ (μg L^{-1})	Recovery (%)			
FQ	Surfaces water (5 mL)	Pretreatment: 0.45 μm filtration, pH adjustment (pH = 5–7); **DES-LLME:** sample + 10 μL DES, 3 min mixing, addition 5.0 mg collector, shaking 1 min, sorbent recovery (external magnet), addition 50 μL MeOH, 3 min manual stirring, 30 μL in MeOH aspirated into chromatographic syringe/8	**HPLC-FLD**: Supelco C18, 30 °C, 0.70 mL min^{-1}, phosphate buffer solution pH 6.4 (A), MeOH (B)/—	0.01–0.04/ 0.03–0.12	89.0–101.0	<LOD–9.9	85/100 0.55	[37]
FQ, MA, PE, SA, TC	Industrial, wastewater treatment plants, river waters (3 mL)	**FP-TFME**: extraction in the 13 mm filter paper coated with p-Poly-(MMA-IL), 1000 μL MeOH elution/3	**LC-MS/MS**: Accucore Polar Premium LC RP, 40 °C, 0.30 mL min^{-1}, 0.1 % HCOOH (A), MeOH (B)/17.5	0.05–4.52/ 0.15–13.54	79.1–126.8	SA:nd–12.84; TC: nd–13.47; FQ: nd–32.35; PE: nd–15.21; MA: nd–54.41	63/100 0.53	[39]
FQ	Surfaces water, wastewater treatment plant effluent (3 mL)	**LIS-automated SDME**: syringe washed, 2 × 500 μL sample; addition of buffer, sample, and DES/16	**HPLC-FLD:** Luna Omega C18, 1 mL min^{-1}, 1 % HCOOH (A), ACN (B)/20	0.006–0.009/ 0.02–0.03	84.6–119.7	<LOD	73/100 0.63	[38]
FQ	Surface water, tap water (10 mL)	**In situ hDES-SALLME:** DES + sample, briefly shaken and incubated (5 min, 52 °C, no stirring), 1 min horizontal shaking, 2 min centrifugation/8	**HPLC-PDA:** Phenomenex Gemini C18, 1 mL min^{-1}, 1 % CH_3COOH (A), MeOH (B)/20	0.003–0.01/ 3.0–9.0	84.1–113.6	<LOD	75/100 0.48	[47]
BL, SA, TC	Surface water (15 mL)	**BE-CNT**: transferred to BE device (gas flow 0.3 mL/min), extraction on triangular pieces of CNT paper, elution/10	**PSI-MS**: positive ionization, 30 V, 300 °C/25	1.0×10^{-9} –5.0 $\times 10^{-9}$/—	78.5–96.9	TC:nd–0.2; SA:nd–0.05; BL: nd–0.1	85/100< 0.60	[43]
SA	Surface water (10 mL)	in-tip **SPME** (sorbent: 10 mg activated charcoal), conditioning 1 mL MeOH, 1 mL ultrapure H_2O, sample loading, washing 1 mL hexane, elution 0.5 mL 1 % NH_4^+ in MeOH/15	**HPLC-PDA**: Synchronic C18, 25 °C, 1.0 mL min^{-1}, 0.1 % CH_3COOH: ACN (70:30, v/v)/10	0.38–1.14/ 1.14–3.35	82.8–108.7	<LOD	72/100 0.5	[48]
FQ	Tap water, river water (5 mL)	**DLLME-DES**: sample + 200 μL DES, 2 min vortex, 6 min centrifugation, upper phase centrifuged 1 min, addition hydrochloric acid + ethanol, mixed, 2 min vortex, 2 min centrifugation/20	**MECC**: 20 121 kV, 25 °C., 122 nm/22	0.006–0.010/ 0.020–0.030	95.0–104.9	<LOD	73/100 0.49	[49]
SA, TMP	River water (100 mL)	**SPE**: Oasis HLB columns, washing and activation 5 mL MeOH + 5 mL H_2O, sample loading, HCl addition, washing 5 mL H_2O, elution 7 mL MeOH + NH_3/40	**LC-MS/MS**: Hypersil Gold C18 RP, 35 °C, 0.2 mL min^{-1}, 5 mM HCOOH (A), ACN (B)/20	$5.0 \times 10^{-6} - 2.0 \times 10^{-5}$/ 0.0001–0.00025	71.0–82.4	SA: 0.0019–1.073; TMP: 0.0012–0.0111	66/100 0.3	[42]
FQ, BL, MA	River water, soil (500 mL/50g)	**LLE**: Water samples-extraction with chloroform (3 times); Soil samples-soaking in MeOH (500 mL), US 2h, filtration/120	**LC-MS/MS**: ACQUITY UHPLC BEH C18, 0.1 % HCOOH (A), 0.1 % HCOOH in ACN (B)/ 7	1.5/5	–	–	62/100 0.34	[44]

BE-CNT - bubbling extraction carbon nanotube paper absorption; BL- β-lactams; DLLME – dispersive liquid-liquid microextraction; FQ-fluoroquinolones; HPLC-FLD- High performance liquid chromatography with fluorescence detector; HPLC-PDA- High performance liquid chromatography equipped with photodiode array detector; LC-MS- Liquid chromatography–mass spectrometry; MA-macrolides; MECC- micellar electrokinetic capillary chromatography; nd - not detected; PSI-MS - Paper spray ionization mass spectrometry; RP- reverse-phase; PE-penicillin; SA-sulfonamides; TC- tetracyclines; TMP- trimethoprim.

5. Analytical methods and instrumentation

Chromatography, notably LC, is one of the most appropriate techniques for combining separation efficiency with low detection and quantification limits. Over the period 2018–2024, according to the PubMed database, the number of studies combining antibiotic microextraction in the food chain and environment with LC was approximately 100. Surprisingly, the combined LC-MS/MS technique, which has a greater potential in terms of analytical performance, has rarely been reported (only 10 % of the reports). Instead, the most commonly used configuration is LC with UV or PDA detection, and some additional reports have used fluorescence detection (Supplementary Tables 1 and 2). The popularity of UV detection is certainly associated with the lower cost of purchasing and maintaining the HPLC-UV (PDA) configuration in routine analyses compared with MS/MS detection. Considering that UV detection is not as sensitive and selective as MS/MS detection, this wide adoption is only possible because the use of highly efficient and selective sample preparation processes compensates for the lower sensitivity of

the detectors. However, returning to MS/MS detection, the combination of electrospray ionization with HPLC in the multiple reaction monitoring (MRM) mode allows highly sensitive and selective analyses. Another advantage of the LC-MS/MS technique in the MRM mode is that analysis, even with a very large number of analytes, is relatively short, usually not exceeding 10 min. The reason for this is the possibility of neglecting the excellent separation of individual analytes, which is required when using the HPLC-UV technique (PDA and FLD). In addition to the high purchase and maintenance costs, LC-MS/MS systems are more prone to contamination and damage. Therefore, efficient and effective sample purification steps, which are difficult to perform for complex samples such as food and clinical samples, need to be followed [50]. In recent decades, special efforts have been made to develop accurate, precise, rapid, economical, and ecologically friendly sample preparation methods. Moreover, all these features must be combined to guarantee sample integrity and analytical stability. Different μExT coupled with LC have been shown to fulfil these conditions, resulting in fast methodologies for antibiotic analysis with appropriate analytical performance, including good selectivity, precision, linear range, robustness, and sensitivity, although with variable accuracies. Such examples have been previously discussed in Table 1 (food samples) and Table 2 (environmental samples) and include different variants of μSPE, LLME, and SPME techniques. Additional methods, such as pipette tip solid-phase microextraction (PT-SPME), salt-assisted liquid-liquid microextraction (SALLME), multiple monolithic fibre solid-phase microextractions (MMF-SPME), microextraction using deep eutectic solvents, drop flow microextraction, and ionic liquid-assisted dispersive liquid-liquid microextraction, are detailed in the Supplementary material.

6. Challenges and future perspectives

The use of antibiotics extends beyond treatment of human ailments. Regulatory authorities have imposed restrictions on the use of antibiotics in animal and poultry farming; however, their widespread use to boost production has resulted in unregulated discharge into the environment and food chain, contributing to antimicrobial resistance (AMR) [51]. Implementing robust measures in alignment with the *One Health* approach is crucial for curbing the spread of antibiotic resistance [12,51,52]. Recently, nanomaterial-based sensors have shown potential for the simple and fast detection of antibiotics using handheld architectures [12]; however, analysing diverse and complex samples such as food and wastewater with high organic loads requires more efficient and precise methods and accurate analytical instruments [51,52]. Furthermore, it is crucial to characterise the mechanisms that impact the dissemination of antibiotics across the food chain and environment. This knowledge is essential to improve the detection and quantification of antibiotics with higher sensitivity and specificity as well as to identify new contaminants and potential health risks. While conventional extraction methods are still used with LC-MS to identify and quantify antibiotics with high selectivity and sensitivity, μExT with more environmentally friendly profiles are progressively replacing them and enhancing the analytical performance of antibiotic detection and quantification. However, many applications and microextraction formats remain unexplored. Novel solvents such as NADES and SUPRAS offer new promise in this field; however, as with many recent formats of μExT, these methodologies need to be transformed into commercial solutions that can be used across different laboratories in a systematic and comparable way. The microextraction step is crucial for achieving good analytical performance because it ensures that the sample is properly prepared for analysis and that the desired compounds are efficiently extracted from the matrix. For this reason, a well-designed microextraction process can help reduce matrix effects, which can lead to inaccurate results if not properly addressed. Additionally, expensive instruments, standard samples requiring complex pretreatments and long detection times, and skilled personnel to operate instruments and analyse data are obstacles that must be overcome for antibiotic analysis using microextraction. Overall, to effectively manage and regulate the use of antibiotics in samples being analysed, it is essential to establish automated online detection protocols that integrate sample processing with chromatographic separation for known antibiotics, as well as innovative methods for detecting both unknown metabolites and transformation products in a timely and efficient manner [51].

CRediT authorship contribution statement

Joanna Antos: Writing – original draft. **Laura García-Cansino:** Writing – original draft. **María Ángeles García:** Writing – original draft. **Dobrochna Ginter-Kramarczyk:** Writing – original draft. **María Luisa Marina:** Writing – original draft. **Joanna Zembrzuska:** Writing – original draft. **José Sousa Câmara:** Writing – review & editing, Writing – original draft, Conceptualization. **Jorge A.M. Pereira:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

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

Abbreviations:

4-epi-CTC - 4-epi-chlortetracycline; 4-epi-OTC - 4-epi-oxytetracycline; 4-epi-TC - 4-epi-tetracycline; μExT - microextraction techniques; AcOH - Acetic acid; ACN - acetonitrile; AMOX - amoxicillin; AMP - ampicillin; BE-CNTPSI- bubbling extraction carbon nanotube paper absorption; BIN - barrel insert needle; BL- β-lactams; CAP - chloramphenicol; $CHCl_3$ - chloroform; CLOX - cloxacillin; CTC - chlortetracycline; DAD - diode array detection; DC - doxycycline; DCM – Dichloromethane; DES - deep eutectic solvents; dLLME - dispersive liquid-liquid microextraction; dSPE - dispersive SPE; EDTA - ethylenediaminetetraacetic acid; EtOH - ethanol; FQ-fluoroquinolones; HCOOH - formic acid; HPLC-FLD- High performance liquid chromatography with fluorescence detector; HPLC-PDA- High performance liquid chromatography equipped with photodiode array detector; GAC - Green Analytical Chemistry; G-Sil - graphene supported on silica; H_3PO_4 - phosphoric acid; HF-LPME - hollow-fibre liquid-phase microextraction; HP-DES - hydrophobic deep eutectic solvent; HPLC - high-performance liquid chromatography; IL - ionic liquids; LC-ESI-MS/MS - electrospray ionization tandem mass spectrometry; LC-MS- Liquid chromatography–mass spectrometry; LL Partitioning - liquid-liquid partitioning; LLE - liquid extraction; LLME - liquid–liquid microextraction; LOD - limit of detection; LOQ - limit of quantification; MA-macrolides; MC - minocycline; MeOH - methanol; MECC- micellar electrokinetic capillary chromatography; MEPS - microextraction by packed sorbent; MSPD - Matrix Solid-Phase Dispersion; MSPE - magnetic-SPE; MTC - methacycline; MNPs - magnetic nanoparticles; MP - mobile phase; M-SPME – magnetic solid-phase

microextraction; MS/MS - tandem mass spectrometry; N_2 - nitrogen; Na_2HPO_4 - sodium dihydrogen phosphate; NaCl - sodium chloride; NADES - natural deep eutectic solvents; NH_4OH - ammonium hydroxide; OTC - oxytetracycline; OXA - oxacillin; PE-penicillin; PEN. G - Penicillin G; POPs - persistent organic pollutants; PT-SPE - Pipette-Tip; QuEChERS - Quick Easy Cheap Effective Rugged Safe; RP- reverse-phase; SA-sulfonamides; SAD - sulfanilamide; SBSE – Stir Bar Sorptive Extraction; SCP - sulfachloropyridazine; SDM - sulfadimethoxine; SDME - Single Drop Microextraction; SDZ - sulfadiazine; SFO - solidification of floating organic drop; SGN - sulfaguanidine; SME - sulfameter; SMM - sulfamonomethoxine; SMP - sulfamethoxypyridazine; SMR - sulfamerazine; SMT - sulfamethizole; SMX - sulfamethoxazole; SMZ - sulfamethazine; SPD - sulfapyridine; SPE -solid-phase extraction; SPME - Solid-Phase Microextraction; SQX - sulfaquinoxaline; STZ - sulfathiazole; SUPRAS - supramolecular solvents; TCA - trichloroacetic acid; TMCNTs - thiol-functionalized magnetic carbon nanotubes; TFME - thin-film microextraction; TC - tetracycline; TMP- trimethoprim; UA-dLLME - ultrasound-assisted dispersive liquid-liquid microextraction; UHPLC - ultra high-performance liquid chromatographic; US - ultrasound; UV – ultraviolet; VAME - vortex-assisted microextraction; WHO - World Health Organization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trac.2024.118009.

Data availability

No data was used for the research described in the article.

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