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REVIEW ARTICLE

Analytical methods for amino acid determination in organisms

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Abstract
Amino acids are important metabolites for tissue metabolism, growth, maintenance, and repair, which are basic life necessities. Therefore, summarizing analytical methods for amino acid determination in organisms is important. In the past decades, analytical methods for amino acids have developed rapidly but have not been fully explored. Thus, this article provides reference to analytical methods for amino acids in organisms for food and human research. Present amino acid analysis methods include thin-layer chromatography, high-performance liquid chromatography, liquid chromatography–mass spectrometer, gas chromatography–mass spectrometry, capillary electrophoresis, nuclear magnetic resonance, and amino acid analyzer analysis.

Keywords Amino acids · Analytical method · Derivation · Liquidity

Abbreviations

AA Amino acid
ACBA 4-Amino-2-chlorobenzoic acid
AQC 6-Aminoquinolyl-*N*-hydroxysuccinimidyl carbamate
BCAA Branched chain amino acid
DEEMM Diethyl ethoxymethylenemalonate
FMOC-Cl Fluorenylmethyl chloroformate
HILIC Hydrophilic interaction liquid chromatography combined
HSCE High-speed capillary electrophoresis
OPA *o*-Phthalaldehyde
PITC Phenylisothiocyanate

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Introduction

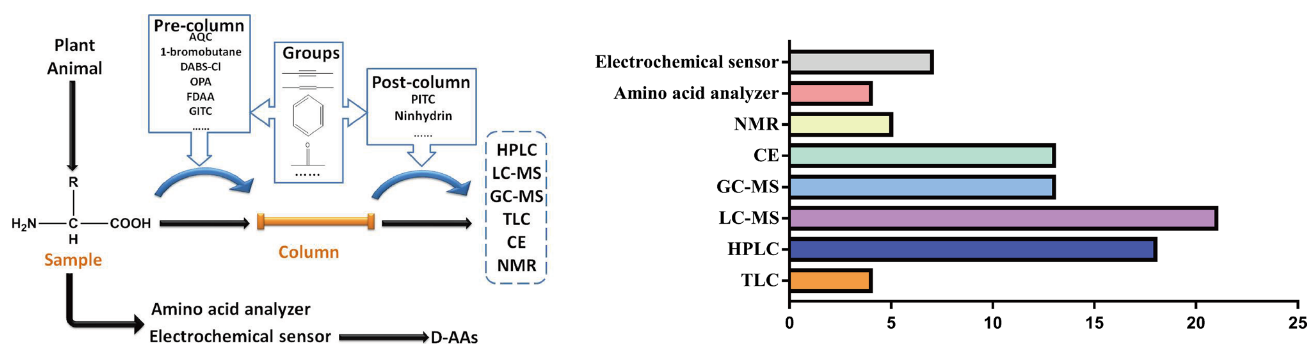
Amino acids (AAs) are the most important chemical structures in organisms and generally categorized into nonessential and essential AAs (Marouzi et al. 2017; Choi et al. 2007). The quantity and quality of AAs are required for analysis in the fields of medicine, food, feed, agriculture, and chemistry. Moreover, essential AAs constitute approximately 20–37% of the protein requirement of a human adult, and some AAs are potential biomarkers of diseases.

Apart from participating in protein biosynthesis (Johnson et al. 2014), AAs also serve as precursors for many hormones, neurotransmitters (Tian et al. 2018), and other specialized metabolites (Broer and Broer 2017; Hildebrandt et al. 2015). For example, glu can be used as an acidic AA in metabolism and as an excitatory neurotransmitter of information. Dietary AA patterns with high levels of gly, cys, arg, and try may be associated with reduced risk of cardiovascular events (Mirmiran et al. 2017). Thus, some AAs in food should be explored, especially those from animals and plants (Mondanelli et al. 2019; Berrazaga et al. 2019; Tosti et al. 2018; Young and Pellett 1987). In addition, AA catabolism can influence plant growth and development, such as intracellular pH control and metabolic energy generation. Furthermore, analytical methods for AAs research enable the evaluation of

plant quality because AAs provide nutrition to humans and can be extracted for medicinal components. D-AAs are considered unnatural AAs (Gao et al. 2015) but are recognized as naturally occurring physiologically active substances and biomarkers in mammals (Miyoshi et al. 2012). Some D-AAs occur in food under high temperatures (Hayase et al. 1975) and alkali treatment (Friedman et al. 1984). Furthermore, D-Asp and D-Asn are found in the peptidoglycans of some bacteria (Veiga et al. 2006). D-AAs have many applications; for example, they can be used as sweeteners. The functions of D-AAs have attracted attention, but sensitive and high-throughput analytical methods for analyzing D-AAs remains inadequate (Muller et al. 2014). To date, electrochemical sensors are generally used to detect D-AAs. Given that most AAs are small aliphatic molecules incapable of fluorescence or UV absorption, analyzing AAs is difficult (Ou et al. 2013). To better analyze AAs, pre-column or post-column derivation of AAs is performed for detection, then the AAs are detected by HPLC, LC–MS, or GC–MS (Furst et al. 1990; Fierabracci et al. 1991; Gogichaeva and Alterman 2012). Advanced techniques for quantifying AAs include CE, NMR, and amino acid analysis.

Other articles discuss several analytical methods for AAs without introducing derivatizations. The current article comprehensively compares current analytical methods and discusses AA applications in food and human research. Induced derivatizations are used to supply information for drug discovery, disease detection, and food nutrition exploration.

The structure diagram of the methods and analytical techniques mentioned in this review and their properties are summarized in Fig. 1.



Properties / Method	Simple	convenient	Cheap	Effective	Sensitivity	Fast time	cost-effective	Wide range	Repeatability	Qualitative	Quantitative	Diadvantages
TLC	+	+	+	+			+			+		No quantitative Poor identification ability
HPLC				+	+		++	+	+	+	+	Extra column effect
LC-MS		+		++	++	+		+		+	+	Poor differentiation of isomers and stereochemistry ion source pollution
GC-MS	+			++	++					+	+	Samples can vaporize and ionize many isomers (especially positional isomerism) cannot be distinguished
CE				+	++	+		+	+	+	+	Weak separation ability high pH requirement
NMR								+		+	+	Expensive
Amino acid analyzer	+			+				+		+	+	Expensive
Electrochemical sensor	+	+				+				+	+	

+ More
++ High

Fig. 1 Analytical techniques for AAs in this review

Derivatizations

Given that most AAs lack natural UV or fluorescence absorption functional groups, chemical derivation has become an effective way for increasing the sensitivity of AA detection (Sharma et al. 2014; Pretorius et al. 2018; Sakaguchi et al. 2015; Stocchi et al. 1992; Sherwood 2000; Hess 2012; Fonseca et al. 2018; de Puit et al. 2014; Toue et al. 2014; Rebane et al. 2012; Oldekop et al. 2017a, b; Yang et al. 2017; Miyoshi et al. 2014). The structure for most common derivation reagents is displayed in Fig. 2. Information about common chemical derivation reagents and derivation conditions is summarized in Table 1. Of these reagents, only with 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate (AQC), fluorenylmethyl chloroformate (FMOC-Cl), and phenylisothiocyanate (PITC) can react with primary and secondary AAs simultaneously. However, AQC and FMOC-Cl hydrolysis products sometimes interfere with detection, and the derivatives of PITC are unstable. Moreover, PITC must be removed from a sample for the prevention of column contamination. *o*-Phthalaldehyde (OPA) does not react with secondary AAs and its derivatives are sometimes unstable. Therefore, derivation reagents should be carefully selected. It must react with AAs directly as soon as possible and stable for a long time.

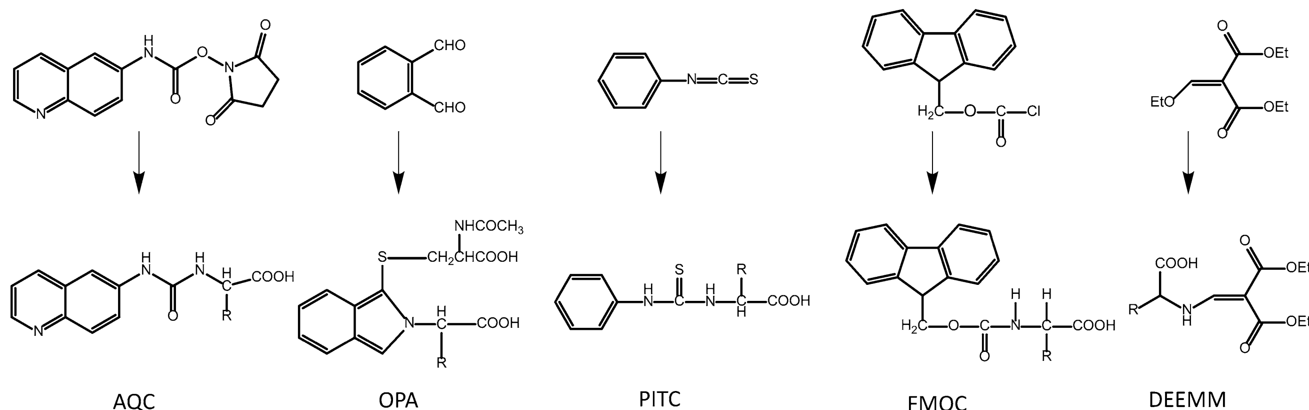


Fig. 2 The common derivation reagents for AAs

Table 1 Commonly derivation reagents and conditions

Derivation reagents	Type	Conditions		Method	References
		Temperature/°C	Time		
AQC	Pre-column	55	10 min	HPLC/LC–MS	Sharma et al. (2014); Pretorius et al. (2018)
1-bromobutane	Pre-column	80	30 min	LC–MS	Sakaguchi et al. (2015)
DABS-Cl	Pre-column	70	10 min	RP–HPLC	Stocchi et al. (1992)
PITC	Pre-column	Less than 45	20 min	HPLC(UV/ECD)	Sherwood (2000)
OPA	Pre-column	RT/dark	20 min/1 min	LC–MS/LC–FID	Hess (2012); Fonseca et al. (2018)
FDAA	Pre-column	50	1 h	LC–MS	Hess (2012)
GITC	Pre-column	RT	10 min	LC–MS	Hess (2012)
FMOC	Pre-column	RT	20 min	LC–MS	de Puit et al. (2014)
TAHS	–	50/RT	10 min	CE–MS/LC–ESI–MS	Toue et al. (2014); Rebane et al. (2012)
FOSF	–	RT	10 min/--	LC–ESI–MS/LC–APCI–MS	Rebane et al. (2012); Oldekop et al. (2017a)
DNS	–	6/dark	45 min	LC–MS	Rebane et al. (2012)
DEEMM	Pre-column	RT/dark	24 h	LC–ESI–MS/MS	Oldekop et al. (2017b)
ECF	–	–	30 s + 30 s	UHR–FTMS	Yang et al. (2017)
NBD-F	Pre-column	60	2 min	HPLC	Miyoshi et al. (2014)

RT room temperature

Amino acid analysis

Thin-layer chromatography

TLC is widely used in the separation and identification of AAs, peptides, lipids, and alkaloids. It is simple, convenient, and cost effective (Yousefinejad et al. 2015; Lu and Olesik 2013). Reversed-phase chromatographic analysis is usually performed on AAs, such as isoleu, leu, val, ala, gly, and orn (Nguyen et al. 2016). Separating racemic mixtures is necessary due to different pharmacological activities. In a previous paper, aromatic AAs were analyzed by using Spi(τ-dec) as a chiral selector for high-performance thin-layer chromatography (Remelli et al. 2014).

High-performance liquid chromatography

HPLC can be used for the qualitative and quantitative analysis of AAs and exhibits high efficiency, high sensitivity, a wide range of applications, and other advantages. In recent years, numerous HPLC methods capable of FL/UV detection have been developed for the analysis of AAs. The concrete detection conditions of the methods are summarized in Table 2.

The analysis of free AAs in biological samples requires the removal of proteins by hydrolysis before derivation and detection. For example, porcine gelatin and bovine gelatins are heated with NaOH to hydrolyze before derivation by OPA (Rezazadeh et al. 2015). Furthermore, pulsed electromembrane extraction is an interesting way for extracting AA derivatives. Finally, Asn and Gln were analyzed within 20 min at 330 nm. Small volumes of plasma samples from children and individuals with critical illnesses are useful in testing. Only 50 μL of plasma volume is required for the simultaneous determination of 33 kinds of derivatized AAs (Wang et al. 2013). A total of 23 kinds of AA PTH derivatives were constructed with HPLC–DAD; this method provides information on the AA contents of peptides (Tasakis and Touraki 2018). Chloroprocaine, especially its inactive metabolite 4-amino-2-chlorobenzoic acid (ACBA), can be quantified through HPLC/MS (De Gregori et al. 2018). A simple HPLC method was developed to directly determine gly in immunoglobulins (Rounova et al. 2018). Plant–animal linkages, such as insect–plant interactions, can be explored by analyzing AAs. First, samples are hydrolyzed into AAs, then plant and insect samples are reconstituted. AA derivatives can be separated by using HPLC–PDA within 36 min (Dhillon et al. 2014). This method is highly sensitive and reproducible and is essential to the analysis of AAs. Core–shell particle columns are potential tools for clarifying the biological activities of AAs (Song et al. 2013). LC–FLD method for quantitative determination neuroactive AAs in rat brain is essential to several neurological diseases (Fonseca et al. 2018). Furthermore, a method for simultaneously detecting 17 kinds of AAs through HPLC is currently available (Nagasaki et al. 2017). Dr. Daniel Armstrong's group suggested that mammalian brains have unreported D-AAs (Gao et al. 2015; Weatherly et al. 2017). They also analyzed D-AAs in mammals by HPLC with FMOC derivation.

AAs in plants play different roles. For example, gly can promote plant photosynthesis. Similar to biological samples, plant samples need to be hydrolyzed and derivatized. Most studies showed that glu is the most abundant AA in plant proteins; however, in manketti seed kernel flour, the most abundant AA is arg (Gwatidzo et al. 2013). AAs are the important components of chamomile flowers, and 14 kinds of AAs were analyzed with HPLC (Ma et al. 2015). The effect of rhizobial strains on the accumulation of AAs in nodules can be analyzed by HPLC with UV (Bertrand et al. 2016). Furthermore, 19 kinds of AAs are usually employed in HPLC–CAD for the detection of underivatized quantization (Furota et al. 2018).

Diethyl ethoxymethylenemalonate (DEEMM) derivation is followed by UHPLC separation and was used to quantify 21 kinds of AAs in beer (Redruello et al. 2017) with high resolution, accuracy, and sensitivity. Seventeen kinds of AAs in different feeds were analyzed with UPLC (Szkudzińska et al. 2017). HPLC–FL was used for the quantification of free AAs in rice and this method has good linearity, repeatability, and reproducibility (Liyanaarachchi et al. 2018). In addition, 20 kinds of AAs were examined at 338 nm and 266 nm by HPLC (Lamp et al. 2018), and 26 kinds of AAs were extracted at 340/450 and 266/305 nm with UPLC (Manninen et al. 2018).

Liquid chromatography–mass spectrometer

With the development of mass spectrometry and separation methods, LC–MS has become an essential analytical tool for separating AAs (Tsai et al. 2016). Here, LC–MS/MS and UPLC–MS/MS are listed. Concrete detection conditions of the methods are summarized in Table 3.

There are some examples of AAs analyzed by LC–MS. The plasma contains a variety of AAs, and each kind of AA has its own effect. For example, met is involved in the formation of hemoglobin, tissue, and serum and promotes the function of the spleen, pancreas, and lymph. By analyzing underivatized AAs by LC–MS/MS, the means to eliminate the variation can be discovered; a method for all clinically relevant AAs is presently available (Le et al. 2014). HCY concentrations in human sera can indicate some diseases, and HCY concentrations can be quantified by LC–MS/MS bioanalytical method (Ghassabian et al. 2014). LC–MS/

Table 2 Analysis of the chromatographic conditions and results of AAs by HPLC

Method	Detected	Column	Mobile phase	Wavelength	References
RP–HPLC	Asn and Gln	ODS—3 (250 mm × 4.6 mm, 5 mm)	A: 65% of a 40 mmol L^{-1} acetate buffer (pH5.5) B: 35% of MeOH	330 nm	Rezazadeh et al. (2015)
HPLC–UV/FL	Hyp, Asp, Asn, Glu, Gln, etc	C_{18} Gemini-NX (150 mm × 4.6 mm, 3 µm)	A: 50 mL buffer glacial acetic acid (pH 4.90)—20 g ethanol B: ACN C: Water D: 1:50 dilution of buffer glacial acetic acid (pH 5.85)	Fluorescence trace (Ex. 250 nm, Em. 395 nm)/UV: 250 nm	Wang et al. (2013)
HPLC–DAD	Asp, Glu, Gln, Asn, Gly, etc	Vydac C_{18} (4.6 mm × 250 mm, 5 µm)	A: Sodium acetate 0.28 M (pH 6.7) – 5% ACN—0.05% triethylamine B: 60% (v/v) of ACN	220, 280, and 254 nm	Tasakis and Touraki (2018)
HPLC–MS/MS	Chloroprocaine, ACBA	Kinetex C_{18} (100 × 4.6 mm, 2.6 µm)	A: Ultrapure water B:MeOH were both acidified with formic acid	291 nm	De Gregori et al. (2018)
HPLC	Gly	SeQuant ZIC-HILIC (250 mm × 4.6 mm, 5 µm)	A: 20 mM ammonium formate (pH 4.5 adjusted with acetic acid) B: 70% (v/v) of ACN	210 nm	Rounova et al. (2018)
HPLC–PDA	Asp, Ser, Glu, Gly, His, etc	Waters Silica-bonded Amino Acid C_{18} (3.9 mm × 150 mm)	A:10% Waters AccQ Tag Eluent A Concentrate B: 60% (v/v) of ACN	254 nm	Dhillon et al. (2014)
HPLC–FL	His, Asn, Gln, Ser, Arg, etc	Kinetex C_{18} (150 mm × 3 mm, 2.6 µm)	A: Water/ACN/TFA (90:10:0.12, v/v/v) B: water/ACN/TFA (10:90:0.12, v/v/v)	Ex. 470 nm Em. 530 nm	Song et al. (2013)
HPLC–FLD	Asp, Glu, Gln, Tau, GABA	LiChroCART® C_{18} Purospher Star (55 mm × 4 mm, 3 µm)	A: Aqueous acetate buffer 25 mM (pH 5.4) B: ACN	Ex. 340 nm Em. 448 nm	Fonseca et al. (2018)
HPLC	His, Arg, Ala, Tyr, Pro, etc	VXODS (250 mm × 4.6 mm, 5 µm)	A: 0.1 M ammonium acetate/ACN (95:5, v/v) (pH 6.3 adjusted with acetic acid) B: 60% (v/v) of ACN	–	Nagasaki et al. (2017)
HPLC	Asp, Glu, Gly, His, Arg, etc	Varian Chromsep SS C_{18} column (250 mm × 4.6 mm)	A: 60 mM sodium acetate (pH 6.35) B: 60% (v/v) of ACN C: Milli-Q water	Ex. 250 nm Em. 395 nm	Gwatidzo et al. (2013)
RP–HPLC	Asp, Glu, Ser, Gly, His, etc	Shimpack C_{18} (12.5 mm × 4.6 mm, 4 µm)	A: 0.3 M sodium acetate containing 5% ACN (pH 6.5); B: ACN/MeOH/Milli-Q water (20:60:20, v/v/v)	Ex. 250 nm Em. 395 nm	Ma et al. (2015)
UPLC	Asn, Pro, Asp, Gln, Glu, etc	AccQ Tag Ultra C_{18} (2.1 × 100 mm)	–	260 nm	Bertrand et al. (2016)
HPLC–CAD	Gly, Ser, Ala, Hyp, Thr, etc	Hypercarb (2.1 mm × 150 mm, 5 µm)	A: Distilled water with 23 mM NFPA B: 100% (v/v) of ACN	–	Furota et al. (2018)

Table 2 (continued)

Method	Detected	Column	Mobile phase	Wavelength	References
UPLC	Asp, Glu, His, Val, Met, etc	–	A: 25 mM acetate buffer plus 0.02% sodium azide B: MeOH C: ACN	–	Redruello et al. (2017)
UPLC	His, Ser, Arg, Gly, Asp, etc	AccQ-Tag Ultra C_{18} (2.1 mm × 100 mm, 1.7 µm)	A: ammonium formate/formic acid/ACN (84:6:10, v/v/v) B: ACN/formic acid (98:2, v/v)	260 nm	Szkudzińska et al. (2017)
HPLC–FL	Asp, Glu, Asn, Ser, Gln, etc	Gemini (4.6 mm × 150 mm, 5 mm)	A: 40 mM Na_2HPO_4 at pH 7.8 B: ACN/MeOH /water (45:45:10, v/v/v)	–	Liyanaarachchi et al. (2018)
HPLC	Ala, Asp, Arg, Glu, Gly, etc	Poroshell LC HPH-18 (4.6 mm × 100 mm, 2.7 µm)	A: aqueous buffer at pH 8.4 B: MeOH/ACN/water (45:45:10, v/v/v)	338, 266 nm	Lamp et al. (2018)
UPLC	β-Alanine, L-Ala, L-Arg, L-His, L-Met, etc	Kinetex C_{18} 100 Å (100 mm × 4.6 mm, 2.6 µm)	A: 20 mM phosphate buffer with pH 6.5 B: ACN/MeOH/water (45:45:115, v/v/v)	Ex. 340, 266 nm Em. 450, 305 nm	Manninen et al. (2018)

MS serve as a useful tool for diabetes because LC–MS/MS directly determines branched chain amino acid (BCAAs) and aromatic AAs in human sera (Yang et al. 2013). Furthermore, plasma AA concentrations in patients with major depressive disorder can be analyzed by LC–MS/MS (Woo et al. 2015). Twenty-four kinds of AAs in human plasma were simultaneously quantified for studying the effects of renal function in de novo kidney (Klepacki et al. 2016). Nakano et al. (2017) simultaneously analyzed 18 kinds of D-AAs without derivation process and applied the method to vinegar for the validation which successfully quantified D-AAs in samples. Multiple AA enantiomers were simultaneously determined in human serum (Han et al. 2018). Moreover, D-Ser in human plasma (Xie et al. 2014) or mouse brains (Kinoshita et al. 2013) can be determined by LC–MS/MS.

Twenty kinds of plant extract AAs with derivation were analyzed by LC–MS/MS based on MRM (Ziegler and Abel 2014). The AAs in natural waters were measured with SPE by LC–MS/MS (How et al. 2014). Guerrasio et al. (2014) developed a novel hydrophilic interaction liquid chromatography combined with electrospray tandem mass spectrometry (HILIC–MS/MS) analytical method for the quantitation of 17 kinds of AAs, and they use a *Pichia pastoris* cell extract grown on uniformly ^{13}C-labeled glu as an internal standard. Free AAs of Polish and Slovak honeys were characterized by using LC–MS/MS without derivation (Kowalski et al. 2017).

UPLC is another new technology that uses small particles as a stationary phase to achieve ultra-high resolution, sensitivity, and analysis speed. MS can analyze mass-to-charge ratios. Furthermore, UPLC is one of the most optimal entrances of MS. The combination of UPLC and MS significantly improves the reproducibility, the reliability, and the accuracy of qualitative analysis. Many AAs are analyzed by UPLC–MS.

Twenty kinds of AAs and their tracer(s) in human plasma and skeletal muscle can be quantified, and the LC–MS/MS method may be applied to other matrices (Borno and van Hall 2014). The derivation procedure is capable of measuring low enrichment levels, and this procedure is important for human plasma (Oosterink et al. 2014). Simultaneously determining 20 kinds of AAs in plasma at different collecting time points can be achieve by UPLC–MS/MS (Xia et al. 2016b). UPLC–ESI–MS/MS can completely separate pairs of nine kinds of AAs and propose a differential analysis of D/L-amino using light and heavy l-PGA-OSu (Mochizuki et al. 2014). A HILIC column can simultaneously quantify 18 kinds of free AAs in the urine, and this method involves simple samples without any derivation (Joyce et al. 2016). AA enantiomers are usually distinguished by RP–UHPLC–Q–TOF–MS method. D-AAs in the different regions of rat brains can be quantified by UPLC–MS/MS (Li et al. 2017). Gao et al. (2015) identified and quantified D-AAs using chemical derivation coupled with nanoliquid chromatography, and this method may open up a window for studying the organic composition of individual micrometeorites.

In the analysis of AAs from food, 22 kinds of DEEMM-derived AAs in 11 herbs and 4 honeys with LC–ESI–MS/

Table 3 Analysis of the chromatographic conditions and results of AAs by LC–MS

Method	Sample	AAs	Column	Mobile phase	Protonation mode	References
LC–MS/MS	Plasma, urine, and cerebrospinal fluid (CSF)	α-Aminobutyrate, β-Ala, β-Ami, Cit, Cys, Eth, etc	Porous graphitic carbon (PGC) (3 µm Hypercarb, 4.6 mm × 50 mm) and a fused-core (2.7 µm Halo C_{18}, 2.1 mm × 100 mm)	A: 1 mM TDFHA acid in water B: 1 mM TDFHA in ACN	SRM^+	Le et al. (2014)
LC–MS/MS	Serum	HCY	XTerra® MS C_{18} (2.1 mm × 150 mm, 5 µm) and Phenomenex Security Guard C_{18}	A: 0.1% acetic acid in water B: 0.1% acetic acid in MeOH	MRM^+	Ghassabian et al. (2014)
LC–MS/MS	Serum	Val, Ile, Leu, Tyr, Phe	Waters Shield C_{18} (3.5 mm, 2.1 × 150 mm)	0.01% formic acid in 10% ACN	MRM^+	Yang et al. (2013)
LC–MS/MS	Plasma	Ala, β-ala, Gly, His, Leu, Hyd, etc	Reverse-phase C_{18} (5 µm, 4.6 mm × 150 mm)	A: 0.1% formic acid in water B: 0.01% hepta fluoro butyric acids in MeOH	MRM^+	Woo et al. (2015)
LC–MS/MS	Plasma	1-Methyl his, 4-Hydroxy pro, Ala, Arg, Cy, His, etc	HILIC (3 µm, 3.0 × 150 mm)	A: ACN/5 mM ammonium acetate (95:5, v/v) B: ACN supplemented with 20 mM ammonium hydroxide	MRM^+	Klepacki et al. (2016)
LC–MS/MS	Vinegars	D-Ala, D-Arg, D-Asn, D-Met, D-Phe, D-Trp, etc	CROWNPAK CR-I(+) and CR-I(-)(5 mm, 3.0 mm × 150 mm)	ACN/EtOH/Water/TFA (80:15:5:0.5, v/v/v)	MRM^+	Nakano et al. (2017)
LC–MS/MS	Human serum, human plasma, urine	D-Ala, D-Arg, D-Asp, D-Gln, D-His, D-Ile, D-Leu, D-Lys, etc	BEH-C_{18} (1.7 µm, 2.1 mm × 150 mm)	A: 20 mM sodium acetate buffer adjusted to pH 6.2 with acetic acid B: 7% ACN in MeOH	–	Muller et al. (2014)
LC–MS/MS	Human serum	D-Arg, D-Ala, D-Ile, D-His, D-Glu, D-Tyr, D-Met, D-Phe, etc	CROWNPAK CR-I(+) (3.0 mm inner diameter × 150 mm, 5 µm)	A: Ethanol, water, and TFA (50:50:0.4, v/v/v) B: ACN/TFA (100:0.4, v/v)	MRM^+	Han et al. (2018)
LC–MS/MS	Human plasma	D-Ser	Zorbax Eclipse XDB-C_{18} (5 µm, 4.6 mm × 150 mm)/CROWNPAK CR(+) (5 µm, 4 mm × 150 mm)	A: Water with 0.3% TFA B: MeOH with 0.3% TFA or 0.3% (v/v) trifluoroacetic acid	MRM^+	Xie et al. (2014); Kinoshita et al. (2013)
LC–MS/MS	Rat brain	D-Ser, D-Ala, D-Pro, D-Val, D-Thr, D-Leu, D-Ile, D-Met	BEH C_{18} (1.7 µm, 2.1 mm × 150 mm)	A: ACN B: 8 mM ammonium hydrogen carbonate	MRM^+	Li et al. (2017)
LC–ESI–MS/MS	*Arabidopsis thaliana* seedling extracts	Ala, Cys, Asp, Glu, Phe, Gly, etc	RP18 (2.7 µm, 50 × 3 mm)	A: 10 mM aqueous ammonium formate buffer pH 4.5 B: ACN	MRM^-	Ziegler and Abel (2014)
LC–MS/MS	Natural waters	Lys, Arg, His, Gly, Se, Asp, etc	Gemini C_{18} column from Phenomenex	30% MeOH(v/v)	MRM^+	How et al. (2014)
HILIC–MS/MS	Pichia pastoris cell extract	Asp, Leu, Tyr, Gln, Phe, etc	Silica-based column (1.8 µm, 100 mm × 2.0 mm)	A: water with 10 mM ammonium formate, pH 3.25 B: ACN	SRM^+	Guerrasio et al. (2014)

Table 3 (continued)

Method	Sample	AAs	Column	Mobile phase	Protonation mode	References
LC–MS/MS	Honeys	Ala, Arg, Asn, Asp, Gln, Glu, etc	Purospher Star RP-8ec (3 µm, 150 mm × 4.6 mm)	A: 1% acetic acid in ACN B:500 mL of 0.05 mM water solution of perfluorooctanoic acid (96%)	MRM^+	Kowalski et al. (2017)
UPLC–MS/MS	Muscle tissue, arterial and femoral venous blood samples	Asp, Glu, Ser, Gly, Asn, Gln, etc	RP C_{18} Kinetex (2.6 µm, 150 mm × 3.00 mm)	A: water with 0.05 M ammonium acetate B: ACN/MeOh/water (44:10:46, v/v/v) with 0.1 M ammonium acetate	SRM^+	Borno and van Hall (2014)
UHPLC–MS	Blood	Cit, Orn, Arg, Phe, Tyr, Glu	Waters Acquity BEH C_{18} (1.7 µm, 100 mm × 2.1 mm)	A:0.5 mM TDFHA and 1 mL/L formic acid B: MeOH with 0.5 mM TDFHA and 1 mL/L formic acid	MRM^+	Oosterink et al. (2014)
UHPLC–MS/MS	Blood	Ser, Cys, Gly, Gln, Thr, Ala, etc	Agilent Zorbax SB-C_{18} (5 µm, 3.0 mm × 150 mm)	A: MeOH B: water (containing 0.2% formic acid and 0.02% heptafluoro butyric acid)	MRM^+	Xia et al. (2016b)
UPLC–ESI–MS/MS	Human serum	Ala, Pro, Tyr, Val, Met, Leu, etc	BEH C_{18} column (1.7 µm, 100 × 2.1 mm)	ACN-water mixture containing 0.1% (v/v) formic acid	SRM^+	Mochizuki et al. (2014)
UPLC–qTOF–MS	Human urine	Phe, Trp, Leu, Ile, Met, Val, etc	Waters ACQUITY UPLC BEH amide column (1.7 µm, 2.1 mm × 100 mm)	A: water with 10 mM ammonium formate and 0.15% formic acid B: ACN, 1 mM ammonium formate, and 0.15% formic acid	MRM^+	Joyce et al. (2016)
UHPLC–ESI–MS/MS	Herbal extracts, honey	His, Arg, Asn, Gln, Ser, Asp, etc	Agilent Zorbax RRHD SB-C_{18} (1.8 mm, 2.1 × 50 mm)	0.1% formic acid in water/ACN(4:96, v/v/v)	MRM^+/MRM^-	Oldekop et al. (2017b)
UPLC–MS/MS	*Pseudomonas aeruginosa* cell extract	Arg, Glu, Cit, Ser, Asp, Gly, etc	Phenomenex EZ: faast AAA-MS (250 mm × 2.0 mm)	A: 10 mM ammonium formate B: 10 mM ammonium formate in MeOH	MRM^+	Ubhi et al. (2013)
UPLC–MS	Murchison meteorite	β-Ala, D-Ala, L-Ala, γ-amino-*n*-butyric acid, D-β-amino-*n*-butyric acid, etc	BEH130 C_{18} (1.7 µm, 150 µm × 100 mm)	A: 10 mM ammonium formate buffer with 5% MeOH, pH 8.3 B: MeOH	–	Callahan et al. (2014)

SRM selected reaction monitoring, *MRM* Multiple reaction monitoring

+ Positive mode, – Negative mode

MS in positive and negative ion ESI modes were found; sample dilution was used for the evaluation of matrix effect (Oldekop et al. 2017b). A rapid, reliable, and high-throughput method for simultaneously measuring AAs, polyamines, and dipeptides in complex biological samples is currently available (Ubhi et al. 2013).

Gas chromatography–mass spectrometry

GC–MS is a widely employed technique for doping test, clinical disease diagnosis, and pharmacokinetics study. GC–MS has a universal detector with high efficiency, simplicity, high sensitivity, and high quantitative accuracy. The concrete detection conditions of the methods are summarized in Table 4.

GC–MS can be used to identify not only the methylated AAs but also the human plasma AAs (Reddy et al. 2016). Lopes et al. (2015) validated GC–MS method for the measurement of six kinds of AAs in canine serum samples and assessed the stability of AAs after sample storage. In TBDMS-derived AAs, 24 novel fragment ions were analyzed by GC–MS/MS; additionally, the precision of ^{13}C-MFA in *Escherichia coli* central carbon metabolism could be improved by introducing the MID data of novel fragment ions (Okahashi et al. 2016). A simple AA extraction method by MAD was developed and 16 kinds of AAs were simultaneously quantified through GC–MS (de Paiva et al. 2013). Furthermore, a rapid method for precisely determining AAs in whole blood is currently available (Kawana et al. 2010). Free and combined AAs in cinobufacini injection were measured with GC–MS (Wu et al. 2015). Twenty kinds of MCF-derived AA enantiomers in serum and urine were separated by comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry (Waldhier et al. 2011). Trp was used as a chiral probe molecule and applied GC was used in the determination of the enantiomeric excess of AAs in solutions that do not have chromophores (Fujihara and Maeda 2017).

With regard to food, GC–MS could simultaneously analyze nine kinds of AAs in mixed starch waste (Liu et al. 2016). This method achieved good linearity and low limit of detection and quantification. The GC–MS can serve as a system for the separation and detection of AAs in potatoes (Uri et al. 2014) and for the quantification of AAs in plant tissues (Vancompernolle et al. 2016). Li et al. (2013) developed a new derivation and microextraction technique for the quantification of AAs in tobacco by GC–MS. Rubino et al. (2014) analyzed the soil AAs by gas chromatography–combustion–isotope ratio mass spectrometry (GC–C–IRMS).

Capillary electrophoresis

CE is a new type of separation technology that uses capillary as separation channel and is driven by high-voltage DC electric field. CE is fast and has high resolution and good repeatability and is widely used in the analysis of AAs, peptides, and proteins. Concrete detection conditions of the methods are summarized in Table 5.

High-speed capillary electrophoresis (HSCE) which can separate 10 kinds of AAs was applied to analyze the composition of AAs in laver, where five kinds of AAs could be completely separated and quantified (Wang et al. 2015). Schiavone et al. (2015) and colleagues employed an electrokinetically pumped, nanospray sheath-flow CE–ESI–MS interface which can illustrate 20 kinds of AA separation in 7 min. Their work led to the separation of leu and isoleu by the structural isomers and reduced the peak trailing and overlapping. A robust, highly selective, and highly sensitive CE–MS method for the direct analysis of phe and tyr in DBS was described. In this method, the CE run time was less than 3 min and exhibited good linearity and lower detection limit (Jeong et al. 2013). A new method which could avoid using chiral selector was presented (Prior et al. 2016). In this method, FLEC was used as a chiral AA-deriving agent and ammonium perfluorooctanoate as volatile pseudo-stationary phase for the separation of the formed diastereomers. They optimized the CE–MS for the analysis of chiral AAs in CSF and indicated that this method has good linearity, acceptable peak area, and electrophoretic mobility and repeatability. Acket et al. (2018) compared CE-HRMS without derivation with classical GC–MS for ^{13}C labeling analysis of AAs form flaxseed. CE as a low-cost method was used for the quantitation of BCAAs in two commercial sport nutritional supplements where good recovery and precision were obtained. The results indicated the analysis of BCAAs in human bioliquid in supplementing the protein to ensure BCAA demand. A method of CE with indirect UV for the separation and determination of nine kinds of AAs (including Asp, Glu, Ser, Thr, Pro, Ile,Trp, Lys, and Met) (Qiu et al. 2017) and this method were applied to determine AAs in honey from different nectar plants and origins (Zhou and Shi 2013).

CE was also used to separate chiral AAs (Yuan et al. 2011). D-ser, D- and L-asp, and L-glu were measured with CE-LIF method by Jakó T (Jako et al. 2014). Furthermore, CE-LIF also measured D-Ala (Ota et al. 2014). Eight kinds of chiral AAs are completely separated with in-capillary derivation (Moldovan et al. 2016). A simple, rapid, and robust method for D-Orn and D-Ser in human plasma based on CE-LIF was developed (Lorenzo et al. 2013). Prof. Soga (Hirayama et al. 2019) described CE–MS to analyze AAs in detail.

Table 4 Analysis of the chromatographic conditions and results of AAs by GC–MS

Method	Sample	Sample preparation	AAs	Column	Column temperature	Injection mode	Ion tramp temperatures/°C	References
GC–MS	Human plasma	Methylation, protein precipitation, centrifugation at 10,000 rpm, vacuum-dried, reconstituted with water, ECF derivatization	Gly, Ala, Val, Leu, Trp, etc	HP-5MS capillary (30 m × 250 µm, 0.25 µm)	50 °C (2 min) → 50–280 °C (10 °C/min) → 280 °C (5 min)	In splitless mode	230	Reddy et al. (2016)
GC–MS	Canine serum	Protein precipitation (MeOH), centrifuge at 15,800×*g* at RT(21 °C) for 15 min, vacuum-dried, derivatization (oximation and silylation reactions)	Gly, Glu, Met, Tyr, Trp, Lys	–	70 °C (4 min) → 70–300 °C (20 °C/min) → 300 °C (4 min)	Split ratio, 4:1	250	Lopes et al. (2015)
GC–MS/MS	*E. coli*	Centrifuged, hydrolyzed in 2 N HCl for 18 h at 105 °C, filtered	Glu, Met, Ala, Gly, Phe, etc	DB-5MS + DG (30 m × 0.25 mm, 0.25 µm)	150 °C (2 min) → 150–270 °C (3 °C/min) → 270–300 °C (10 °C/min) → 300 °C (5 min)	Split ratio, 1:10	230	Okahashi et al. (2016)
GC–MS	Cerebrospinal fluid	Protein precipitation (MeOH), centrifuged at 10,000 rpm for 10 min (RT), evaporated to dryness, MAD use BSTFA	L-Ala, Gly, Sar, L-Val, L-Leu, L-Isoleu, etc	Rtx-5MS fused-silica capillary (30 m × 0.25 mm, 0.25 µm)	80–200 °C (8 °C/min) → 200–300 °C (30 °C/min) → 300 °C (3 min)	In splitless mode for 3 min, split ratio, 1:20	200	de Paiva et al. (2013)
GC–MS	Whole blood	Filter paper technique, 1/8 in blood spot pounch	Val, Leu, Ile, Met, Phe	Capillary (10 m × 0.25 mm)	110–320 °C (30 °C / min)	Split ratio, 1:15	/	Kawana et al. (2010)

Table 4 (continued)

Method	Sample	Sample preparation	AAs	Column	Column temperature	Injection mode	Ion tramp temperatures/°C	References
GC–MS	Mixed starch waste-water	Remove proteins and inorganic salts (centrifuged with adding the ACN), dried at 40 °C, derivatized with MSTFA and chloro trimethyl silane (1:1), centrifuged at 10,000 rpm for 10 min	Ala, Leu, Val, Pro, Met, etc	DB-5 ms capillary (30 m × 0.25 mm, 0.1 μm)	20–100 °C (2 °C/min) → 100–220 °C (15 °C/min) → 220–300 °C (30 °C/min) → 300 °C (5 min)	–	200	Liu et al. (2016)
GC–MS	Cinobufacini injection	FAA: derivatization, extraction; CAA: hydrolyzed with thioglycolic acid	Ala, Gly, Val, Leu, Ile, etc	Fast AAA capillary column (10 m × 250 μm)	100–320 °C (30 °C / min)	In splitless mode	240	Wu et al. (2015)
GC–MS	Potato	Derivatized with MSTFA	Ala, β-ala, Asp, Glu, Gly, etc	30 m capillary column (Rxi-5 ms, 0.25 mm ID, 0.25 μm *df*, Restek)	90 °C (2 min) → 9–330 °C (5 °C/min)	In splitless mode	250	Uri et al. (2014)
GC–MS	Plant tissue	Solid phase extraction (SPE), Derivatization (pyridine and methyl chloroformate)	Gly, Ala, Val, Leu, Ile, etc	Silica capillary (HP5-ms, 30 mm × 25 mm, 0.25 μm)	70 °C (3 min) → 70–280 °C (25 °C/min) → 280 °C (5 min)	In splitless mode	200	Vancompernolle et al. (2016)
GC–MS	Tobacco	Ultrasonic bath, centrifuged, derivatized with IBCF, DLLME-SFO	Ala, Gly, Val, Leu, Ile, etc	HP-5 (30 m × 0.32 mm, 0.25 μm)	70 °C (1 min) → 70–180 °C (6 °C/min) → 180–280 °C (40 °C/min) → 280 °C (3 min)	In splitless mode	230	Li et al. (2013)
GC–C–IRMS	Soil	Hydrolyzed with HCL, cation exchange resin, vacuum-dried, derivatized with TMS	Ala, Gly, Val, Leu, Ile, etc	DB5 column (30 m × 0.25 mm, 0.25 μm)	100 °C → 150 °C (2 °C/min) → 198 °C (4 °C/min) → 230 °C (40 °C/min)	Split ratio, 1:10	–	Rubino et al. (2014)

Table 5 Analysis of the chromatographic conditions and results of AAs by CE

Method	Sample	Sample preparation	AAs	Capillary	Running buffer	Separation voltage	References
HSCE	Laver	Pulverized, added 70% v/v ethanol, water bathed (100 °C) for 15 min, dissolved with proper volume citric acid buffer, centrifuged and adjusted to pH 9.2, derivatized with FITC	Tyr, Glu, Gly, Lys, Asp, etc	80 mm	10 mol/L Na_2HPO_4–NaOH buffer (pH 11.5) including 30 mmol/L SDS	Separation electric field strength: 300 V/cm	Wang et al. (2015)
CZE–MS	Bovine serum albumin	Denatured at 37 °C for 30 min, alkylation with DTT and IAA, protein digestion was performed for 12 h at 37 °C, acidification, desalted	Cys, Lys, Arg, His, Gly, etc	150 µmo.d., 20 µm i.d	0.5% (v/v) formic acid	16 kV	Schiavone et al. (2015)
CE–MS	Dried blood spot	Deproteinization, centrifuged for 10 min at 12,000 rpm	Phe, Tyr	Uncoated fused-silica capillaries with a 50 µm i.d. and a 40-cm separation capillary and a 4-cm emitter tip	Background electrolytes (BGE): 3 mM NH_4Ac adjust pH of 10.7 with NH_4OH	25 kV	Jeong et al. (2013)
CE-UV	Commercial sport nutritional supplements	Hydrolyze with 6.0 mL HCl (24 h), neutralized by 1.0 mol/L NaOH, centrifugation at 10,000 rpm for 10 min	Leu, Ile, Val	60 cm long (effective length 50 cm)	BGE: 2.0 mmol/L Na_2HPO_4, 10.0 mmol/L PAS, 40.0 mmol/L β-CD at pH 12.2	15.0 kV	Prior et al. (2016), Qiu et al. (2017)
CE- HRMS	Flaxseed	Extracted with HCl in a water bath, cation exchange resin, lyophilized	Val, Ala, Gly, Ser, Pro, etc	50 µm i.d. × 125 cm total length, o.d. 360 µm	SL: 2.5 µM ammonium acetate in 50% (v/v) MeOH	25 kV	Acket et al. (2018)
CE-UV	Honey	Cation exchange, purify with ammonia water, concentrate to dryness, dissolve with water	Asp, Glu, Ser, Thr, Pro, etc	48.5 cm long (effective length 40 cm)	0.5 mmol/LCTAB, 20 mmol/L niacin, 1 mmol/L sodium dihydrogen phosphate 10% MeOH buffer solution (pH 10.2)	− 15 kV	Zhou and Shi (2013)
CE-LIF	Brain regions of adult mice	Protein precipitation with ACN: water 2:1, derivatization (NBD-F)	D-Asp, D-Ser	60 cm long (effective length 50 cm)	50 mM pH 7.0 HEPES buffer, 6 mM HPA-β-CD	− 24 kV	Jako et al. (2014)

Table 5 (continued)

Method	Sample	Sample preparation	AAs	Capillary	Running buffer	Separation voltage	References
CE-LIF	Islets	Krebs–Ringer solution Derivatization (NBD)	D-Ala	40 cm long (effective length 30 cm)	40 mM HP-c-CD, 80 mM CS, 80 mM QN, and 10 mM sodium acetate in FA	27 kV	Ota et al. (2014)
MEKC-MS	aCSF	Derivatization (FLEC)	D-Ala, D-Ser, D-Val, D-Thr, D-Gln, etc	80.5 cm long	BGE: 150 mM ammonium perfluorooctanoate [APFO] [pH 9.5]	25 kV	Moldovan et al. (2016)
CE-LIF	Human plasma	Filtration, Derivatization (NBD-F)	D-Orn, D-Ser	60 cm long	BGE: 175 mM borate buffer at pH 10.25 (pH adjusted with 2 M NaOH) and 12.5 mM β-CD	21 kV	Lorenzo et al. (2013)

Nuclear magnetic resonance

NMR is a useful tool in studying the composition and structure of various organic and inorganic substances. In addition, NMR does not require complex sample preparation (Munz et al. 2016; Yuan et al. 2017). The main drawback of the method is its limited sensitivity. The AA (Gly, Ala, Glu, Leu, Ser, etc.) composition of spider dragline silk was determined by ^{1}H NMR (Shi et al. 2013). This method is used to quantify the changes of AA (Ile, Leu, Val, Ala, Met, etc.) concentration occurring in Bogue fish during storage. The result indicates that the greatest concentration change was ala and gly which is a key role in determining the individual taste of different fish species (Ciampa et al. 2012). NMR also provides a reliable method to determine AAs in Lycii Fructus (Hsieh et al. 2018).

Amino acid analyzer

The AA analyzer is used to analyze the content of protein hydrolysate and free AAs by the post-column derivation of three-ketone column by cation exchange chromatography. Plasma AAs in female rats were measured by automatic AA analyzer (Okame et al. 2015). Zhao et al. (2014) used automatic AA analyzer to analyze the concentrations of free AAs in the lungs. They investigated the change of AA concentrations (Try, Gly, Orn, Pro, Phe) in plasma free AAs and the change in AA concentrations (Tau, Glu, Gly, Lys, and Orn) in TFAAs and concluded that plasma free AA profiles may reflect the status of cancer tissues. In addition, 17 kinds of AAs in tobacco leaves were eluted on an ion-exchange column (Zeng et al. 2015). Reacting with ninhydrin, the derivatives of AAs were detected by ultraviolet detection. The AAs of beef jerky were analyzed with an AA analyzer for the evaluation of the quality traits of beef jerky (Shikha Ojha et al. 2018). Thirty-eight kinds of free AAs in human plasma were detected with a automated pre-column derivatization AA analyzer (Hirayama et al. 2019).

Electrochemical sensor

Electrochemical (bio-) sensor is a fast, simple, and reliable tool for simultaneously resolving and determining D-AAs (Martin et al. 2015; Wang et al. 2016; Zor et al. 2013). D-Thr and L-Thr were distinguished by novel potential-type electrochemical chiral biosensing system, and the distinguished and quantitative determination of Tyr enantiomers was achieved (Guo et al. 2017). An electrochemical sensor based on 2,2,6,6-tetramethylpiperidine-1-oxyl cellulose nanocrystals and a L-cys-modified Au electrode can be used for the detection and discrimination of phe, leu, and Val enantiomers (Bi et al. 2016). A biosensor based on 3,4,9, 10-perylene tetracarboxylic acid-functionalized multiwalled

carbon nanotubes and D-AA oxidase showed high sensitivity and selectivity for the chiral recognition of D-Ala (Xia et al. 2016a). Furthermore, organic electrochemical transistors with gate electrodes modified with molecularly imprinted polymer films dramatically improved the sensitivity of chiral recognition biosensors for D/L-Trp and D/L-Tyr (Zhang et al. 2018). Electrochemical (bio-) sensors can be applied to monitor D/L-Trp or other D/L AAs (Wang et al. 2016; Zor et al. 2013).

Outlook

This current review generalizes the analytical methods of AAs in recent years. Furthermore, we found that the HPLC, LC–MS, and GC–MS are the commonly used analytical methods. Compared with HPLC, LC–MS and GC–MS are more sensitive and more effective; however, the HPLC is more cost-effective. Moreover, TLC, CE, NMR, and AA analyzer can also be used for the analysis AAs. Moreover, there are specific detection methods for D-AAs that provide great convenience for AA analysis. Presently, using an AA analyzer may be the most convenient method, but the necessary equipment is expensive and has many limits. According to literature, LC–MS is the most popular method. However, the problem for the analysis of cost and time has not been dissolved.

There is room for improved methodology for AA analysis, such as simplification of sample preparation process and optimization analysis method (including increasing sensitivity, etc.). With the development of modern science and technology, more sensitive and accurate methods of analyzing AAs are expected. Thus, these methods promote biological metabolism and synthesis of polypeptide drugs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Obtaining informed consent for this type of study is not required.

Research involving human participants and/or animals This article reviews published studies and does not require either the approval of animal use or human consent.

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