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Biogenic Amines (BA)

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EDITOR

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Chapter 1

BIOGENIC AMINES IN FOOD: OCCURRENCE AND ANALYTICAL CHALLENGES FOR THEIR ANALYSIS

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ABSTRACT

Biogenic amines (BAs) are naturally occurring nitrogenous organic compounds of low molecular weight organic bases with aliphatic, aromatic or heterocyclic structures. They are generally formed through

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microbiological activity during food processing and storage, and can be found in a wide variety of foods, particularly fermented foods and beverages as cheese, wine, beer, in addition to fishery products and meat. At low concentrations, BAs participate in the regulation of several physiological functions, but when present at high concentrations, they may cause several health problems in consumers, as headaches, hypo- or hypertension, nausea and cardiac palpitations, especially to sensitive persons. Therefore, the control of BAs levels in different food products is an important issue for food safety monitoring policies. Due to their low levels in complex food matrices, the analysis of BAs is not an easy task and several methods for their separation, identification, and determination have been described during the last decades. Overall, the chromatographic approaches are the most popular, although the recent trends points to the development of sensors able to measure BAs in food matrices without involving the laborious and complex laboratorial sample analysis methodologies. In this review we will essentially focus on the occurrence of BAs in different foodstuffs and in the correspondent challenges of their analysis.

Keywords: biogenic amines, foodstuffs, derivatization, extraction, analysis, liquid chromatography

ABBREVIATIONS

AGM -	agmatine
AQC -	6-aminoquinolyl-N-hydroxysuccinimidyl carbamate
BAs -	biogenic amines
BCl -	benzoyl chloride
CNBF -	4-chloro-3,5-dinitrobenzotrifluoride
CAD -	cadaverine
CE -	capillary electrophoresis
cITP-CZE -	capillary isotachophoresis coupled to capillary zone electrophoresis
DbsCl -	dabsyl chloride
DnsCl -	dansyl chloride
DMA -	dimethylmethylamine
DMETA -	dimethylethylamine

ETA - ethylamine
ETAN - ethanolamine
ECF - ethylchloroformate
FLD - fluorescence detection
FMOC - fluorenylmethoxycarbonyl chloride
GC - gas chromatography
HEX - 1,6-hexamethylenediamine
HIS - histamine
HPLC - high-performance liquid chromatography
ISO - isopentylamine
ITP - isotachophoretic analysis
LLE - liquid-liquid extraction
MA - methylamine
MASC - 10-methyl-acridone-2-sulfonyl chloride
MECC - micellar electrokinetic capillary chromatography
META - methylethylamine
NQS - 1,2-naphthoquinone-4-sulfonate
OCP - octopamine
OPA - ortho-phthalaldehyde
PHE - phenylethylamine
PUT - putrescine
PVPP - poly(vinylpolypyrrolidone)
SALLE - salting-out assisted liquid-liquid extraction
SER - serotonin
SERA - seramine
SLE - solid-liquid extraction
SPE - solid-phase extraction
SPD - spermidine
SPM - spermine
TRYP - tryptamine
TYR - tyramine

1. BIOGENIC AMINES (BAS)

1.1. Definition

Biogenic amines (BAs) constitute a group of basic nitrogen compounds that are important to cell's metabolism and viability. These compounds can be naturally synthetized by certain plants, although their major source is the amino acids decarboxylation mediated by different microorganisms.

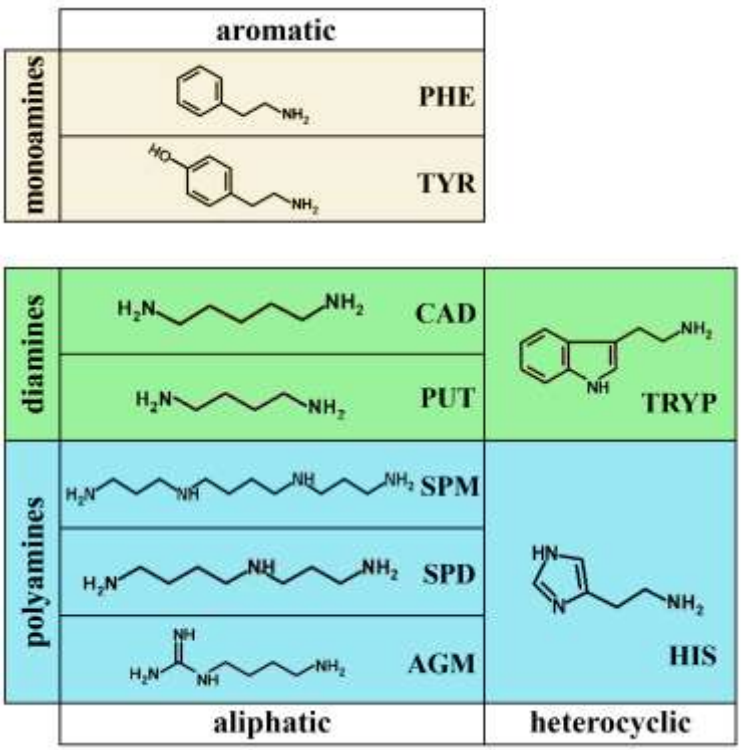

Figure 1. BAs classification according to their structure and number of amine groups. Legend: AGM - agmatine, CAD - cadaverine, HIS - histamine, PHE - phenylethylamine, PUT - putrescine, SPD - spermidine, SPM - spermine, TRYP - tryptamine, TYR - tyramine.

BAs are usually classified according to their chemical structure, as aliphatic (as putrescine - PUT, cadaverine - CAD, agmatine - AGM, spermine - SPM and spermidine - SPD), aromatic (as tyramine - TYR and phenylethylamine - PHE), or heterocyclic (as histamine - HIS and tryptamine - TRYP), or also considering the number of amines, as monoamines (as PHE and TYR), diamines (as CAD and PUT), or polyamines (as SPD and SPM) (Reviewed in (Plonka, 2015) and (Mohammed et al., 2016)) (Figure 1).

1.2. Occurrence in Food Matrices

BAs are formed and degraded during the normal cell metabolism of certain animals, plants and microorganisms. In vegetables, for instance, BAs participate in the fruit development, response to stress and secondary metabolites synthesis. However, BAs can be also generated exogenously under certain circumstances, namely the presence of free precursors amino acids, microorganisms with appropriate catabolic pathways and a suitable environment to the decarboxylation activity (Kantaria & Gokani, 2011). These conditions can be met during food processing, particularly of matrices of animal origin, as fish and meat and their derivatives, which are naturally rich in free amino acids and so susceptible to BAs contamination. Moreover, soon after cells death, a high number of proteolytic enzymes become active and BAs levels can increase several orders of magnitude, creating important food safety concerns (Cardozo et al., 2013). Therefore, the levels of BAs in food matrices are inversely correlated with the freshness and quality of those products, being BAs almost absent or residual in fresh foods. There are, however, some foods in which BAs are naturally present in significant levels, as fish, cheese, meat, eggs and fermented foods (Cardozo et al., 2013). Overall, the BAs most often found in foodstuffs are HIS, TYR, PHE, TRYP, PUT and CAD (Cardozo et al., 2013). Table 1 present indicative ranges of BAs usually found in different foodstuffs.

To prevent BAs contamination, food industry usually employs methods to inhibit microbial growth and reduce decarboxylase activity, as refrigeration (low temperature) or pasteurization (fast treatment with high temperatures to kill the species responsible for BAs formation). However, some bacteria produce BAs even at temperatures lower than 5°C and so additional measures to temperature control are emerging, as the application of hydrostatic pressures, irradiation, packaging, use of additives and preservatives, as well as the use of organisms that do not produce BAs, in the case of fermented products (Naila et al., 2010).

Table 1. BAs presence in different foodstuffs

Food type	BAs identified	Range	Reference
Fish	HIS	10^{-6}-10^{-2} M	Basozabal et al., 2014
Cheese	HIS, TYR, PUT, TRYP, CAD, PHE, SPD, SPM, ETA	0.5-5 mM 0.002-8 mg/L	Redruello et al., 2013 Esatbeyoglu et al., 2016
Meat	METH, AGM, TRYP, PHE, PUT, CAD, HIS, TYR, SPD, SPM	50-250 μM 0.01-15 mg/L	Yang et al., 2014 Sirocchi et al., 2014
Eggs	PUT, CAD, PHE, SPD, SPM, HIS, TYR	0.7-22.4 mg/kg	de Figueiredo et al., 2015
Fermented foods	TRYP, PUT, CAD, HIS, PHE, TYR, SPD, SPM	0.02-10 3.5-200 (μg/ml)	Jia et al., 2011 Gong et al., 2014
Wine	HIS, META, ETA, TYR, DMETA, PHE, ISO, SPM, PUT, CAD, SPD, AGM, TRYP, SERA, ETAN	0.1-100 0.03-1.7 0.01-7.20 (mg/L)	Wang et al., 2014 Ramos et al., 2014 Tuberoso et al., 2015

1.3. Biological Effects

BAs are essential endogenous components that have important metabolic roles in living cells. HIS, TYR and serotonin (SER), for instance, are involved in nervous system functions and control of blood pressure, while the polyamines PUT, CAD, SPM, and SPD are important in the synthesis of proteins, RNA and DNA and are involved in cell signaling, growth and proliferation. Mammals have a relatively efficient detoxification system capable of metabolizing the normal daily intake of

BAs, so their consumption in low concentrations in the normal diet is not dangerous (Özdestan & Üren, 2009; Naila et al., 2010). However, when ingested in excess, BAs have several toxic effects, that can range from reactions of intolerance, to intoxication or even poisoning. The severity of clinical symptoms depends on the amount and variety of BAs ingested, individual susceptibility and the level of detoxification activity in the gut (Ladero et al., 2010). The lighter symptoms include nausea, sweating, rashes, slight variations in blood pressure and mild headache. If symptoms become more severe, including diarrhea, nausea, facial flushing, red rash, respiratory distress, heart palpitation, oral burning, hypo- or hypertension and migraine, then some intoxication is already affecting the organism (Ladero et al., 2010; Yoon et al., 2015). In exceptional cases of BAs poisoning, severe effects will occur, causing damage to different organs, including heart and the central nervous system (Ladero et al., 2010). The BAs that cause most concerns are HIS, TYR and PUT, being able of causing food poisoning (Esatbeyoglu et al., 2016). HIS and TYR poisoning have similar effects in the organism, causing an allergen-type reaction characterized by difficulty in breathing, itching, rash, vomiting, fever, and headaches (Naila et al., 2010), while PUT itself is not toxic, but potentiates the toxicity of HIS and TYR by affecting their clearance from the body (Ladero et al., 2010). Scombroid food poisoning is eventually the most often reported type of BAs intoxication. It is mainly caused by excessive intake of HIS from spoilage fish, particularly those from the *Scombridae* and *Scomberesocidae* families, as tuna, bonito and mackerel.

2. Methodologies Used in Quantification of Food Biogenic Amines

2.1. Sample Preparation

The analysis of BAs in food matrices requires a suitable experimental layout which generically involves a sample pretreatment, then the

extraction and derivatization steps, whose order is often reversed, and finally the quantification of the BAs present in the sample (Figure 2).

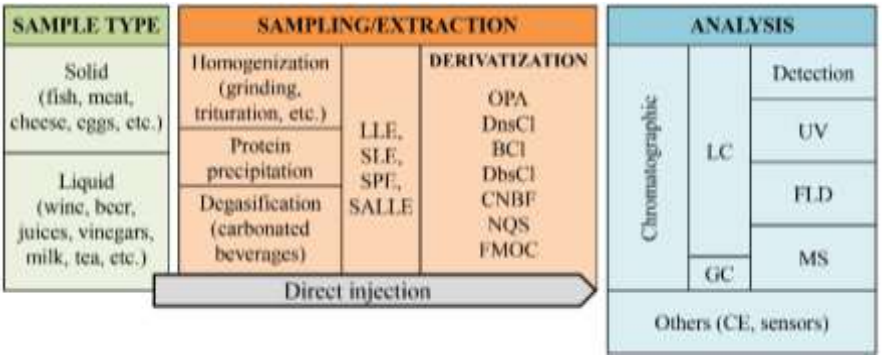

Figure 2. Overview of the generic experimental layout involved in BAs analysis in different food matrices. Legend: AQC - 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate, BCl - benzoyl chloride, CE - capillary electrophoresis, CNBF - 4-chloro-3,5-dinitrobenzotrifluoride, DbsCl - dabsyl chloride, DnsCl - dansyl chloride, FLD - fluorescence detection, FMOC - fluorenylmethoxycarbonyl chloride, GC - gas chromatography, LC - liquid chromatography, LLE - liquid-liquid extraction, NQS - 1,2-naphthoquinone-4-sulfonate, OPA - ortho-phthalaldehyde, SALLE - salting-out assisted liquid-liquid extraction, SLE - solid-liquid extraction, SPE - solid-phase extraction.

This procedure, however, is highly dependent on the nature and complexity of the food samples. In solid matrices, as fish and meat, samples need to be triturated (and eventually added a solvent) to obtain homogeneous moistures (Sirocchi et al., 2014; Pinto et al., 2016). Then, BAs extraction can proceed using different approaches, usually liquid-liquid extraction (LLE), solid-liquid extraction (SLE), solid-phase extraction (SPE) and salting-out assisted liquid-liquid extraction (SALLE), or alternatively a simple precipitation and centrifugation step, as illustrated in Figure 2. For liquid matrices, the major challenges to overcome are the degasification of the carbonated beverages, as beers, which is usually performed in a ultrasonic bath (Jastrzębska et al., 2014) and the interference of phenolic compounds in red wines. In this case, wine samples are often filtrated with certain resins (as poly (vinylpolypyrrolidone - PVPP), that retain these compounds (Daniel et al.,

2015). In other cases, the wines samples are simply diluted and analyzed directly without any further sample treatment (Ramos et al., 2014). In Table 2 are presented selected examples of methodologies used to quantify BAs in different food samples.

2.2. Chromatographic Approaches

2.2.1. Derivatization Procedures

From an analytical point of view, a fast, simple and reliable methodology for simultaneous determination of BAs in food matrices is highly desirable (Brückner et al., 2012; Ramos et al., 2014). This is crucial for the identification and quantification of these molecules in different samples and particularly the control of their presence in human diet. Different methodologies have been proposed to analyze BAs, being high-performance liquid chromatography (HPLC) (Romero et al., 2000; Innocente et al., 2007; Ramos et al., 2014) and gas chromatography (GC) (Cunha et al., 2011) the most often used. The major challenge in BAs analysis is their detection since most of them lack a chromophore group and for that reason do not show a satisfactory fluorescence or absorption in UV-visible range. To overcome this, a common strategy is the derivatization of the amino groups with different reagents to increase the sensitivity and specificity of the detection (Jia et al., 2011; Ramos et al., 2014; Preti et al., 2015). Additionally, this modification also alters BAs chromatographic properties (e.g., reduce the polarity for reversed phase separations) (Innocente et al., 2007; Hernández-Cassou & Saurina, 2011). Regardless the nature of the agent used in the derivatization, it must be ensured that the factors affecting the reaction are carefully controlled (e.g., pH, temperature, etc.), the derivatization agent is available in excess in order to complete the reaction in a wide range of concentrations for the selected BAs and the chromophore molecule formed is stable, at least during the time of analysis (Romero et al., 2000; Romero et al., 2001).

Table 2. Different methodologies used in BAs extraction from foodstuffs

Matrix	Sample treatment	Extraction	Derivatization	Analytical methodology	BAs analyzed	LOD	Reference
Fish	Grinding	SLE	DnsCl	LC-UV	CAD, HIS, PHE, PUT, TRYP	0.14-0.50 μg mL^{-1}	Pinto et al., 2016
		LLE	BCl	MECC	CAD, HIS, PHE, PUT, SPD, SPM, TRYP	-	Su et al., 2000
		SLE (US)	-	Screen-printed carbon electrodes sensor	PUT, CAD, TRYP, SPD, SPM, HIS, TYR	0.18-0.40 (μM)	Alonso-Lomillo et al., 2010
Capelin fish meal	TCA	SLE	OPA	LC-FLD	TYR, HIST, PHE, PUT, CAD, TRYP, AGM, SPD, SPM	-	Ruiz-Capillas et al., 2015
Meat	TCA	SPE	-	LC/MS	AGM, CAD, HIS, PUT, PHE, SER, SPD, SPM, TRYP, TYR.	0.03-0.1 mg L^{-1}	Sirocchi et al., 2014
	TCA	SLE	OPA/DnsCl	LC-UV	HIST, TYR, TRYP, PUT, PHE, CAD, SPD, SPM	0.0012-0.0046 ng	Smela et al., 2003
Meat and Cheese	MeOH	SLE	ECF	GC/MS, optical sensor	HIS, PUT, SPD, TYR.	0.165 (μg mL^{-1})	Khairy et al., 2016
Cheese and anchovy	-	SLE (US)	-	Amperometric biosensor	PUT, CAD, HIS	0.33-50 (μM)	Carelli et al., 2007
Cheese	Grinding	SLE	DnsCl	LC-UV	CAD, HIS, PHE, PUT, SPD, SPM, TRYP, TYR.	-	Torracca et al., 2015

Matrix	Sample treatment	Extraction	Derivatization	Analytical methodology	BAs analyzed	LOD	Reference
Eggs	Yolk and albumin separation	SLE	DnsCl	LC-UV	PHE, CAD, HIS, PUT, SPM, SPD, TYR	0.2-0.3 mg kg^{-1}	de Figueiredo et al., 2015
Wine	-	SALLE	DnsCl	LC-FLD	CAD, DMA, EA, HIS, ISO, MA, PHE, PUT, SPD, SPM,	0.005-0.028 (mg L^{-1})	Ramos et al., 2014
	Degasifi-cation	LLE	CNBF	LC-UV	DIEA, HIS, PHE, TRYP, TYR.	0.02-0.03 (mg L^{-1})	Piasta et al., 2014
	-	LLE	BCl	LC-UV	AGM, CAD, HIS, MA, PHE, PUT, SPD, SPM, TRYP, TYR.	0.2-2.5 (mg L^{-1})	Özdestan & Üren, 2009
	-	-	OPA	LC-FLD	HIST, MH, MET, EA, TYR, TRYP, PHE, PUT, CAD	0.03-0.12 (mg L^{-1})	Soleas et al., 1999
	-	dilution	-	cITP-CZE-UV	HIS, TYR, PHE	0.33-0.35 (mg L^{-1})	Ginterová et al., 2012
	-	dilution	NQS	CE	AGM, PHE, CAD, ETA, HIS, TYR, PUT, SER, TRYP.	0.02-0.91 (mg L^{-1})	García-Villar et al., 2006
Rice wine	-	SLE	MASC	LC/MS	CAD, HEX, HIS, PHE, PUT, TRYP, TYR.	0.15-0.23 (μM)	Cai et al., 2016
Wine and juice fruits	-	LLE	DnsCl	LC-UV/FLD	AGM, PHE, CAD, EA, HIS, MA, PUT, SER, SPD, SPM, TYR.	0.002-0.023 (mg L^{-1})	Preti et al., 2015

Table 2. (Continued)

Matrix	Sample treatment	Extraction	Derivatization	Analytical methodology	BAs analyzed	LOD	Reference
Wines and cider	Degasifi-cation	-	OPA	LC-FLD	AGM, CAD, DOP, HIST, OCT, PHE, PUT, SPM, SPD, TYR, TRYP	0.03-0.06 (mg L^{-1})	Vidal-Carou et al., 2003
Wine and fish	-	-	SLE	Solid-phase imprinted nanoparticles sensor	HIS	$1.12x10^{-6}$ (M)	Basozabal et al., 2014
Wine and beer	Degasifi-cation	-	DnsCl	LC-UV/ITP	CAD, HIS, PHE, PUT, SPD, SPM, TRYP, TYR.	0.2-1.4 (mg L^{-1})	Jastrzębska et al., 2014
	PVPP filtration	-	-	CE-MS/MS	HIS, TYR, PUT, CAD, SPM, SPD, TRY, PHE, URO	1-2 (μg L^{-1})	Daniel et al., 2015
Vinegars	-	SPE	AQC	LC-FLD	AGM, CAD, HIS, MA, PHE, PUT, SPD, SPM, TYR.	7-26 (μg mL^{-1})	Ordóñez et al., 2013
Cocoa products	-	SLE SPE	DnsCl	LC-UV	CAD, HIS, PHE, PUT, SER, SPM, SPD, TYR.	0.02-0.04 (μg mL^{-1})	Restuccia et al., 2015

Matrix	Sample treatment	Extraction	Derivatization	Analytical methodology	BAs analyzed	LOD	Reference
Tea	Infusion	SLE	FMOC	LC-FLD	CAD, HIS, OCP, PHE, PUT, SPD, SPM, TYR	-	Brückner et al., 2012
Donkey Milk	Protein precipitat.	LLE	DnsCl	LC/MS	CAD, HIS, PHE, PUT, SPD, SPM, TRYP, TYR.	0.5-15 (μg L^{-1})	La Torre et al., 2010

Legend: AGM - agmatine, AQC - 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate, BCl - benzoyl chloride, CAD - cadaverine, CNBF - 4-chloro-3,5-dinitrobenzotrifluoride, DbsCl - dabsyl chloride, DMA - dimethylmethylamine, DMETH - dimethylethylamine, ETA - ethylamine, ECF - ethylchloroformate, FLD - fluorescence detection, FMOC - fluorenylmethoxycarbonyl chloride, HEX - 1,6-hexamethylenediamine, HIS - histamine, ISO - isopentylamine, ITP - isotachophoretic analysis, LLE - liquid-liquid extraction, MA - methylamine, MASC - 10-methyl-acridone-2-sulfonyl chloride, METH - methylethylamine, NQS - 1,2-naphthoquinone-4-sulfonate, OCP - octopamine, OPA - ortho-phthalaldehyde, PHE - phenylethylamine, PUT - putrescine, PVPP - poly(vinylpolypyrrolidone), SALLE - salting-out assisted liquid-liquid extraction, SER - serotonin, SLE - solid-liquid extraction, SPD - spermidine, SPE - solid-phase extraction, SPM - spermine, TCA - trichloroacetic acid extraction, TRYP - tryptamine, TYR - tyramine, UV - ultraviolet detection.

In the literature, several derivatization reagents have been successfully used in BAs analysis in different food matrices, as shown in Table 2. Nowadays, dansyl chloride (DnsCl) is possibly the most popular derivatization reagent for BAs. DnsCl is able to react with primary and secondary amino groups and even with tertiary amines, in extreme conditions, providing very stable dansylamines and dansylamides derivatives (Innocente et al., 2007; Hernández-Cassou & Saurina, 2011). The identification and quantification of these derivatives in different food matrices was the goal of many studies in the last years. However, the dansylation may require high temperatures (more than 40°C) and be a time-consuming process (taking more than 20 min just for derivatization reaction) (Erim, 2013). In recent years, different modifications have been proposed to the original protocol of dansylation to improve this methodology (Innocente et al., 2007; Jiang et al., 2011; Erim, 2013). Jiang et al. (2011), for instance, reported the use of ionic liquids as a media for the derivatization of BAs in wine samples. This modification allowed to complete the derivatization reaction at room temperature in 20 min, considerably improving the cost and time of analysis of BAs in wines (Jiang et al., 2011). Despite of the popularity of DnsCl derivatization, many parameters that affect the efficiency of this reaction, as pH, temperature or concentration of the derivatization reagent, were never been properly studied and there are many opportunities for further optimization that can still can be addressed. The derivatization of BAs using O-phthalaldehyde (OPA) is also very popular. The greatest advantage of using this reagent is the speed of the reaction (Hanczkó & Molnár-Perl, 2003; Notou et al., 2014). In fact, according Hanczkó and Molnár-Perl (2003) for some selected BAs, OPA derivatization can be a very fast reaction, being complete between 1.5 and 7 min. However, the OPA reagents are self-fluorescent and self-UV absorbent, and for this reason blank measurements are always necessary (Hanczkó & Molnár-Perl, 2003). Moreover, OPA only reacts with primary amines and compounds that have the CH_2-NH_2 moiety in their initial structure, result in more than one OPA derivative that has to be considered to obtain reliable data (Hanczkó &

Molnár-Perl, 2003). Beyond, OPA and DnsCl, several other derivatization reagents have been used in BAs analysis, as indicated in Table 2.

2.3. Other Methodologies

Different forms of capillary electrophoresis (CE) have been reported in the literature for the determination of BAs, particularly in wines and beers (García-Villar et al., 2006; Ginterová et al., 2012; Daniel et al., 2015). Overall these approaches, exemplified in Table 2, can be a good alternative to chromatographic analysis, being fast and reliable. Ginterová et al. (2012), for instance, reported a methodology using capillary isotachophoresis coupled to capillary zone electrophoresis (cITP-CZE), not requiring derivatization, to screen BAs in red wines that allowed a good analytical performance in the analysis of HIS, TYR and PHE (0.35, 0.37 and 0.33 mg L-1). In recent years, alternative methodologies using different sensors architectures and chemistries have been proposed for BAs detection and quantification. These solutions are mostly targeted to detect specific BAs using custom designed sensors. Their use in analytical chemistry is particularly interesting as sensors have the potential to allow faster and real-time analysis using disposable lab-on-chips systems that do not require specialized instrumentation or complex laboratory facilities or procedures. However, these approaches are still in their infancy and their application to BAs analysis need further developments before being considered a real alternative to conventional methodologies. Nevertheless, it is noteworthy to refer the work from Alonso-Lomillo et al. (2010), where the authors covalently immobilized monoamine and diamine oxidases coupled with horseradish peroxidase into screen-printed carbon electrodes to quantify different BAs. Using these disposable biosensors, it was possible to measure seven different BAs in fish samples with LODs in the 0.18-0.40 µM range (Table 2). In a similar approach, Carelli et al. (2007) developed an amperometric biosensor also using the diamino oxidase, this time entrapped onto an electrosynthesized bilayer film, to quantify PUT, CAD and HIS. The sensitive biosensor could reach low detection limits

(0.33-050 µM) and was successfully applied to cheese and anchovy samples. In another report, Basozabal et al. (2014), reported a promising potentiometric sensor based on molecularly imprinted nanoparticles for HIS quantification. This approach has the great advantage of allowing fast, specific and label-free quantification of HIS, while achieving excellent analytical performance, with a LOD of 1.12 µM of HIS in wine and fish samples.

3. FINAL REMARKS

Human population exponential growth is already requiring major efforts to obtain more food using natural resources that are not available in the same proportion. This will create enormous challenges in the control of the quality and safety of food chain supplies worldwide. In this aspect, the control of BAs levels in foodstuffs will require more expedite methodologies than the currently used, which often involve laborious and cumbersome protocols. Furthermore, the control of BAs presence in food continues to rely essentially in HIS to which are defined maximum admissible levels. However, other BAs have been already shown to interfere with human metabolism and so more extensive studies are necessary to define safety levels for those compounds. This will be crucial to include the quantification of more BAs in the assessment of food safety and consequently contribute to improve its quality and protect human health.

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