An Overview of Different Methods for Aminoglycoside Residue Determination

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Authors’ contributions
This work was carried out in collaboration among all authors. Author SM prepared the data, prepared tables, performed and wrote the first draft of the manuscript. Author BK designed the study, prepared the tables, wrote the first draft and revised the manuscript. Author ZK wrote part of the first draft, and revised the manuscript. Author BSF designed and supervised the study and revising the manuscript. All the authors read and approved the final version of the manuscript.

ABSTRACT
Aminoglycosides (AGs) are chemical substances that exist in the bacteriologic category of traditional antibiotic (AB) therapy. The importance of the determination of AG as has been described in many situations by researchers. Because of the narrow therapeutic ranges of AGs, considerable efforts have been attributed to the analysis of AGs in pharmaceutical preparations, serum, and urine specimens for therapeutic drug monitoring purposes. Residues of ABs in many different cases like environment and human food, causes a major concern, as prolonged exposure to ABs is a serious health hazard, related to both side effects of prolonged use and the risk of developing bacterial resistance to various ABs. The major challenge is finding a sensitive and reliable method to determine AGs in a complex matrix. The microbiological assay was a simple and...
old method for the determination of AGs. Chromatography and spectroscopy methods are the main instrumental methods for analysis that have been employed for these purposes. Biosensor based instrumental systems have been recently used to determine the AG residues in many cases. Each of these methods has its advantages and disadvantages. This review summarizes different ways (microbiological methods, instrumental methods, and biosensor) for the determination of AGs in all cases. Different databases including PubMed, Scopus, and Web of Science with the words of AGs determination and related words for antimicrobial keywords searched without time limitation.

Keywords: Aminoglycoside; antibiotic residues; antibiotic resistance; instrumental method; biosensor; microbiological assay.

1. INTRODUCTION

Aminoglycosides (AGs) are potent, broad-spectrum antibiotics (ABs) that have been used extensively in clinical and consisting of various molecules including gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, and paromomycin [1]. These ABs have been used either alone or as part of combination therapy for the treatment of serious infections caused by aerobic Gram-negative bacteria. They also in combination with other ABs have been used for the treatment of selective Gram-positive infections [2,3]. Additionally, AGs have been used for other infectious diseases such as protozoa (paromomycin), Neisseria gonorrhoea (spectinomycin), and mycobacterial infections (tobramycin, streptomycin, and amikacin) [4,5].

The antibacterial activity of AGs is related to the binding to the aminoacyl site of 16S ribosomal RNA (rRNA) within the 30S ribosomal subunit. They show pronounced advantages such as rapid bactericidal activity, synergistic activities with β-lactams, and other cell wall-active agents. They also have been shown significant post-antibiotic effects, while the persistent suppression of bacterial growth is observed up to 7.5 h after the drug has been cleared. These effects are related to both Gram-negative bacilli and Staphyloccocus aureus, but not other Gram-positive cocci [6,7].

AGs are weakly base compounds with polyatomic nature; they are soluble in water and insoluble in organic solvents, and also stable and
difficult to decompose. They are characterized by two or more amino sugars linked by glycosidic bonds to an aminocyclitol component and the whole structure containing many free hydroxyls and at least two amino groups (structural formulas see Fig. 1) [8,9]. The polycationic nature leads to the poor Oral absorption, poor penetration into the cerebrospinal fluid, bronchial secretions, biliary tree and a rapid renal clearance which concentrate very efficiently within the urine. The polycationic charge may also contribute to the nephrotoxicity of AGs [4,10,11].

Because of the broad-spectrum activities and good therapeutic effect, AGs have been used extensively in veterinary medicine and play an important role in the prevention and treatment of animal diseases and also used as feed additives for growth promotion of animals [12,13]. The residues of AGs in animal edible tissues, which due to improper or over-use, may cause harm to the human, such as ototoxicity and nephrotoxicity and environment [14,15]. The other potential problem with AGs is related to the fact that AGs cannot be completely absorbed by the organism and therefore the unabsorbed ABs will not be filtered into groundwater or surface water which finally leads to environmental water pollution [16]. Additionally, the development of AB resistance in bacteria has direct connections with all of them and the relationship between veterinary use of ABs and antibacterial resistance in humans has been a subject of much concern [17,18]. Hence, accurate determination of the residues of AGs is of huge importance [9,19].

This paper reviews different methods for the determination of AGs in various matrices.

Fig. 1. Chemical structures of the aminoglycoside antibiotics
2. MATERIALS AND METHODS

This review evaluates and compares researches on AGs residues determination in different samples in published literature from PubMed, Scopus, Electronic Journals Library, Global Health Databases, and Google Scholar.

2.1 Amikacin

Amikacin is a semi-synthetic antimicrobial compound that is derived from kanamycin A [20]. Amikacin is particularly effective in many serious diseases caused by Gram-negative bacteria that resistant to other AGs [21].

U+ Babends et al. (1955) compared the agar-well diffusion technique and high-performance liquid chromatography (HPLC)– ultraviolet (UV) detector for the determination of amikacin in human serum. The results of in vivo Analysis were similar to those of microbiological tests [22]. In another instrumental method LC with fluorescence detector could detect amikacin with a limit of detection (LOD) and quantification (LOQ) values of 0.05 and 0.1 μg/mL, respectively [23].

In another study, amikacin in the presence of other AGs in pure form and some pharmaceutical preparations was analyzed by Lanthanide Ion Probe Spectrofluorometry (LIPS). The result of the study showed there was not any significant difference between LIPS and fluorimetric method, whereas LIPS is more useful than fluorimetric in the industry because it has no interaction with other ingredients and is more rapid and simple than fluorimetric method [24]. Another method that has been used in both industry and clinical laboratory is the fluorimetric method. This method can detect kanamycin, neomycin, and tobramycin with LOD of 10.0 ng/mL [25] and fluorescence spectrophotometer to quantify amikacin with LOQ of 400.0 μg/mL, that is a poor method for the determination of amikacin now [26] but in 2019 a specific fluorometric depend on molecularly imprinted polymer on high fluorescent g-C3N4 quantum dots method was developed. The LOD values of this method were lower than the previous one (LOD was 1.2 ng/mL), so this method is a reliable method for clinical monitoring [27].

HPLC with Resonance Rayleigh Scattering (RRS) was used for the detection of amikacin, netilmicin, and gentamicin with very low LOD values. This method is validated because of high sensitivity, simplicity, low cost, and lack of interference and could be used for serum and urine sample analysis in hospitals [28] and Electrospray-Ionization Mass Spectrometry (ESI-MS) also, can be used for clinical monitoring. The linear dynamic ranges of detection for amikacin was 10.0–1000.0 ng/mL [29].

Liquid chromatography with tandem mass spectrometry (LC-MS) (2017) was developed for the determination of amikacin in milk, honey, and pork samples. The LOD and LOQ values were 11.0 μg/kg, 33.0 μg/kg in milk and honey respectively, and 12.0 μg/kg, and 40.0 μg/kg respectively in pork sample [31]. LOQ for liver, kidney, muscle and fish sample were 5.0 μg/kg, 1.0 μg/kg, 1.0 μg/kg, 2.0 μg/kg, respectively [32]. In 2020 the dummy Moleculary Imprinted Solid-Phase Extraction (MSPE) coupling with hydrophilic interaction-HPLC with MS was developed for the determination of every AGs in water sample with the lowest concentration (LOD was 0.006 to 0.6 ng/mL) [33]. Hydrophilic interaction MSPE combined with HILIC–MS/MS was developed for the determination of amikacin in a meat sample with LOD of 2.0 μg/kg and LOQ of 7.3 μg/kg [34].

By the colorimetric method, AGs could be detected in milk or pharmaceutical products with LOD value of 0.999 ng/mL [35]. Amikacin also was detected in human serum, with a molecularly imprinted SPR sensor method (LOD 0.0025 μg/mL and LOQ 0.01 μg/mL). This method is rapid and sensitive for the determination of AGs in therapeutic ranges [36] and in the industry was used for simultaneous determination of netilmicin, tobramycin, lincomycin, kanamycin, and amikacin with LOD lower than 2.2 μM except for lincomycin that is 6.7 μM [37]. The most selective method for the detection of amikacin, gentamicin, and tobramycin are colorimetric methods based on the aggregation of gold nanoparticles (0.999 ng/mL).
Amikacin is an AG that is used in cases of resistance to gentamicin. The biosensor method is a novel method that has been used to a considerable extent to determine the amount of amikacin, but the recent instrumental method has good improvement and they are more sensitive than the biosensor method, therefore, it can be used instead of expensive and difficult methods. Generally, the microbiological assay can be used as an analysis for any laboratory due to its ease of operation and may be able to replace device methods. A comparison of different methods of determination of amikacin residues was illustrated in Table 1.

| Method                      | Description                                      | Matrix                      | LOD    | LOQ    | Additional information                                                                 | Reference |
|-----------------------------|--------------------------------------------------|-----------------------------|--------|--------|----------------------------------------------------------------------------------------|-----------|
| Microbiological / Instrumental | Disk diffusion assays/ HPLC-UV ESI-MS             | Human serum                 | _      | _      |                                                                                        | [22]      |
| Instrumental                | Fluorimetric                                     | Industry and clinical samples | 10.0   | _      | The linear dynamic ranges of detection for amikacin was 10.0–1000.0 ng/mL Selective method for those AGs which contain primary amino groups | [29]      |
| Instrumental                | Fourier-transform infrared derivative spectroscopy | Aqueous sample              | 0.4 mg/mL | _      | A fast and simple method that can be determined amikacin sulfate in pharmaceuticals preparation | [25]      |
| Instrumental                | Fluorescence spectrophotometer                   | _                           | _      | 400.0 µg/mL | Poor method for determination of amikacin in nowadays.                                  | [26]      |
| Instrumental                | HPLC- RRS                                        | Human serum                 | _      | _      | Hasn’t any interference with matrices                                                 | [28]      |
| Instrumental                | HPLC – CAD                                       | In solution                 | 2.0 µg/mL | 5.0 µg/mL | Good for the pharmaceutical industry because prefect in detection and determination of amikacin | [30]      |
| Instrumental                | Strong cation-exchange chromatographic (SCX)- HPLC with chemiluminescence (CL) | Water samples              | 0.7 µg/L | _      |                                                                                        | [38]      |
| Method         | Description                                                                 | Matrix                              | LOD     | LOQ     | Additional information                                                                 | Reference |
|---------------|------------------------------------------------------------------------------|-------------------------------------|---------|---------|----------------------------------------------------------------------------------------|-----------|
| Instrumental  | detection Instrumentation methods combined with HILIC-MS/MS/MS analysis     | Meat sample                         | 2.0 µg/kg | 7.3 µg/kg |                                                                                         | [34]      |
| Instrumental  | LIPS                                                                          | Pure form and some pharmaceutical preparations |         |         |                                                                                         | [24]      |
| Instrumental  | LC-MS/MS                                                                     | Liver, kidney, muscle and fish samples |         |         | Sensitive for the determination of different AGs in the food industry                    | [32]      |
| Instrumental  | LC with MS                                                                   | Honey, milk and pork samples        |         |         | Determine different AGs in honey, milk, and pork                                        | [31]      |
| Instrumental  | LC                                                                            | Dosage Forms and human plasma       | 0.05 µg/mL | 0.1 µg/mL | This method can determine gentamicin and neomycin with a similar result                | [23]      |
| Biosensor     | A copper micro particle-modified carbon fiber microdisk array electrode was fabricated and employed in capillary electrophoresis | Pharmacutical injections below 2.0 mM |         |         | This method determines netilmicin, tobramycin, lincomycin, kanamycin with LOD below 2 mM, and for lincomycin, LOD is 6.7 mM. | [37]      |
| Biosensor     | The colorimetric method based on the aggregation of gold nanoparticles        | Milk and medicine product           | 0.999 ng/mL |         | A sensitive and fast method for the determination of food and clinical analysis         | [35]      |
| Biosensor     | Molecular imprinted SPR nano sensor                                          | Human plasma                        | 0.002 µg/mL | 0.01 µg/mL | Rapid and sensitive methods can make improvements in clinical monitoring in the future. | [36]      |
2.2 Astromicin

HPLC method was used for the determination of astromicin in the is of cefsulodin and piperacillin in human serum. The LOD value was 0.1 µg/mL for astromicin and 0.5 µg/mL for piperacillin and cefsulodin [39]. In another study, the HPLC-evaporative light scattering detector (ELSD) method was employed for easy and fast determination of astromicin. The results showed that LOD and LOQ values were 2.0 µg/mL and 5.0 µg/mL, respectively [40]. Both of these methods can be used for clinical laboratory [39, 40] and there was HPLC method to determine astromicin and other AGs with LOQ 1.58 µg/mL. This method is useful for clinical monitoring in hospital [41].

In 1988, fluorescence polarization immunoassay was developed for the determination of astromicin in the blood sample. The result of the analysis showed it was a good method for clinical monitoring in hospital [42].

Astromycin is a new AG which is mostly measured in blood serum samples by instrumental methods. There is no microbiological assay for this AG, which may be because it is a new AG. A comparison of different methods of determination of astromycin residues is shown in Table 2.

2.3 Gentamicin

Gentamicin has been used extensively to combat both Gram-negative and positive bacterial infections [43, 44].

Barends et al. compared HPLC with UV detector and microbiological assay (S. aureus Alkmaar was used as a microorganism tester) for the determination of gentamicin and tobramycin. The results of the experiment indicated, although they had some small differences, they are interchangeable [45]. Jacques Nouws et al. (1999) developed a microbiological assay to evaluate residual ABs like AGs in milk. For determination of spectinomycin, Bacillus calidolactis was used and for others, AGs like neomycin, kanamycin, gentamycin, dihydro (DH) streptomycin, Bacillus subtilis was employed. The data indicated that this method can determine these AGs in milk under the maximum residue level (MRL) [46].

Felipe Rebello Lourenço et al. studied the agar diffusion method with Staphylococcus epidermidis as a selected microorganism to determine gentamicin in raw material, injectable solution, and dermatological cream with 3 different kinds of design assay (3 x 1, 2x2, and 5 x 1). These three design didn’t show any significant difference and each design was used for a specific condition, for example, the 2 x 2 assay was used for research and both the 5 x 1 and 3 x 1 designs were the most suitable assays for the routine analysis in quality controls in the laboratory [47].

Researchers compared the microbiological method (the organism tested was Staphylococcus for framycetin and B. subtilis for other AGs ABs) with TLC and HPLC-fluorimetric detector in pharmaceutical preparations for determination of gentamicin, tobramycin, sisomicin, diebekacin, framycetin, kanamycin, and netilmicin.

These three methods did not show any significant differences but LOD was 56.0-76.0 ng/mL, 60.0 ng/mL, 60.0 ng/mL, 100.0 ng/mL, 100.0 ng/mL, 60.0 ng/mL, 60.0 ng/mL.

| Method         | Description                  | Matrix     | LOD    | LOQ    | Additional information                                                                 | Reference |
|----------------|-------------------------------|------------|--------|--------|----------------------------------------------------------------------------------------|-----------|
| Instrumental   | HPLC                          | Human serum| –      | 1.58 µg/mL | –                                                                                      | [41]      |
| Instrumental   | HPLC                          | Human serum| –      | –      | –                                                                                      | [39]      |
| Instrumental   | HPLC-ELSD                     | Human serum| 2.0 µg/mL | 5.0 µg/mL | –                                                                                      | [40]      |
| Biosensor      | A fluorescence polarization    | Blood samples| –      | –      | Good for monitoring of astromicin in hospital                                          | [42]      |
respectively for gentamicin, tobramycin, sisomicin, diebekacin, framyctin, kanamycin and netilminic in TLC, and in HPLC was 0.6–1.5 ng/mL, 1.1 ng/mL, 0.9 ng/mL, 0.7 ng/mL, 0.2–1.8 ng/mL and 0.8 ng/mL respectively; therefore they concluded HPLC is the best method for determination of AGs in pharmaceutical preparations but chemical method (HPLC- fluorimetric detector) had little difference in sensitivity in comparison with radioimmunoassay (radioimmunoassay is more sensitive than chemical assay) [48,49].

LC-MS method determined the lowest concentration of gentamycin even the enzyme-linked immunosorbent assay (ELISA) method in food products. LOD and LOQ were 6.0 µg/kg, 20.0 µg/kg respectively in milk and pork samples, and 4.0 µg/kg, 13.0 µg/kg in honey, respectively [31]. Also, LC-MS/MS was employed for the determination of gentamicin C1, C1a, and C2 with LOQ 30.0 µg/kg in food samples and clinical monitoring [32]. LC-MS method developed (2010) for the determination of AGs in seafood with LOD of 0.0017–0.0100 mg/kg and LOQ of 0.0056–0.0333 mg/kg. The great advantage of this method is the simultaneous determination of neomycin and gentamicin in seafood [50]. In 2020 LC-MS used to detect gentamicin C1, C1a, and C2 with LOQ 0.01 mg/kg in bovine muscle, bovine liver, milk, chicken egg, fish, and shrimp samples [51]. The advantage of this method is the simultaneous determination of different AGs. HILIC–MS/MS method was employed for bovine muscle with LOQ of 23.0 µg/kg [52]. LC-MS determines residual gentamicin C1a/C1/C2/C2a in the kidney and honey. LOQ value for gentamicin C1 was 8.0 µg/kg in honey and 94.0 µg/kg in the kidney, for gentamicin C1a was 12.0 µg/kg in honey and 59.0 µg/kg in kidney and for gentamicin, C2/C2a was 24.0 µg/kg in honey and 70.0 µg/kg in kidney sample [53].

Residual of gentamicin in wastewater was determined by LC–ES-tandem MS method with LOQ of 0.20 1/µg [44]. Resonance Rayleigh Scattering was developed for the determination of gentamicin. The LOD was 6.1–8.1 ng/mL. This method is used for both quality control and clinical laboratories [54].

Capillary electrophoresis tandem mass spectrometry and extraction with molecularly imprinted polymers (CE-MS/MS) device, can detect different types of gentamicin in honey. LOD for gentamicin C1a, gentamicin C1, and gentamicin C2 were 20.7 µg/kg, 28.5 µg/kg and 24.0 µg/kg, respectively and LOQ were 69.1 µg/kg, 94.8 µg/kg, 80.1 µg/kg, respectively [55]. Also, in 2020, Electro spray-Ionization Mass Spectrometry (ESI-MS) and a Flow-Injection Analysis Selected-Ion Monitoring (FIA-SIM) was developed for rapid determination and monitoring of gentamicin, tobramycin, and amikacin, respectively. The linear dynamic ranges of detection for both methods were 10.0–1000.0 ng/mL [29].

In 1997, HPTLC with fluorodensitometric was used to determine gentamicin in plasma and urine. The results indicated that the method was a reliable and valuable technique for quantitative analysis of the bulk drug gentamicin and gentamicin from urine and plasma samples [56].

Capillary electrophoresis electrochemical (CE-EC) was developed for the determination of gentamicin in pharmaceutical preparations with LOD of 9.1 µM [57].

In another article, the ELISA method was good for the determination of gentamicin in milk and kidney with LOD < 0.01 mg/L <0.05 mg/kg, respectively (Also neomycin, streptomycin, and DH streptomycin can be detected by this method in milk and kidney). In comparison with explained methods, the ELISA method has a long distance from MRLs [58].

The determination of gentamicin via enzyme immunoassay method in pharmaceuticals and food was done in 2002. The LOD of this method was 1×10^{-9} mg/ml and gentamicin could be detected in less than 20 minutes [59]. In another study, gentamicin nanoparticle was employed with the LOD value of 0.35 ng/ml. The selectivity and sensitivity of the method were remarkably improved for gentamicin in pharmaceuticals and food [35].

Gentamicin is one of the most widely used AGs for the treatment of infectious diseases. Most reports to determine the amount of gentamicin are the instrumental method, which is both faster than the microbiological assay and less expensive than the biosensor method. In some cases, the microbiological assay can replace the instrumental method with the same sensitivity. A comparison of different methods of gentamicin residues determination is shown in Table 3.
| Method                  | Description                                           | Matrix                  | LOD        | LOQ        | Additional information                                                                 | Reference |
|------------------------|-------------------------------------------------------|-------------------------|------------|------------|-----------------------------------------------------------------------------------------|-----------|
| Microbiological        | Microbiological assay comparison TLC and HPLC         | Pharmaceutical preparations | –          | –          | –                                                                                       | [48, 49]  |
| Microbiological        | Multiple systems                                      | Raw milk                | 25.0 µg   | 1 µg       | –                                                                                       | [46]      |
| Microbiological        | Agar diffusion                                        | Raw material, injectable solution, and dermatologic cream | –          | –          | –                                                                                       | [47]      |
| Microbiological/       | Agar-well diffusion/HPLC                              | Honey sample            | –          | –          | Good strategy for determine three kind of gentamicin (gentamicin C1a/C2/C1) in honey    | [55]      |
| Instrumental           | CE-MS                                                 | Honey sample            | –          | –          | –                                                                                       |           |
| Instrumental           | CE-EC                                                 | Pharmaceutical preparations | 9.1 µM    | –          | –                                                                                       | [57]      |
| Instrumental           | ESI-MS                                                | Human serum             | –          | –          | The linear dynamic ranges of detection were 10–1000 ng/mL                                | [29]      |
| Instrumental           | HPLC with Fluorodensitometric                         | Plasma and urine        | 20.0 ng   | –          | 40.0–200.0 ng Because of the selectivity and cheapness of this method can be used for routine analysis of plasma and urine. | [56]      |
| Instrumental           | HILIC-MS/MS                                           | Bovine muscle           | –          | 23.0 µg/kg | Suitable for industry                                                                   | [52]      |
| Instrumental           | FIA-SIM                                               | –                       | –          | –          | The linear dynamic ranges of detection were 10–1000 ng/mL                                | [29]      |
| Instrumental           | LC–mass spectrometry                                  | Seafood                 | 0.0017/0.0100 0 mg/kg | 0.0056–0.0333 mg/kg | –                                                                                       | [50]      |
| Instrumental           | LC–ES-tandem MS                                       | Wastewater              | –          | 0.20 µg    | This method can be used for aqueous environmental samples                               | [44]      |
| Method                  | Description                                      | Matrix                              | LOD       | LOQ       | Additional information                      | Reference |
|------------------------|--------------------------------------------------|-------------------------------------|-----------|-----------|---------------------------------------------|-----------|
| Instrumental           | LC-MS/MS                                         | Liver, muscle, fish samples         | _         | _         | Gentamic in C1/C1a/C2/2a/2b: 30.0 µg/kg    | [32]      |
| Instrumental           | LC with tandem mass spectrometry                 | Honey and pork samples              | _         | _         |                                             | [31]      |
| Instrumental           | LC-MS                                            | Kidney and honey samples            | _         | _         |                                             | [53]      |
| Instrumental           | LIPS                                             | Pure form and some pharmaceutical preparations | _         | _         | There isn’t a significant difference between LIPS and fluorimetric | [24]      |
| Instrumental           | Phenylboronic acid solid-phase extraction and LC-MS | Bovine muscle, bovine liver, milk, chicken egg, fish and shrimp samples | _         | 0.01 mg/kg |                                             | [51]      |
| Instrumental           | RRS method                                       |                                    | 6.1–8.1 ng/mL | _         |                                             | [54]      |
| Biosensor              | Colorimetric method base on the aggregation of gold nanoparticles | Pharmaceutic als and food samples | 0.354 ng/mL | _         | For determination of AGs in food and clinical analysis | [35]      |
| Biosensor              | ELSA                                             | Milk and kidney samples             | _         | _         |                                             | [58]      |
| Biosensor              | Enzyme immunoassay with the use of amperometric enzyme immunosensor | Pharmaceutic als and food samples | 10^10 mg/mL | _         | This method good for evaluation of residual of gentamicin in food and industry | [59]      |

### 2.4 Isepamicin

The general method for the determination of isepamicin is the HPLC method with different detectors. In 1997, researchers compared microbiological, instrumental method (HPLC) and biosensor method (Radioimmunoassay) for the determination of isepamicin in human serum. The LOQ was 0.1 µg/ml for HPLC and radioimmunoassay and 0.5µg/ml for microbiological assay. The result of regression analysis shows a good relationship between these methods and they have not significant differences [60].

In 2001, Vogel et al. developed HPLC-ELSD for the determination of isepamicin in solution. The results indicated that this method was a simple and rapid assay method for the determination of isepamicin with no
derivatization problems but also LOQ was sufficient enough for the quantitative assay of isepamicin sulfate and d-isepamicin [61]. In 1990, researchers used post-column derivatization with o-phthalaldehyde for determination of isepamicin with a spectrofluorometric detector that causes many problems including the creation of degradation products. The LOD value was 100 ng/ml for isepamicin in plasma and 50 ng/ml in urine and dialysate [62]. Both explained assay methods can be used for the measurement of other AGs like gentamicin, kanamycin, etc [61,62].

Also, isepamicin was determined in human serum and rat plasma with HPLC-Fluorescence detector and HPLC-RRS respectively. The results of these methods show that they can be used instead of each other [63,64]. An instrumental method has been the main method for measuring isepamicin but for simplicity in measuring this AG, it is better to use microbiological assay. With the increasing use of isepamicin, a variety of biosensor methods may be developed. A comparison of different methods of isepamicin residues determination is illustrated in Table 4.

| Method                        | Description                          | Matrix           | LOD      | LOQ       | Additional Information | Reference |
|-------------------------------|--------------------------------------|------------------|----------|-----------|-------------------------|-----------|
| Microbiological/Instrumental/Biosensor | Microbiological assay/HPLC/radioimmunoassay | Human serum     | –        | 0.1 µg/ml for HPLC and radioimmunoassay and 0.5 µg/ml for microbiological assay | –         | [60]                   |
| Instrumental                  | HPLC                                 | Urine and plasma samples | –        | In plasma: 100.0 ng/mL and in urine and dialysate 50.0 ng/mL | Clinical monitoring of isepamicin, tobramycin, kanamycin, netilmicin, and gentamicin | [62]       |
| Instrumental                  | HPLC-ELSD                            | –                | –        | –         | –                       | [61]       |
| Instrumental                  | HPLC-fluorescence detector           | Human serum     | –        | 0.5 µg/ml | Useful for clinical monitoring. | [63]       |
| Instrumental                  | HPLC with RRS                        | Rat plasma      | –        | –         | A good method for clinical monitoring | [64]       |
2.5 Kanamycin

Multiple systems were used to determine kanamycin with LOD of 150.0 1/µg [46]. Copper-one capillary electrodes (OCE) provided µM detection limits, in pharmaceutical preparations (LOD=2.2 µM). Capillary electrophoresis with an ion laser-induced fluorescence detector (CE-LIF) was developed in human serum with LOD of 14.4 nM [65].

HILIC–MS/MS method (2016) was used to detect kanamycin in bovine muscle with LOQ of 56.0 µg/kg [52] also, in 2020 hydrophilic interaction MSPE combined with HILIC–MS/MS was developed for the determination of kanamycin with good sensitivity and selectivity in meat sample. LOD and LOQ values were 0.6 µg/kg and 2.4 µg/kg, respectively [34].

LC-MS was used for the detection of kanamycin in milk, honey, and pork (2017). LOD and LOQ values were 11.0 µg/kg, 36.0 µg/kg in milk, 10.0 µg/kg, 34.0 µg/kg in honey, and 11.0 µg/kg, 36.0 µg/kg in pork, respectively [31]. Also, LC-MS determined kanamycin A with LOQ of 41.0 µg/kg in honey and 85.0 µg/kg in the kidney [53]. LC-MS were used for the determination of kanamycin in 6 different samples. The LOQ value was 0.01 mg/kg [51].

LC-MS/MS was used for the detection of kanamycin in anatolian buffalo milk with LOD of 3.56 µg/kg [66]. Ultra Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS) was used for the determination of kanamycin in pork meat with LOD and LOQ of 3.3 µg/kg and 10.9 µg/kg, respectively [67].

An unmodified silver nanoparticle method was employed for the determination of kanamycin in milk with LOD of 2.6 ng/ml which was much lower than MRL [68]. The gold nanoparticle was the most sensitive method for the determination of kanamycin in aqueous solutions (LOD was less than 0.1 nM). This method was used for analyzing milk or meat samples [69]. Aptamer-immobilized electrosprnanoe gold nanoparticles were used for the determination of kanamycin in aqueous solution with LOD values in 120–480 picomolar [71].

Photoluminescence response of an off-on probe based on the spherical gold nanoparticles method was used to determine kanamycin in yellow-fever vaccine and veterinary pharmaceuticals and medical compounds. The LOD and LOQ values were 0.06 µM/mL and 0.2 µM/mL, respectively [72].

As previously explained, the instrumental method is usually for the determination of AGs, and the usual method used for the determination of kanamycin in the food sample was the LC-MS method. Biosensor methods that have been used for the determination of kanamycin have good sensitivity and selectivity. Table 5 showed the comparison of different methods of kanamycin residues determination.

| Method       | Description | Matrix                | LOD            | LOQ            | Additional information                                      | Reference |
|--------------|-------------|-----------------------|----------------|----------------|-------------------------------------------------------------|-----------|
| Microbiological | Multiple   | Raw milk              | 150.0 1/µg     | 1/µg           | This method is detected kanamycin lower than the MRL range   | [46]      |
| Instrumental | CE-LIF      | Human serum           | 14.4 nM        | 0.2 µg         | This method needs both a short time and a small sample for analysis. | [65]      |
| Instrumental | CE-EC       | Pharmaceutical        | 2.2 µM         | 1/µg           |                                                             | [57]      |
| Method     | Description                                                                 | Matrix                        | LOD   | LOQ    | Additional Information                                                   | Reference |
|------------|------------------------------------------------------------------------------|-------------------------------|-------|--------|---------------------------------------------------------------------------|-----------|
| Instrumental | HILIC–MS/MS                                                                  | ns Bovine muscle              | –     | 56.0 µg/kg |                                                                           | [52]      |
| Instrumental | MSPE combined with HILIC–MS/MS analysis                                       | Meat sample                   | 0.6 µg/kg | 2.4 µg/kg |                                                                           | [34]      |
| Instrumental | SCX-HPLC CL                                                                  | Water sample                  | 10.0 µg/L | –       | A simple and sensitive method comparison other instrumental methods.     | [38]      |
| Instrumental | Ultra-high-performance liquid chromatography-tandem mass spectrometry        | Pork sample                   | 3.3 µg/kg | 10.9 µg/kg|                                                                           | [67]      |
| Instrumental | LIPS spectrofluorometric technique                                            | Pharmaceutical preparations  | –     | –       |                                                                           | [24]      |
| Instrumental | LC-MS                                                                        | Honey and kidney samples      | –     | In kidney was 85 µg/kg and honey was 41 µg/kg|                                                                           | [53]      |
| Instrumental | LC-MS/MS                                                                     | Liver, fish, kidney and muscle samples | –     | In liver and fish is 15.0 µg/kg, kidney and muscle is 5.0 µg/kg | A sensitive method for the determination of kanamycin in animal products. | [32]      |
| Instrumental | LC-MS/MS                                                                     | Anatolian buffalo milk        | 3.56 µg/kg | –       |                                                                           | [66]      |
| Instrumental | LC-MS                                                                        | Bovine muscle, bovine liver, milk, chicken egg, fish and shrimp samples | –     | 0.01 mg/kg |                                                                           | [51]      |
| Method     | Description                                                      | Matrix                                      | LOD     | LOQ     | Additional information                                      | Reference |
|------------|------------------------------------------------------------------|---------------------------------------------|---------|---------|-------------------------------------------------------------|-----------|
| Instrumental | LC with tandem mass spectrometry                                 | Honey, milk and pork samples                | –       | –       | –                                                           | [31]      |
| Biosensor   | Gold nanoparticles                                               | Aqueous solution                            | 0.1 nM  | –       | –                                                           | [69]      |
| Biosensor   | Chlortetracycline-coated silver nanoparticles–UV                 | Aqueous solution                            | 120-480 picomolar | –       | The most sensitive method for detection of kanamycin              | [71]      |
| Biosensor   | Photoluminescence response of an off-on probe based on spherical gold nanoparticles | In yellow-fever vaccine and veterinary pharmaceutical and medical compound | 0.06 µM/mL | 0.2 µM/mL | –                                                           | [72]      |
| Biosensor   | Colorimetric has been developed using unmodified silver nanoparticles | In milk                                     | 2.6 ng/mL | –       | –                                                           | [68]      |

2.6 Neomycin

There is one microbiological method for the determination of neomycin that is used in multiple systems. The LOD of this method was 2.5 1/µg [46].

In 2005, Regazzeti et al. employed HPLC-ELSD for the determination of neomycin and framycetin sulfate in commercial samples. This method was good for measurement of the neomycin B and C in the industry [73]. HPLC-CL can detect neomycin in the aqueous sample with LOD of 1.5 µg/L [38]. Liquid Chromatography (LC)-Fluorescence Detector (2008) was developed for evaluating the neomycin level in dosage forms and human plasma with LOD of 0.05 µg/mL and LOQ of 0.1 µg/mL [23]. Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) employed for the determination of neomycin in the sample like liver, kidney and muscle and the LOD were 5.0 µg/kg in the liver, 15.0 µg/kg in the kidney, and muscle 30.0 µg/kg [32]. Liquid Chromatography–Mass Spectrometry (LC-MS) can quantify neomycin in bovine muscle, bovine liver, milk, chicken egg, fish and shrimp with LOD of 0.01 mg/kg [51] also LC-MS determine neomycin B (and other AGs) in honey and kidney with LOQ of 125.0 µg/kg and 264.0 µg/kg, receptively [53].

Capillary Electrophoresis-Tandem Mass Spectrometry (CE-MS/MS) methods were developed for the determination of nine AGs in honey samples. LOD and LOQ values of neomycin were 25.7 µg /kg and 85.8 µg /kg, respectively [55]. Hydrophilic Interaction Chromatography With Tandem Mass Spectrometry (HILIC–MS/MS) method developed for the determination of neomycin in bovine muscle, and LOQ was163.0 µg/kg [52] and hydrophilic interaction MSPE combined with HILIC–MS/MS was developed for meat sample with LOD of 13.5 µg/kg and LOQ of 38.0 µg/kg [34]. HPLC-ELSD method was detected
neomycin in the tilapia sample with a LOQ of 5.3 µg/kg [74].

RNA aptamers detected neomycin in the range of µM in solutions [75]. ssDNA method was successfully applied for the detection of heavy metal mercury (II) ion (Hg$^{2+}$) and silver (I) ion (Ag$^{+}$) and AG ABs residues in food [76].

Because the biosensor method is new, few articles have been existed to measure neomycin in different samples. The instrumental method is a both sensitive and available method. Modified-RNA aptamer-based sensor detects neomycin in the submicromolar range. Table 6 Compares the different methods for neomycin residues determination in various samples.

Table 6. Comparison of different determination methods for neomycin in various samples

| Method                  | Description | Matrix          | LOD     | LOQ     | Additional information                                                                 | Reference |
|-------------------------|-------------|-----------------|---------|---------|----------------------------------------------------------------------------------------|-----------|
| Microbiological         | Multiple    | Raw milk        | 2.5 1/µg | _       | Evaluated different kind of ABs that is residual in milk with a lower range of MRLs.   | [46]      |
| Instrumental            | CE-MS       | Honey sample    | 25.7 µg/kg | 85.8 µg/kg | Good sensitivity and selectivity for determination of neomycin in the food industry like honey | [55]      |
| Instrumental            | HILIC–MS/MS | Bovine sample   | 163.0 µg/kg | _       | A good method for the detection of neomycin and other ABs in bovine.                  | [52]      |
| Instrumental            | MSPE combined with HILIC–MS/MS analysis | Meat sample | 13.5 µg/kg | 38 µg/kg | _                                                                                     | [34]      |
| Instrumental            | HPLC–ELSD   | Commercial samples | _       | _       | LOD has good relation with European Pharmacopoeia                                    | [73]      |
| Instrumental            | SPME–HPLC–ELSD | Tilapia    | 5.3 µg/kg | _       | This method can detect the lower concentration of AGs                                | [74]      |
| Instrumental            | SCX–HPLC–CL | Water sample    | 1.5 µg/L  | _       | Useful for aqueous sample, but maybe decreased in sensitivity for the complex sample. | [38]      |
| Instrumental            | LC–MS/MS    | Liver, kidney, fish and muscle samples | _       | _       | This method can be used for all AGs in every matrix with the most sensitivity and selectivity. | [32]      |
| Instrumental            | LC-MS       | Kidney and honey | _       | In kidney was _ | _                                                                                     | [53]      |
| Method       | Description                  | Matrix                      | LOD       | LOQ       | Additional information                                                                 | Reference |
|--------------|------------------------------|-----------------------------|-----------|-----------|----------------------------------------------------------------------------------------|-----------|
| Instrumental | LIPS                         | Pharmaceutial preparations  | 265 µg/kg |           | and in honey was 125 µg/kg                                                             | [52]      |
| Instrumental | LC-MS                        | Bovine muscle, bovine liver, milk, chicken egg, fish and shrimp samples | 0.01 mg/kg |           |                                                                                        | [51]      |
| Biosensor    | Modified-RNA aptamer-based sensor | Submicromolar range |           |           | It using for another small molecule in the complex matrix                                | [75]      |
| Biosensor    | ssDNA for different analyses associated with graphene oxide | Food samples |           |           | This method is developed for simultaneous determination of heavy mental and AG antibiotics | [76]      |

### 2.7 Sisomicin

For the determination of sisomicin, limited methods have been developed. In one study, Broughton et al. (1976) compared two types of quantification methods (radioimmunoassay and microbiological assay) in the human serum. In the microbiological assay, the agar well diffusion method was used and *Klebsiella* was set as the test organism. The result of radioimmunoassay showed the sensitivity as 140 pg/mL, and in comparison with the microbiological assay, there were not significant differences [77] also, microbiological assay did not show any significant difference with TLC and HPLC-fluorescence method [48,49].

HPLC with UV and fluorescence detectors were used for clinical monitoring of sisomicin and LOD was 62.5 ng/ml [78].

LC-MS method was used for the determination of sisomicin. The LOD and LOQ values were 5.0 µg/kg, 17.0 µg/kg in honey, 4.0 µg/kg, 13.0 µg/kg in milk and 7.0 µg/kg, 23.0 µg/kg in pork, respectively [31] and with LC-MS/MS determine sisomicin in liver, kidney muscle and fish with LOQ of 10.0 µg/kg, 20.0 µg/kg, 10.0 µg/kg, 5.0 µg/kg, respectively [32]. Both methods are useful for the determination of other AGs in food samples.

Microbiological and instrumental methods have been used to determine the amount of sisomicin, and the biosensor method has been compared with the microbiological method. There are good instrumental methods for evaluation of sisomicin in the clinical monitoring and food industry and maybe the microbiological method could be used instead of chemical methods in any laboratories. The comparison of different determination methods for analyzing the sisomicin residues is shown in Table 7.
Table 7. Comparison of different determination methods for sisomicin in various samples

| Method                  | Description                        | Matrix                  | LOD       | LOQ       | Additional information                                                      | Reference |
|-------------------------|------------------------------------|-------------------------|-----------|-----------|-----------------------------------------------------------------------------|-----------|
| Microbiological/Instrumental | Microbiological assay/TLC          | Human serum             | –         | –         | The sensitivity of radioimmunoassay was 140 pg.                             | [77]      |
| Microbiological/Instrumental | Microbiological assay/HPLC         | Human serum             | –         | –         | This method can determine netilmicin, astromycin, and micronomicin. It’s a good method for using for serum monitoring because of reproducibility. | [41]      |
| Microbiological/Biosensor | Microbiological assay/HPLC         | Human serum             | 62.5 ng/ml| –         | By using this method one can detect the lowest concentration of sisomicin. | [78]      |
| Instrumental            | HPLC with fluorescence detector    | Milk, honey             | –         | –         | It’s the best method for the determination of AG in the food industry.       | [32]      |
| Instrumental            | HPLC-UV                            | Milk                    | 62.5 ng/ml| –         | With this method, we can determine different AGs.                          | [31]      |

2.8 Streptomycin

Streptomycin is the first AG that was discovered in 1943 [79] and it has lots of uses in many cases (from prevention to treatment in veterinary medicine to human diseases) [80]. Streptomycin usually is in the first line of antibiotic therapy and has good effects on Gram-negative bacterial infections which occur in veterinary and human [81,82]. It also administered as anti-tuberculosis agents in the second-line for the resistant strains to isoniazid and rifampin [83]. The residues of streptomycin in animal-derived products could pose health hazards to consumers [18].

Jacques Nouws et al. (1999) suggested microbiological assay for the determination of AGs in milk. For the determination of spectinomycin multiple systems with B. calidolactis have been described and for other AGs (neomycin, kanamycin, gentamycin, DH streptomycin) B. subtilis was used. The LOD values for neomycin, kanamycin, gentamycin, DH streptomycin, and spectinomycin were 50.0 1/µg, 150.0 1/µg, 25.0 1/µg, 100.0 1/µg, and 3000.0 1/µg, respectively [46].

Liquid Chromatography And Tandem Mass Spectrometry (HPLC-MS/MS) was a robust, rapid, and sensitive method to quantify streptomycin in mice plasma with LOQ of 10.0 ng/mL. This instrumental method could be applied for the preclinical determination of
streptomycin [80] but previously Han et al. [84] and Kim et al. [85] had developed UPLC-MS/MS for anti-tuberculosis drug samples and LC-MS/MS method for human serum respectively. During sample preparation for these methods, there was a decrease in polarity that has a negative effect on the detection and quantification of AGs [84,85]. LC-MS/MS was also used for the determination of streptomycin in honey with LOD of 4.7 µg/kg. This method can be used in a laboratory because it is a fast and accurate method. It also needs small sample and reagents [86].

Both HILIC–MS/MS (2016) and hydrophilic interaction MSPE combined with HILIC–MS/MS were developed for the determination of streptomycin in bovine muscle. LOQ values for these methods were 176.0 µg/kg and 7.3 µg/kg respectively. Hydrophilic interaction MSPE combined with HILIC–MS/MS shows improvement for the determination of streptomycin in comparison with HILIC–MS/MS [34,52]. LOD for hydrophilic interaction MSPE combined with HILIC–MS/MS was 2.2 µg/kg [34]. UPLC–MS was developed for screening drug residues in pork. The LOD and LOQ values were 0.6 µg/kg and 2.0 µg/kg respectively. Compared to the conventional quantitative method, this method could improve instrumental efficiency, thus can be applied in prompt screening for large batch samples [67]. By the HPLC-ELSD method, AG in food could be determined with LOD of 3.0 µg/kg [74].

LC-MS (2017) was developed for the detection of streptomycin and DH streptomycin in honey, milk, pork. The LOD and LOQ values for streptomycin were 4.0 µg/kg, 13.0 µg/kg in honey and 3.0 µg/kg 10.0 µg/kg in milk and 5.0 µg/kg 17.0 µg/kg in pork, respectively. LOD and LOQ were 3.0 µg/kg, 10.0 µg/kg in honey and milk, 4.0 µg/kg, 13.0 µg/kg in pork, respectively for DH streptomycin [31]. CE-MS method detected these AGs with LOD and LOQ of 0.4 µg/kg, 1.4 µg/kg, and 4.7 µg/kg, 15.7 µg/kg, for streptomycin and DH streptomycin, respectively [55]. For the determination of streptomycin and DH streptomycin in food LC-MS/MS was used. The LOQ was 25.0 ng/mL and 30.0 ng/mL, respectively [32], and LC with fluorescence detector was used for the detection of streptomycin and DH streptomycin in food. LOD values were 7.5 µg/kg and 15.0 µg/kg, respectively for streptomycin and DH streptomycin [87]. LC-MS determined streptomycin and DH streptomycin with LOQ of 0.02 and 0.01 mg/kg, respectively in bovine muscle, bovine liver, milk, chicken egg, fish, and shrimp samples [51].

The colorimetric technique was developed for the determination of streptomycin with LOD 60.2 nM in raw milk. These aptamers used to detect very low levels of streptomycin [88]. By colorimetric aptasensor, streptomycin with LOD of 108.7 nM in milk and human serum could be detected [89] and by multi-color quantum dot-based fluorescence immunoassay array streptomycin was detected with LOD of 5.0 pg/mL [90]. In 2020 chlortetracycline-coated silver nanoparticles–UV spectroscopy detected streptomycin in aqueous solution with LOD 1000–11000 picomolar [71].

There is a microbiological assay method for the determination of streptomycin that may be useful for routine analysis in milk. The use of the biosensor method is expanding; as predicted in the next few years, it will replace other methods, even though it is expensive. Table 8 compares the different methods which have been used for the determination of streptomycin residues.

Table 8. Comparison of different determination methods for streptomycin in various samples

| Method             | Description          | Matrix       | LOD       | LOQ       | Additional information                                      | Reference |
|--------------------|----------------------|--------------|-----------|-----------|------------------------------------------------------------|-----------|
| Microbiologic      | Multiple             | Raw milk     | 100.0 1/µg| _         | A good method for milk factories for estimating the amount of ABs in milk. | [46]      |
| Instrumental       | CE-MS                | _            | _         | _         | For determination of both streptomycin and DH streptomycin | [55]      |
| Instrumental       | HILIC–MS/MS          | Bovine       | DH        | _         |                                                            | [52]      |
| Method            | Description                                      | Matrix         | LOD  | LOQ  | Additional information | Reference |
|-------------------|--------------------------------------------------|----------------|------|------|-------------------------|-----------|
| Instrumental      | Hydrophilic interaction MSPE combined with HILIC–MS/MS (SCX)-HPLC-CL detection | Meat sample    | 2.2  | 7.3  |                         | [34]      |
| Instrumental      | UPLC-MS/MS                                       | Water sample   | 7.5  |      | For determination of the AGs in the aqueous sample. | [38]      |
| Instrumental      | UPLC-MS                                          | For drug residues in pork samples | 0.6  | 2.0  |                         | [67]      |
| Instrumental      | HPLC-ELSD                                        | Food sample    | 3.0  |      | Using for evaluation of residual AGs in seafood like fish | [74]      |
| Instrumental      | HPLC-MS/MS                                       | Mice plasma    |      | 10.0 |                         | [80]      |
| Instrumental      | LIPS spectrofluorometric technique LC-MS/MS       | Pharmacutical preparations |      |      |                         | [24]      |
| Instrumental      | LC-MS/MS                                         | Liver, fish, kidney and muscle samples |      |      |                         | [32]      |
| Instrumental      | LC-MS/MS                                         | Human serum    |      |      |                         | [85]      |
| Instrumental      | LC-MS/MS                                         | Honey sample   | 4.7  |      | Using for routine assay in laboratories | [86]      |
| Instrumental      | LC-electrospray ionization-MS                    | Meat sample    | 1.0-6.0 |  | For determination of both streptomycin and DH streptomycin with good sensitivity | [91]      |
| Instrumental      | LC with                                          | Food           |      |      | For determination     | [87]      |
| Method          | Description                                     | Matrix Description                      | LOD  | LOQ  | Additional Information                                                                 | Reference |
|-----------------|-------------------------------------------------|------------------------------------------|------|------|-----------------------------------------------------------------------------------------|-----------|
| Instrumental    | LC-MS                                           | Honey and kidney samples                 |      |      | Good for the determination of streptomycin and DH streptomycin in food.                 | [53]      |
| Instrumental    | LC-MS                                           | Honey, milk and pork samples             |      |      |                                                                                         | [31]      |
| Instrumental    | LC-MS                                           | Bovine muscle, bovine liver, milk, chicken egg, fish and shrimp samples |      | Strept | Streptomycin 0.02 mg/kg, DH streptomycin 0.01 mg/kg                                      | [51]      |
| Biosensor       | Colorimetric technique                          | Raw milk                                 | 60.2 nM |      |                                                                                         | [88]      |
| Biosensor       | Colorimetric aptasensor                          | Milk and human serum samples             | 108.7 nM |      |                                                                                         | [89]      |
| Biosensor       | Chlortetracycline-coated silver nanoparticles–UV spectroscopy | Aqueous solution | 1000-11000 picomolar |      |                                                                                         | [71]      |
| Biosensor       | Multi-color quantum dot-based fluorescence immunoassay | Milk sample | 5.0 pg/mL |      |                                                                                         | [90]      |

2.9 Tobramycin

Tobramycin is another AG that is similar to gentamicin and kanamycin in many properties such as pharmacokinetic, toxicological, and some microbiological ones [92]. Tobramycin has a good influence on Gram-negative bacteria especially many strain of the *Enterobacteriaceae* and *Pseudomonas* and also, *S. aureus* that have resistance against gentamicin [93].

Lamb et al. (1972) reported factors that influence the microbiological assay to find the most suitable methods for the determination of tobramycin in blood, urine, and pharmaceutical preparations. Various factors such as sample diluents, pH, molarity, iron, and sodium ions were checked and the important ones were diluents, pH, and molarity. They used three kinds of methods including the disc-plate method, turbidimetric assay, and cylinder-plate method. The tested microorganisms were *B. subtilis* and *S. aureus* for turbidimetric and cylinder-plate, respectively.

For diluents effect, the results of the article showed the sensitivity of the cylinder-plate assay was increased 10 times more than the disc assay when increasing pH, therefore the dilution factor affected more on the cylinder-plate assay. By the addition of the ionic compounds like Na⁺ and Fe³⁺ in agar base, the sensitivity of tobramycin determination was decreased even though variations in pH and ion concentration were more...
critical for the cylinder assay, but this assay system was more reproducible and sensitive than the disc [94].

Lode et al. (1975) used the agar diffusion method with B. subtilis as a test organism for the estimate of pharmacokinetic of gentamycin, sisomicin, and tobramycin. They concluded that because of similar chemical structures and molecular weights the pharmacokinetic parameters obtained for the three AGs did not show any significant differences [95]. Also, Hubenov et al. (2007) employed two methods for evaluating the pharmacokinetics of tobramycin with HPLC-fluorescence detection (LOQ of 0.2 µg/and LOD of 0.1 µg/mL) and microbiological assay with B. subtilis (ATCC 6633) as a test organism. The LOD and LOQ values were 0.024 and 0.048 µg/mL, respectively [96].

For determination of tobramycin in food samples LC/MS and LC-MS/MS methods were used. LC/MS determined tobramycin in honey, milk and pork tissue with LOD 6.0 µg/kg, 7.0 µg/kg, and 11.0 µg/kg, and with LOQ 20.0 µg/kg, 23.0 µg/kg and 36.0 µg/kg, respectively. LC-MS/MS determined tobramycin in liver, kidney, muscle and fish with LOQ 1.0 µg/kg, 1.0 µg/kg, 15.0 µg/kg and 3.0 µg/kg, respectively [31,32]. More recently a new method that developed for the determination of tobramycin in food is hydrophilic interaction MSPE combined with HILIC-MS/MS. LOD and LOQ values for this method were 4.3 µg/kg and 15.7 µg/kg, respectively [34].

CE-LIF device was developed to detect tobramycin in human serum (LOD=17.1 nM). The advantages were small sample requirements and short analysis time to quantify drugs in biological samples. Also, CE-LIF detected paromomycin, bekamycin, and kanamycin with LOD of 24.0 nM, 15.0 nM, and 14.4 nM, respectively [65].

HPLC-ELSD method was developed for the detection of tobramycin in tilapia with LOD of 3.0 µg/kg. This method could be used for the detection of residual of AGs in food [74].

The copper-OCE method provided a determination of tobramycin with LOD of 4.7 µM in pharmaceutical preparations (LOD for bekamycin, lincomycin, ribostamycin were 3.4 µM, 4.9 µM, 5.1 µM, respectively) [57].

Working on the determination of tobramycin with biosensor method has been started since 1997 with RNA aptamers [97], but after 9 years, the researchers were able to detect tobramycin with potentiometric measurements only in aqueous solutions [98].

In 2011 RNA aptamer for determination of tobramycin in human serum was developed. The LOD depended on the ratio of serum/buffer (LOD was between 15.0 µM and 17.0 µM) [99], but in 2019 with voltammetric sensor tobramycin could be detected in blood and human serum with LOD of 2.0 µM [100].

For milk and medicine products colorimetric method based on the aggregation of gold nanoparticles with LOD of 0.579 ng/ml was developed. This method is the most sensitive biosensor method [35], and for ophthalmic preparations, it used the visible light effect on surface plasmon resonance of gold nanoparticles with LOD of 3.8×10⁻³M, with the advantage of no chemical derivatization [101]. For the first time in 2020, dynamic aggregation of Sodium Dodecyl Sulfate (SDS)-capped silver nanoparticles have been developed for the determination of tobramycin in exhaled breath dense. LOD values for this method was 0.5 ng/mL [102].

Tobramycin is one of the most widely used AGs in the treatment of diseases. Microbiological, instrumental, and biosensor methods have been used to measure this compound, but given that the biosensor method is a new way to measure in the coming years, it is expected that more and more diverse methods will be used to determine the amount of this AG with more accuracy. The comparison between different methods of tobramycin residue determination is illustrated in Table 9.

Table 9. Comparison of different determination methods for tobramycin in various samples

| Method                  | Description                        | Matrix          | LOD     | LOQ     | Additional information | Reference |
|-------------------------|------------------------------------|-----------------|---------|---------|------------------------|-----------|
| Microbiological         | Agar diffusion assay               | –               | –       | –       |                        | [95]      |
| Microbiological         | Agar-diffusion assays, disc plate, and | Blood, urine, and | –       | –       |                        | [94]      |


| Method                          | Description                          | Matrix                    | LOD                        | LOQ                        | Additional information                                                                 | Reference |
|--------------------------------|--------------------------------------|---------------------------|----------------------------|----------------------------|----------------------------------------------------------------------------------------|-----------|
| Turbidimetric assay            |                                      | Cal preparations samples  | Microbiological assay: 0.2 µg/mL HPLC assay | Microbiological assay: 0.2 µg/mL HPLC assay | –                                                                                      | [96]      |
| Microbiological assay in meat peptone agar/HPLC | –                                   | Microbiological assay: 0.024 µg/mL HPLC assay | Microbiological assay: 0.048 µg/mL HPLC assay | –                                                                                      | [49]      |
| Microbiological assay/TLC      | –                                    | –                         | –                          | –                          | –                                                                                      | [48]      |
| Electrospray-ionization mass spectrometry | –                                   | Human serum               | –                          | –                          | The linear dynamic ranges of detection for tobramycin was 25–2500 ng/mL                  | [29]      |
| CE-EC                          | Pharmacetical preparations           |                            | 4.7 µM                     |                            | –                                                                                      | [57]      |
| Copper-Based Electrodes        |                                      |                            |                            |                            | A suitable method for clinical monitoring A good method for the detection of tobramycin in pharmaceuti products. | [65]      |
| CE-LIF                         | Human serum                          |                            | 17.1 nM                    |                            | –                                                                                      | [25]      |
| Fluorimetric                   |                                      |                            | 10.0 ng/mL                 |                            | –                                                                                      |           |
| MSPE combined with HILIC-MS/MS analysis | Meat sample                          |                            | 4.3 µg kg                  | 18.7 µg kg                 | –                                                                                      | [34]      |
| SPME-HPLC-ELSD                 | Tiliapia                              |                            | 3.9 µg/kg                  |                            | –                                                                                      | [74]      |
| LC-MS/MS                       | Liver, kidney, muscle and fish samples |                            |                            |                            | In liver, kidney, muscle and fish 1.0 µg/kg, 1.0 µg/kg, 15.0 µg/kg and 3.0 µg/kg       | [32]      |
| Method       | Description                                      | Matrix                          | LOD        | LOQ        | Additional Information                                                                 | Reference |
|--------------|--------------------------------------------------|---------------------------------|------------|------------|----------------------------------------------------------------------------------------|-----------|
| Instrumental | Liquid Chromatography with MS LIPS               | Honey, milk and pork samples   | –          | –          | Use for both clinical monitoring and in industry                                         | [31]      |
| Instrumental | RRS method                                       | Pure form and some pharmaceutical preparations | –          | –          | In 1997 just detected tobramycin in solution                                           | [24]      |
| Instrumental | RRS method                                       |                                  |            |            | Use for both clinical monitoring and in industry                                         | [54]      |
| Biosensor    | RNA aptamer                                      | Aqueous solution                | –          | –          | In 1997 just detected tobramycin in solution                                           | [97]      |
| Biosensor    | Voltametric sensor                               | Human serum                     | 2.0 μM     | –          | Doesn’t need any derivatization for the determination of tobramycin.                    | [100]     |
| Biosensor    | Visible light effect on surface                  | For ophthalmic preparations     | 3.8 × 10⁻⁹ | 1/mol      | Must need any derivatization for the determination of tobramycin.                      | [101]     |
| Biosensor    | RNA aptamers                                     | Human serum                     | –          | –          | For determination of all AGs in therapeutic range                                      | [99]      |
| Biosensor    | Colorimetric nanoprobe based on the dynamic aggregation of SDS-capped silver nanoparticles Colorimetric | Exhaled breath dense            | 0.5 ng/mL  | –          | A sensitive method for both in the food industry and clinical monitoring                | [102]     |
| Biosensor    | Colorimetric nanoprobe based on the dynamic aggregation of SDS-capped silver nanoparticles Colorimetric | For milk and medicine products  | 0.354 ng/mL| –          | A sensitive method for both in the food industry and clinical monitoring                | [35]      |
| Biosensor    | Potentiometric measurement s                     | Aqueous solutions               | 1×10⁻⁵ M   | –          | –                                                                                        | [98]      |
2.10 Other AGs

Ultra Performance Liquid Chromatography - Tandem Mass (UPLC-MS) was employed for the determination of etimicin (2016) in pork tissue. LOQ and LOD values were 27.9 μg/kg, and 8.4 μg/kg, respectively [67].

Apramycin and spectinomycin were determined by the LC-MS method in the kidney and honey samples. LOQ and LOD values were 112.0 μg/kg and 2.0 μg/kg for apramycin and spectinomycin were 151.0 μg/kg and 13.0 μg/kg, respectively. Other AGs like streptomycin, paromomycin, kanamycin A, gentamycin C1, gentamycin C2/C2a, gentamycin C1a, and neomycin B can determine, too [53]. Apramycin and DH streptomycin detected by HILIC-MS/MS method in bovine muscle with LOD of 74.0 μg/kg, and 32.0 μg/kg [52]. The report indicates that hydrophilic interaction MSPE combined with HILIC-MS/MS determines apramycin, spectinomycin, netilmicin, and hygromycin B in the meat sample. LOD and LOQ values were 23.6 μg/kg and 40.2 μg/kg for apramycin, 3.4 μg/kg and 8.1 μg/kg for spectinomycin, 2.5 μg/kg and 13.3 μg/kg for netilmicin and 3.2 μg/kg and 9.8 μg/kg for hygromycin B, respectively [34].

Apramycin sulfate is detected by two spectrofluorimetric methods. The first one was based on measuring the inherent native fluorescence and the second one was dependent on enhancing the native fluorescence intensity of the drug-using SDS in veterinary AB drug, pharmaceutical preparations, and milk samples. LOD values for first and second methods were 0.05 μg/mL and 0.02 μg/mL respectively [103]. LC-MS detected apramycin and spectinomycin with LOQ of 0.01 mg/kg and 0.02 mg/kg in bovine muscle, bovine liver, milk, chicken egg, fish, and shrimp [51].

Fortimicin A and 3-0-demethylfortimicin detected by HPLC-UV detector in the range of pg/mL. The assay procedure was also applicable to the determination of other AGs such as gentamicin, tobramycin, kanamycin, and amikacin [104].

Paromomycin was determined with reversed-phase ion-pair HPLC separation coupled with the pulsed amperometric detector (2000) in animal feed matrices (rabbit, chicken, and pig feeds). The statistical analysis of the performance of the method demonstrated its very good reliability and allows us to propose it as the reference procedure for the determination of paromomycin in the considered matrices [105]. In 2010 HPLC-ELSD was employed in the commercial sample which the authors of the article showed that the method is reliable and repeatable for determination of paromomycin (the LOD and LOQ of paromomycin were 2.25 μg/ml and 25.5 μg/ml respectively) [106]. The LOD and LOQ values were 25.0 μg/kg, 83.0 μg/kg in honey, 26.0 μg/kg 90.0 μg/kg in milk and 30.0 μg/kg, 100.0 μg/kg in pork, respectively [31]. LC-MS was used for the determination of paromomycin with LOQ of 117.0 μg/kg and 23.0 μg/kg in kidney and honey samples, receptively [53].

LOD and LOQ values of spectinomycin were 2.0 μg/kg, 7.0 μg/kg respectively in honey and milk and in pork were 3.0 μg/kg, and 10.0 μg/kg, respectively. For netilmicin LOD and LOQ values were 5.0 μg/kg, 17.0 μg/kg in honey, 4.0 μg/kg, 13.0 μg/kg in milk and 8.0 μg/kg, and 27.0 μg/kg in pork, respectively and for hygromycin LOD and LOQ were 5.0 μg/kg, 17.0 μg/kg in honey, 7.0 μg/kg, 23.0 μg/kg in milk, 10.0 μg/kg and 34.0 μg/kg in pork, respectively [31].

For determination of vertilmicin sulfate, arbekacin and dibekacin were developed HPLC-ELSD method that LOD of vertilmicin sulfate was 10.0 μg/mL, arbekacin was 4.5 μg/mL and dibekacin was 5.0 μg/mL[70]. The advantage of this method was the determination of AGs without any derivation [107,108].

3. CONCLUSIONS

AGs are one of the oldest ABs due to their good effects on Gram-negative bacteria; they are widely used in the treatment of diseases today. For this reason, the measurement of AGs in different matrices is of particular importance. Different types of methods have been developed for the determination of a wide variety of AG by microbiological, instrumental, and biosensors in various cases. The increasing number of articles published in this caption reflects a great concern in public health and drug resistance especially for gentamycin and streptomycin because of wide use in the treatment of different diseases.

Generally, based on the kind of AG, different methods have been used to determine the related residues. The microbiological assay is an old, less sensitive, and slow method (needs time of incubation). Due to that, the method is less operational and does not need a very special
expert and experience, it could be used for the determination of AGs in some cases. The instrumental methods are popular methods from past to present. These methods are not only more sensitive than microbiological, but also are faster.

The biosensor method is a new one and attracts attention. The main advantages of them are higher selectivity and sensitivity in compared with conventional ones. But the main drawbacks of the biosensor method are related to the high cost and Availability of experts that make it impossible to use for every laboratory.

The first part is the determination of AGs in human serum or plasma due to the evaluated concentration of AG in the blood that patients give a proper treatment with reductions of ototoxicity and nephrotoxicity. This is especially important for streptomycin and gentamicin, the most common AGs. We predict that the device will be more sensitive and faster in the future.

The second one is, the determination of AGs in food, water, and environment that all people have always exposed and can produce drug resistance in society, therefore in this section should develop methods to separate AGs from other components.

The third one is, using different methods for the determination of AG in the industry. Like the previous part, it needs to develop methods to separate AGs from the other components.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It’s not applicable.

ETHICAL APPROVAL

It’s not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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