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Challenges in the development of analytical test procedure for aminoglycosides: A critical review

Radhakrishnan Hari, Shaik Taherunnisa, Sushil Yadaorao Raut, Srinivas Mutalik, Kunnatur B. Koteshwara*
Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal 576104, India.

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ABSTRACT

The present article reviews the challenges and hurdles in the development of an analytical method for aminoglycosides (AG). The article emphasizes on the attempts made to develop analytical methods based on HPLC and other sophisticated techniques, such as LC-MS, radioimmunoassay, microbial assay, enzyme linked immunosorbent assay (ELISA), extractive colorimetry, anion-exchange chromatography with pulsed amperometric detection, high performance thin layer chromatography, densitometry, and microbial agar diffusion assay. The various media mostly used for the *in vitro* as well as *in vivo* estimation of AG by HPLC and LC-MS are heptafluorobutyric acid, ammonium acetate, ammonium formate and formic acid. Estimation of AG by radioimmunoassay and ELISA can be suitably done by using TRIS-HCl and saline phosphate buffer. The buffer media used for *ex vivo* analysis mostly include MEM, TRIS and saline phosphate. The presence of AG in food from the animal sources, water bodies, and its prolonged exposure may result in serious health issues. The present article outlined the various sensitive, robust and precise analytical techniques for the estimation of the various aminoglycosides in many sources, and discussed the hurdles faced during the development of the analytical techniques.

INTRODUCTION

Aminoglycosides (AG) are broad-spectrum antibiotics, discovered in the year 1944 with streptomycin being the first molecule. Streptomycin is a water-soluble molecule, which is active against Gram-negative bacteria but when the bacteria started showing the resistance toward the molecule, kanamycin was identified in the year 1954 which was active against the streptomycin resistant bacteria (Farouk *et al*., 2015). Later, the mechanism behind the bacterial resistance was identified and was resolved by developing many semi-synthetic AG, namely, amikacin, dibekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, streptomycin, dihydrostreptomycin, and tobramycin being currently used (McGlinchey *et al*., 2008).

The word aminoglycoside originates from its structure—two amino sugars are joined together through a glycosidic linkage to an aminocyclitol. The aminocyclitol unit can be 1,3 or 1,4 di-substituted, based on which it is divided into two (i) 2-deoxy streptamine (ii) streptamine. The 2-deoxy streptamine is further divided into two based on the number and the position of substituent attached (Isoherranen and Soback, 1999).

The AG are produced from the natural source through fermentation, mainly from *Streptomyces* and *Micromonospora* species of bacteria. Based on the source from which it originates the antibiotics are given suitable names. The antibiotics from *Streptomyces* species are given "mycin" as a suffix and those from *Micromonospora* are given "micin" as a suffix (Farouk *et al*., 2015).

The AG has potential veterinary application in treating the bacterial infections due to bacterial enteritis (scours) and mastitis; these are added with the feed for the prophylaxis or as growth promoters. These days it is not allowed to use aminoglycoside as growth promoters according to the European legislation. The commonly used aminoglycoside for the veterinary purpose includes gentamicin, neomycin, dihydrostreptomycin, and streptomycin (Stead, 2000).

*Corresponding Author
Kunnatur B. Koteshwara, Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal 576104, India. E-mail: kb.koteshwara @ manipal.edu

The AG are poorly absorbed from the intestine/gut after oral or rectal administration. So, it is given as an intramuscular or intravenous injection. They are poorly bound to plasma protein and get excreted through renal route mainly by the glomerular filtration. The plasma half-life of the drug is only 2 hours, but it is found to be sufficient to be administered once in a day (Forge and Schacht, 2000)

NEED FOR THE ANALYTICAL METHODS

For the characterization of a new molecule from the fermentation, the analytical methods have a broader sense of application. (e.g., TLC). For the therapeutic drug monitoring, the quantitative determination of AG in the biological samples are done by an analytical technique which serves as a guide for drug dosing and to reduce toxicity. During pharmacokinetic and other research studies, the level of AG is determined in various biological and tissue fluids. Hence, to apply these analytical methods for these various purposes, it should be sensitive and specific enough. At present, HPLC serves to meet these requirements (Tawa *et al*., 1998). The analytical method should be sensitive enough to detect the veterinary drug residue, from the food of animal origin. They are used by various regulatory bodies to ensure food safety and to enforce regulations that serve as a guide for the usage of drugs in animals (Carlier *et al*., 2015).

The microbial assay is preferred as a screening method for drug residue present in food of the animal origin; it can detect the presence of all class of antibiotics at one shot. For the confirmation on what type of residue, hyphenated methods, such as GC-MS or HPLC-MS, are used. The method finds its application in the analysis of bulk pharmaceuticals, stability studies, quality control, etc.

CHALLENGES INVOLVED IN THE DETERMINATION OF AG

With the wider area of application, the analytical methods have a greater role to play in AG analysis. At the same time next to the application, it put forward some important general issues. The AG because of its high polar nature, in aqueous liquids they are present as polyionic forms, therefore the extraction or pre-concentration is difficult to achieve. The AG when considered are having a weak chromophore or fluorophore, hence rules out the possibility of direct analysis by HPLC with UV or Fluorescence detector (Farouk *et al*., 2015; McGlinchey, 2011). AGs demonstrate bad retention features in RPLC due to their extremely polar character, i.e., in-solution protonated species in the relevant pH range. It seems that the use of ion-pair fluid chromatography or HILIC is the simplest way to fix this issue. Some trials have used an elevated pH mobile phase to make AG a unionized molecule that demonstrates RPLC retention. Thus, that retention makes easy detection as well as quantification of the AG in various samples (Tan *et al*., 2012). AG detection and quantification relies mainly on the particular region of implementation. If the purpose of the evaluation is to determine degradation products or impurities, derivation may trigger unwanted or unexpected changes to unknown impurities or degradation products. Due to lack of chromophore, volatility, and high water solubility of AGs, it found to be difficult to analyse. Thus, many researchers adopted the derivatization techniques (Isoherranen & Soback, 1999). Holzgrabe *et al*. (2011) developed the HPLC method for streptomycin sulfate and reported the use of penta-fluoro-propionic anhydride as mobile phase with high column temperature conditions in order better resolution takes place through the efficient ion pairing. Pre-derivatization or post-derivatization methods was used to HPLC and LC-MS applications. Pang *et al*. (2004) estimated streptomycin in honey samples by using post-derivatization technique and analyzed by using liquid chromatography. It has been found that the recoveries obtained from 73.7%–78.5% along with the relative standard deviations of 1.64%–3.80%. The relative stability of aminoglycoside in the honey samples was determined by this technique. The streptomycin was stable in honey samples (Pang *et al*., 2004). The environmental impact of the use of AG is stirring the world due to enormous veterinary. That has been adversely affecting the human life indirectly due to the consumption of animal products and also affects the economic status. Thus, it is necessary to estimate the residual content of AGs in various foodstuffs from animal sources. The currently available analytical techniques are quite expensive and time consuming (Krause *et al*., 2016). Other than these aspects, there are various challenges involved in the analysis of AG are given in Figure 1.

AG as residues in food substance from animal origin

The analysis of AG in food substance is challenging since the type of antibiotic is unknown and its level of presence is also unknown. Therefore, initially, a screening method must be applied to confirm its presence followed by the application of a quantitative method. Here, it put forwards challenges in the extraction and both detection and quantification (Isoherranen and Soback, 1999; Mucklow, 2004).

In the developing countries, strict documentation on residual analysis and enforcement of the law on food safety are less common, unlike European Union. At present, a maximum residual

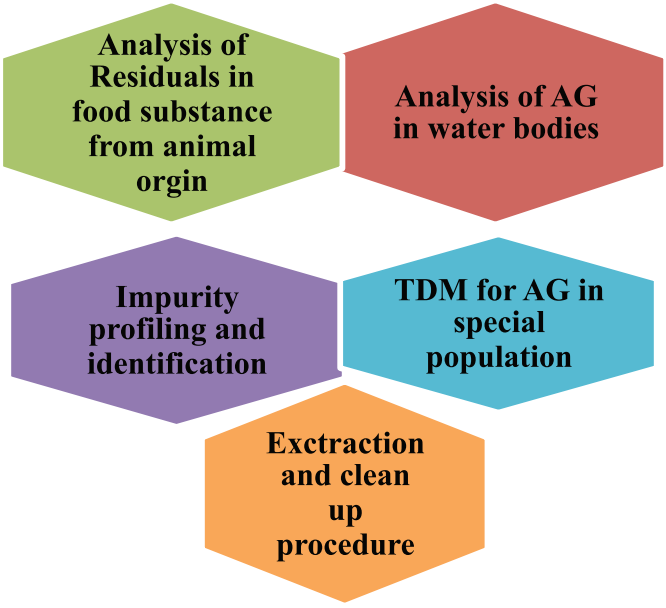

Figure 1. Challenges involved in AG analysis.

limit (MRL) has been established compared to zero AG residual limits in the past. These regulatory bodies have established the residual limit for AG in milk, edible tissue, and other foodstuff (Farouk *et al*., 2015). The residual limits for AGs in food from animal origin are given in Table 1.

To ensure that the food substance from the animal origin meets the accepted MRL the analyst must develop a fast and economical method to analyze the sample instantaneously, which help them to grade and prohibit if found to have residuals above the accepted limit. The analytical methods employed are divided as screening method where the residue should be less than the detection limit and, quantitative method.

AG as residue in water

The antimicrobials like AG when administered are excreted unchanged from human body and animals, in addition to this the disposal of medical waste deliberately or non-deliberately from the medical industry to the surface water has increased the level of contamination compared to the past.

In case of analysis for residuals in water, the major challenge involved is in pre-concentrating the sample so that the content is in the required detection limit. As per the report published by the International Joint Commission, only 50% of the medical wastes are removed through sewage treatment before disposal into water bodies. In the developing countries, sewage water treatment is an important concern where health and environmental shortcomings are present. The presence of antibiotics in the water will affect the aquatic environment too. As mentioned preconcentrating the sample remains the major challenge, e.g., the use of solid phase extraction by using a cationic exchanger is employed in the analysis of Gentamicin in hospital wastewater. The immunoassay like enzyme linked immunosorbent assay (ELISA) is a reported method for screening of AG, such as streptomycin, neomycin, and gentamicin. Considering the presence of weak chromophore, the spectroscopic method is applicable only after derivatization. It has been reported that the method is applicable only to a dynamic range but not up to the residual limit in ng/kg; therefore, the LC remains the most appropriate method (Forge and Schacht, 2000).

Profiling impurities and its identification

The AG is mostly present as a mixture of components. For instance, if we take gentamicin the compound is present as a mixture of isomeric components called gentamicin complex. The components namely are gentamicin C1, C1A, C2A, C2, and C2B. The problem associated in such case during method development is, the individual standard for each of the components are not available for comparison. The order of elution is made based on the existing literature or based on compendial data (Stypulkowska *et al*., 2010).

When it comes to the related substance of AG, most of them are difficult to separate and some are yet to be discovered. If we take gentamicin itself, the US pharmacopoeia mentions four related substance for gentamicin, but only for two substances, the individual standard is available and are included in the pharmacopoeia method (Clarot *et al*., 2004).

In the developing countries like India, profiling impurities are of at most important where the local industries prefer to procure raw materials of poor quality from which the final product is also made. The current methods may not be sufficient to detect these impurities sometime and, with respect to AG, the situation is more demanding and challenging, hence sophisticated instruments are used. The current reported methods for AG include LC-MS, LC–ELSD, etc. The microbial assay is recommended as a determination method for gentamicin by WHO (Farouk *et al*., 2015).

Therapeutic drug monitoring (TDM) for AG

The AG at present are used to treat serious infection caused due to Gram-negative bacteria. Though newer and less toxic antibiotics are available, the AG remain the choice for serious infection. TDM for AG are important since they have a short therapeutic range. The abusive use of AG will have potential side effects, such as ototoxicity, nephrotoxicity, and neuromuscular paralysis (Carlier *et al*., 2015).

To maintain an adequate plasma level and to avoid toxicity, TDM of AG is important. The therapeutic window of AG is less; moreover, the excretion depends greatly on the renal function. Therefore, variation in the plasma concentration exists

Table 1. Residual limits of various AGs in food materials.

Aminoglycosides	Residual limits (µg/kg)				References
	Meat	Milk	Eggs	Honey	
Streptomycin	500	200	-	40	Ferguson *et al*., 2002
Gentamycin	2.7	200	-	-	Chen *et al*., 2008 Tan *et al*., 2009
Neomycin	500	1,500	500	-	Jin *et al*., 2006b
Kanamycin	50	150	0.01	-	Loomans *et al*., 2003 Bousova *et al*., 2013 Jiang *et al*., 2019
Tobramycin	0.61×10^{-3}	0.548	-	-	Jiang *et al*., 2018 Pavlov, 2005
Spectinomycin	5,000	200	-	-	Di Corcia *et al*., 2002
Apramycin	5,000		-	-	Di Corcia *et al*., 2002
Paromomycin	1,500	100	-	-	Bohm *et al*., 2013

from patients to patients, e.g., in elderly and renal impaired patients. Hence in hospitals, a suitable method for its analysis is required for constant plasma concentration monitoring.

The current analytical methods for TDM is microbial assay, HPLC method with UV detector is reported (Li *et al*., 2012), LC-MS and GC-MS. The preferred method used is immunoassay and is the official assay method by USP-NF. The common problem faced during immunoassay is interference due to inhibitors and other degradation products. The HPLC method with UV detector is reported for the analysis, but the absence of chromophore makes the process of analysis more critical and complex due to the involvement of derivatization.

In recent time, computer-based software, such as Aladdin®, TCIWorks®, or SeBagen®, has been utilized to calculate pharmacokinetics by two sample measurements for aminoglycoside. This software can also suggest future dosing compared to dosage adjustment from the obtained data in the conventional method (trial and error until a steady state) (Reeves, 1980).

EXTRACTION AND CLEAN-UP PROCEDURE

The AG due to their physio-chemical property put forward some challenges in the extraction and clean up before application of the analytical method to the biological samples. The properties, such as basicity, high water solubility, and hydrophilicity, make AG highly susceptible to photodegradation making the sample extraction process complex (Santos and Ramos, 2016). Moreover, the selective removal of possible interfering substance in a biological sample is difficult to achieve (Reeves, 1980).

General procedure for the extraction

The general procedure for the extraction of AG from the tissue is shown in Figure 2. It involved the tissue homogenization by using the suitable homogenizer. Protein precipitation from the tissue homogenate can be performed with the addition of chilled methanol or acetonitrile along with the vigorous mechanical shaking. Later, the sample can be centrifuged or settled down to separate the precipitate from the supernatant.

METHODS FOR ANALYSIS OF AG

The analytical method involved in the analysis of AG can be divided into two, qualitative method and quantitative method.

Quantitative method

As the AGs having poor oral bioavailability, it's detection and quantification in plasma is challenging due to less drug availability. Thus, the quantitative analysis of AGs in plasma or tissue from the oral dosage forms (solid) is quite tough as compared to the parenteral dosage forms. Thus, the very sensitive analytical technique with very low limit of detection as well as quantification will be expected to develop (Omar *et al*., 2013). The quantitative method for AG includes microbial and liquid chromatographic method. The microbial assay remains as a traditional method for assay. The microbial method is used for the estimation of AG potency by comparing the area of inhibition of microbial growth for a known amount of test sample in a biological medium and a reference substance. The method is inexpensive and easy to perform but is subjected to interference by other inhibitors. It has been reported that the microbial assay fails to meet the acceptance criteria for precision and accuracy in the analysis of neomycin; hence, the monograph method has been changed to LC method (Gunawardana *et al*., 1997). The AG being hydrophilic in nature does not strongly bind to the protein in the matrix, which makes the microbial method challenging. The other microbial methods include radioimmunoassay, radiochemical assay, and enzyme-linked immunosorbent assay. The various quantitative analytical techniques reported are given in Table 2.

These methods are highly sensitive and precise; but they possess drawbacks like high equipment cost, difficulty in handling of radioactive substances. Like microbial assay, cross-reactivity is observed in these methods too. Physio-chemical property of AG put forward challenges in development and use of the LC method. The highlighted challenges have already been covered in the previous section of this article. The challenges faced during the development of the method have been resolved and adequate literature has been published. The absence of the chromophore in

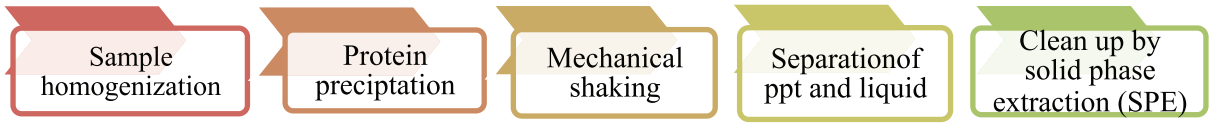

Figure 2. General procedure for the extraction of AG from the tissue.

Table 2. Reported analytical techniques for various AGs.

Types of AG	Reported quantitative analytical techniques	References
Tobramycin	RP-HPLC, RP-HPLC-MS, Radioimmuno assay, HPLC-ELSD	(Ruckmani *et al*., 2011; Guo *et al*., 2006; Broughton *et al*., 1976; Megoulas and Koupparis, 2005b)
Streptomycin	RP-HPLC, LC-MS/MS	(Granados and Meza, 2007; Bohm *et al*., 2012)
Amikacin	LC-MS, RP-HPLC,	(Dijkstra *et al*., 2014; Teja *et al*., 2018)
Kanamycin	HPLC-NQAD (nano quantity analyte detector) and HPLC-ELSD, Colorometric estimation,	(Zhu *et al*., 2014; Hussien *et al*., 2017; Dijkstra *et al*., 2016)
Gentamycin	Microbial assay and RP-HPLC, ELISA, Extractive colorimetry	(Kumar and Ramya, 2012; Brion *et al*., 2002; Fraihat, 2015)
Neomycin	HPTLC and densitometry, microbial agar diffusion assay, HPLC-ELSD	(Hubicka *et al*., 2015; Yamamoto and Pinto, 1996; Zhang and Zhang, 2007)

AG is overcome using universal detectors like CAD, ELSD and RI detector (Clarot *et al*., 2004; Li *et al*., 2012; Samain *et al*., 1987) or can be applied to UV/Fluorescence detector by pre or post-column derivatization (Kowalczuk *et al*., 2010).

The choice between the pre and post-column derivatization is done based on a few factors, such as desired sensitivity, sample size, and instrument availability. The pre-column derivatization is simple compared to post column derivatization were complex instrumentation is required.

The process of derivatization is basically achieved by modifying the primary amine group present. The various agents used include fluorenylmethyloxycarbonyl chloride, dansyl chloride, 1-fluoro-2,4-dinitrobenzene, and o-phthalaldehyde (OPA). The OPA is commonly used in both pre and post-column derivatization, in which it reacts with a primary amine in an aqueous basic medium (pH 9-11) in the presence of mercaptans to give an isoindole derivative (Coppex and Walz, 2000). Hence, this enables the use of RP-HPLC rather than complex ion pair liquid chromatography (IP-LC) method.

The process of derivatization always remains critical with few drawbacks, such as loss of analyte due to additional treatment step, incomplete reaction, formation of the unstable product, and insufficient reaction time are present. The post column derivatization is generally limited in use due to a various additional complex process.

The LC-MS is widely applied for the analysis of AG. The challenge faced during the analysis is, upon fragmentation the different ion of AG show almost the same mass to charge ratio due to high structural similarity. This is to be added to the challenges in LC separation, already addressed in the previous section. Thus, care should be taken to avoid interference in the selection of product-ion combination or precursor-ion for selected reaction monitoring. As per the problems associated with the estimation of AG by using current analytical techniques, the alternatives methods has been developed and are in progress of modifications in order to easy and effective quantification. These methods are quite expensive due to involvement of additional steps and chemicals. Methods like use of molecularly imprinted polymers for solid phase extraction for clean-up procedure in application with LC-MS techniques, use of zwitterionic HILIC stationary phase along with MS as well as use of light scattering techniques has future scope for AG estimation.

The varieties of buffer mediums are available for AG estimation in various samples based on stability as well as ability for ion pairing. The selection of specific buffer medium is depends upon the analytical technique and sample stability. The various media used in AG analysis are shown in Table 3. Varieties of analytical techniques are available for the quantitative analysis of AGs. Choice of specific technique depends on the sensitivity, selectivity, time, and economy. As extensive data of various analytical techniques are available on quantitation of AGs from variety of samples, that found to be quite difficult correlate and compare. Thus, in this review the specific analytical data of RP-HPLC of various AGs with their internal standards, limits of detection (LOD), limits of quantification (LOQ), and retention time have been depicted in Table 4.

Stability indicating analytical techniques for AGs

Stability is the major concern of any drug in its dosage form during the storage period. International Conference on Harmonization guidelines provides the specific stability indicating protocol for AGs in pure as well as in pharmaceutical dosage forms. The most preferred technique is force degradation studies under

Table 3. Various types of media used for AG detection.

Type of detection	Analytes	Method	Medium used	Refrences
In-vitro	Standards and test solutions	HPLC	Heptafluorobutyric acid (HFBA); ammonium formate; formic acid (FA); sodium sulphate, sodium octanesulphate and phosphate buffer mixture; ammonium acetate; ammonium formate	Megoulas and Koupparis, 2005; Wei *et al*., 2014; Adams *et al*., 1997; Cheng *et al*., 2010; Lee *et al*., 2016; Zhang *et al*., 2019
Ex vivo	Cell analytes	Immunofluoroscence	Minimal essential medium (MEM) and saline phosphate buffer; TRIS buffer;	Myrdal *et al*., 2005; Karasawa *et al*., 2008
In-vivo	Organ extract, chicken meat, human plasma, milk, egg	LC-MS	HFBA; HFBA and FA mixture; tetrafluoroacetic acid; ammonium acetate; ammonium formate	Zhu *et al*., 2008; Bousova *et al*., 2013; Tao *et al*. 2012; Wang *et al*., 2016; Kumar *et al*., 2011; Zhang *et al*., 2019
	Plasma and milk	ELISA, Radioimmunoassay	TRIS-HCl, saline phosphate buffer	Jin *et al*., 2006a; Dols and Van Zanten, 1981

Table 4. Various analytical details of AGs by RP-HPLC technique.

Types of AG	Internal standards used	LOD	LOQ	Retention Time (Min)	Reference
Gentamycin	Tobramycin	25 µg/kg	50 µg/kg	6	Salah *et al*., 2015
Tobramycin	Gentamycin C1	3 mg/l	10 mg/l	3	Blanchaert *et al*., 2017
Amikacin	Gentamycin C1	0.5 mg/l	1.5 mg/l	4.5	Blanchaert *et al*., 2017
Streptomycin	Dihydrostreptomycin	0.5 µg/ml	3 µg/ml	6.10	Granados *et al*., 2007
Kanamycin	Tobramycin	15 ng/g	25 ng/g	8.5	Zhang *et al*., 2019
Neomycin	Amikacin	0.02 µg/ml	0.06 µg/ml	3.30	Balaswami *et al*., 2018

thermal, photolytic, acidic, alkaline, and oxidizing conditions. The thermal degradation AG will be conducted at 70°C for 48 hours. In case of photo-degradation studies, specific amount of AG solution will be exposed to sunlight for 48 hours. The drug will be heated at 0.1 MHCl at 80°C for 2 hours under reflux for acid degradation. For alkaline degradation, the drug will be treated at 80oC with 0.1 M NaOH for 2 hours, whereas in case of oxidative degradation, the drug will be heated with H_2O_2 at 80°C for 2 hours under reflux (Blanchaert *et al*., 2017).

Qualitative methods

The qualitative method used for AG analysis includes X-ray crystallography, nuclear magnetic resonance, mass spectroscopy. The preparation of purified AG form amorphous solid, hence not suitable for aminoglycoside analysis. The proton and 13 C-NMR spectroscopic methods are used for structural determination of AG. MS is also used in structural and enzyme modified analysis. Recently, a study has reported the use of fast atom bombardment or electron spray with tandem MS in the determination of positional isomers of kanamycin A (Cox and Serpersu, 1995; Kotretsou and Constantinou-Kokotou, 1998).

CONCLUSION

Although newer and less toxic antimicrobials are introduced into the market, the AG remains to be the drug of choice for serious infection due to Gram-negative bacteria. AG being a potent class of antibiotics with a shorter therapeutic window and potential side effects. Constant monitoring on its level of presence in the biological system needs to be done. For this reason, a simple, economic, and relatively fast analytical method for routine analysis is required. Although microbial assay is but it lacks specificity, accuracy, and may subject to interference, so the chromatographic method remains as a better choice to meet the requirement. The detector of interest is based on availability and financial aspect, due to the absence of chromophore UV is not a common method of choice and thus, its properties restrict the use of common RP-HPLC method. Hence, there is a huge potential gap in AG analysis where more research can be carried out. The use of combination of chromatographic techniques along with mass spectroscopy will be the best methods for AG quantification.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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