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1 **Literature update of analytical methods for biogenic amines determination in food and**
2 **beverages**

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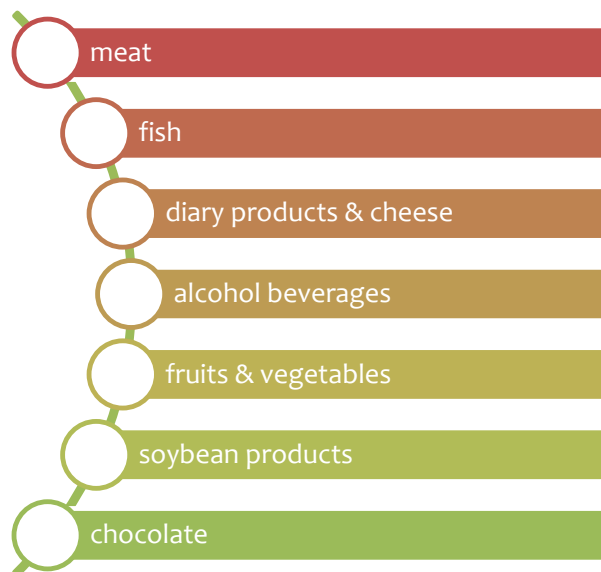
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16 **Graphical Abstract**

17

Biogenic Amines (BA)



18

19

1 **Abstract**

2 Biogenic amines (BAs) have been reported in a variety of foods, such as fish, meat, cheese,
3 and wines. The formation of BAs in food by the microbial decarboxylation of amino acids can
4 result in human allergic reactions, characterized by difficulty in breathing, rash, vomiting, and
5 hypertension. Control measures to prevent biogenic amine formation in foods and/or reduce
6 their levels should be considered. Therefore, monitoring of BAs in food samples with the
7 application of analytical techniques is of high importance.

8 This review is based on literature data from 2010 until today and refers to food samples and
9 alcoholic beverages. The rationale of this study is to provide data for the occurrence of BAs
10 in food and beverages samples and a comparison of the analytical techniques and challenges
11 in liquid and solid matrices. Importantly, BAs can be used as future markers for quality and
12 freshness of the food products and alcoholic beverages.

13

14 **Keywords**

15 Biogenic amines, food samples, chromatographic techniques, capillary electrophoresis, green
16 assessment

17 **1. Introduction**

18 Nowadays, food products are manufactured and distributed worldwide, while deficiencies in
19 regulation increases the concern for consumer's health. Heavy metals, pesticides,
20 pharmaceuticals, personal care products and biogenic amines have been detected in different
21 food matrices worldwide. A so called -chemical contamination- include multi-residues, may
22 enter the food chain from different routes. Some sources linked with chemical contamination
23 potentially include the application of pesticides in the field, veterinary medicines in animals,
24 natural toxins and residues formed during the food processing or intentional contamination,
25 such as food adulteration or contamination from sources which have not yet been identified.

26 Amino acids are the main compounds which offer nutrition value, aroma and flavor in
27 products such as cheese, wine, honey and other fermented foodstuffs after microbial or
28 enzymatic conversion [1]. Therefore, the bacterial decarboxylation of amino acids or
29 transamination of aldehydes and ketones leads to formation of active biogenic amines (BAs)
30 [2, 3]. BAs are nitrogenous organic bases of low molecular weight, polar or semi-polar
31 compounds with aliphatic (putrescine, cadaverine, spermine and spermidine), aromatic
32 (tyramine, phenylethylamine) or heterocyclic (histamine, pyrrolidine) structure.

33

1 The demand for safer foods has promoted more research into biogenic amines over the past
2 few years, and thus many countries are involved in the analysis of food samples in terms of
3 biogenic amines occurrence (Figure 1). However, there are still some questions that remain
4 unanswered. Despite the fact that biogenic amines are present in foods and beverages and can
5 cause toxic effect to the body, a shared regulation limiting the amounts of biogenic amines in
6 food and beverages is still lacking. Knowledge on their presence in wine is also important for
7 the food trade sector.

8 Referring to BAs, their occurrence has been detected in a broad range of protein-rich food
9 matrices (from plant or animals origin) that are regularly consumed by humans and placed
10 within a daily dietary program, such as meat [4-7], fish [4, 5, 8-14], dairy products [15] and
11 alcoholic beverages. This could place them as markers for food and beverages quality and
12 freshness being connected to the degree of food storage, processing or degradation [16].
13 Therefore, any food stuff produced by fermentation or exposed to microbial contamination
14 during processing or storage may contain BAs [17].

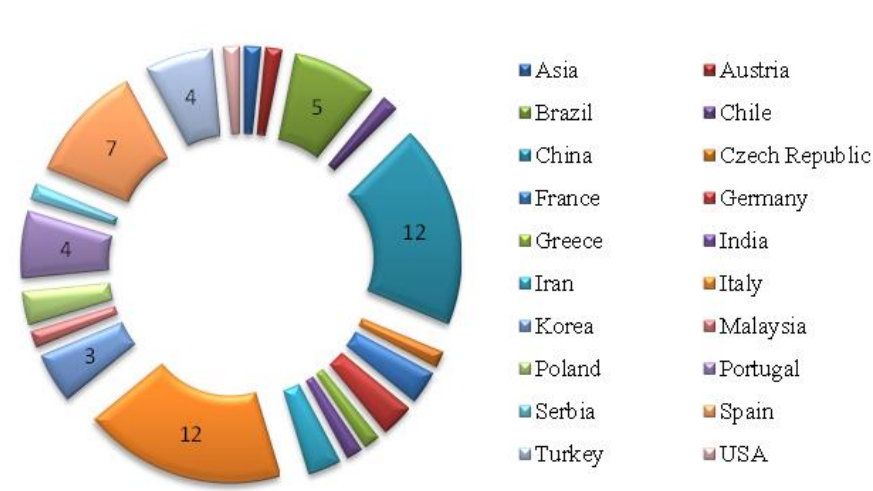
15 With respect to health risks, little legislation exists; in low concentration BAs are essential for
16 many physiological functions in humans, acting as hormones or neurotransmitters. The key
17 roles of BAs are important for growth, renewal, and metabolism in organs, for high metabolic
18 activity of the normal functioning and immunological system of the gut and for temperature
19 regulation [18-20]. While in high concentrations, effects such as headache, nausea, hypo- or
20 hypertension, migraine, skin allergy and digestive problems of food poisoning have been
21 observed by biogenic amines [21, 22]. Also, Biogenic Amines (BAs) are precursors of
22 nitrosamines, which have been linked to carcinogenic and mutagenic activity. Generally, BAs
23 are not destroyed during cooking, treatment with high temperature, storage and are stable and
24 difficult to degrade [23].

25 The determination of biogenic amines is laborious and challenging due in part to the
26 physicochemical properties of these compounds. Numerous analytical methods have been
27 developed while few of them can overcome the step of the derivatization process easily. A
28 pre-concentration step is generally needed, when the analysts deal with complex matrices.
29 During the last decade, new articles have developed extractions which can be more
30 environmental friendly, with the use of less toxic, organic solvents combined with sensitive
31 and selective analytical instrumentation using mass spectrometer and tandem mass
32 spectrometer detectors [5, 24, 25].

33 The aim of this review is to summarize the concentration of biogenic amines in different food
34 and beverage products from 2010 until today, to highlight which matrices have not been

1 analyzed and also, which matrices are the most popular and should continue to be monitored
 2 for their toxicity. Regarding the physicochemical characteristics of BAs, an overview of the
 3 analytical methodologies, cleanup and pre-concentration techniques, a comparison between
 4 the derivatization agents and environmental assessment of the analytical methodologies have
 5 been made, so we can underline the development of more green, environmental friendly
 6 extraction procedures. Finally, the regulation policy and the toxicity of BA's have been
 7 discussed. The study concludes with a focus on the main issues that should be further
 8 investigated.

9



10

11 **Figure 1.** Percentage breakdown of biogenic amine researches related to food products
 12 published since 2010 categorized with the geographical region of the analyzed samples
 13

14 2. Function and occurrence of biogenic amines

15 Generally, BAs are sources of nitrogen and precursors for the synthesis of many specific
 16 compounds in organisms such as alkaloids, hormones, nucleic acids, and proteins. Moreover,
 17 they are also responsible for several processes in the organism such as the regulation of body
 18 temperature, intake of nutrition, increase/decrease of blood pressure [26]. In plants,
 19 putrescine, spermidine and spermine are implicated in a numerous of physiological processes,
 20 such as cell division, fruit development, flowering, response to stress and senescence.
 21 Generally, polyamines are important for processes of every organ in the body including
 22 growth, renovation, metabolism and are essential for maintaining the high metabolic activity
 23 of the normal functioning and immunological system of gut [26].

24 It has been shown that BAs are potential precursors for the formation of carcinogenic N-
 25 nitroso compounds. The reaction of primary amines and nitrosating-agents produces short-
 26 lived alkylating species, which can react with other components present in the food matrix to

1 generate products for example alcohols, devoid of toxic activity in the relevant contents [26].
2 The secondary amines such as agmatine, spermine, spermidine and others can react with
3 nitrile and, in sum, generate the nitrosamines, while tertiary amines produce a range of labile
4 N-nitroso products [27]. In foods contain high level of fat (e.g. bacon), in the presence of
5 water and at high temperature, the carcinogen N-nitrosopyrrolidine can be formed from
6 putrescine or spermidine. Moreover, several of BA including putrescine, spermidine and
7 cadaverine, can act as free radical scavengers, while tyramine has a remarkable antioxidative
8 activity, which increases with its content. Thus, inhibiting effect depends on amino and
9 hydroxy groups. Another function of BAs is impact on flavour and taste of food [26, 28].
10 Theoretically, all foods that contain free amino acids or protein and are exposed to conditions
11 enabling microbial or biochemical activity, BA presence can be expected [28]. BAs generally
12 occur in fermented products such as cheese (5-4500 mg/kg), wine (5-50 mg/dm³), beer (2.8-
13 13 mg/dm³), sauerkraut (110-300 mg/kg), but they can be present in food that is not properly
14 stored, for example fish (2400-5000 mg/kg), beef liver (340 mg/kg), prepared meats (10-700
15 mg/kg) [4, 29]. In fact, BAs are found as indicators and markers of food decomposition of
16 non-fermented foods [1, 26]. Spoiled foods are also rich in BA and usually contain high levels
17 of putrescine and cadaverine [1, 26].
18 It is worth to notice, that amine content and profiles may vary depending on several extrinsic
19 and intrinsic factors during the manufacturing process, such as the ripening conditions,
20 formulation, physico-chemical and proteolytic parameters, as well as microflora development
21 and its decarboxylase activity. In fact, every country has its own traditions of food, which
22 differ in both the microbial characteristics, the way of production and processing methods. In
23 addition, each country is characterized by a specific climate, which also affects the presence
24 of biogenic amine in the substrate, for example, beverages. These differences, can be
25 observed in the following section of this review [30, 31].

26

27 **2.1. Biogenic amines in seafood and its products**

28 Since the maximum levels for histamine are legally established for seafood and its products,
29 most research is related to these products. Seafood is a specific type of food which may
30 harbor several biological, chemical, and physical hazards, the most common of which are
31 biotoxins, pathogenic bacteria and viruses, metal inclusion and biogenic amines [32].

32 It is proven that both specific as well as non-specific microbial contaminants originating from
33 the natural environment or being acquired during processing impact on the microbiological

1 complexity of seafood [32]. The wide range of environmental habitats and the variety of
2 processing practices (iced seafood products to canned products) are all important parameters
3 in determining the initial contamination of fish and their products. The microorganisms of
4 seafood intended for human consumption depend on the environmental conditions of its
5 natural habitat, but here can be mentioned, Gram-negative bacteria belonging to the genera
6 *Pseudomonas*, *Moraxella*, *Acinetobacter*, *Shewanella*, *Flavobacterium*, *Vibrionaceae* (*Vibrio*
7 and *Photobacterium*) and the *Aeromonadaceae*. Although Gram-negative bacteria are the
8 predominant microorganisms, Gram-positive bacteria such as *Bacillus*, *Micrococcus*,
9 *Clostridium*, *Lactobacillus*, and *Coryneforms* can also be found at various levels. In polluted
10 waters, high numbers of *Enterobacteriaceae* may be found. In clean temperate waters, these
11 organisms disappear rapidly, but it has been shown that *Escherichia coli* and *Salmonella* can
12 survive for long periods in tropical waters, and once introduced, may become indigenous to
13 the environment [32].

14 The composition of seafood microbiota changes quite dramatically during spoilage. For
15 example, *Shewanella putrefaciens* and *Pseudomonas aeruginosa* have been identified as the
16 prominent spoilage bacteria of fresh fish, while at ambient temperature (25°C), the microbiota
17 at the point of spoilage is dominated by mesophilic *Vibrionaceae* and, particularly if the fish
18 is caught in polluted waters, *Enterobacteriaceae* [33].

19 The important biogenic amines in seafood are tyramine, histamine, putrescine, tryptamine,
20 and cadaverine. These are formed from their respective free amino acids tyrosine, histidine,
21 ornithine, tryptophan, and lysine. Spermidine and spermine are produced from putrescine
22 [34]. Thus, the concentration of free amino acids especially histidine is important since
23 histidine is the precursor in the biosynthesis of histamine. Glutamic acid together with lysine,
24 arginine, leucine, aspartic acid, isoleucine, glycine, alanine, threonine and valine represented
25 77.6 % of total amino acids in naturally fermented fish [34].

26 Histamine levels in freshly caught fish are generally low, usually below 0.1mg/100g [32].
27 However, exposure of certain fish to elevated temperatures after the catch and before
28 consumption can cause formation of histamine from histidine by bacterial histidine
29 decarboxylases and thus, the level of histamine can increase.

30 Some technological processes such as salting, ripening, fermentation or marination can
31 increase the possibility of BA formation. BAs can also be produced throughout the
32 manufacturing process, as well as during storage of the end product if improper holding
33 temperatures are employed [32].

1 In studies conducted in fish and fish products, the presence of BAs has been also reported.
2 Among the analyzed samples were smoked mackerel and salmon, tuna, anchovies, tinned
3 tuna, canned fish, mackerel, sardines, tuna, marinated anchovies and shrimp sauce. Bilgin et
4 al., 2015 [13] detected the mean concentration of cadaverine (up to 122.18 ± 68 mg/kg) in
5 canned tuna and sardines from Turkey, tryptamine (up to 190.61 ± 7.67 mg/kg) in marinated
6 anchovies, histamine in maximum concentration up to 110.33 ± 9.87 mg/kg) and putrescine
7 (up to 116.53 ± 2.90 mg/kg) in canned tuna. Bilgin et al., 2015 connected the high values of
8 BAs (upper the safe level) with the bad quality of the raw fish and the processes needed for
9 the formation of these products. Also, Palermo et al., 2013 [9] detected trimethylamine in
10 fresh anchovy samples from the Italian market in concentrations up to 120 ± 1 mg/kg
11 indicating poor storage conditions. Lower concentrations were observed for the analyzed BAs
12 in all the other fish samples from other regions. Only one survey was conducted in shrimp
13 sauce from Malaysia detecting tryptamine, putrescine and tyramine up to 57.9 mg/L, followed
14 by 2-phenylethylamine, histamine and spermidine (up to 5.4 mg/L) [35].

15 **2.2. Biogenic amines in meat**

16 Meat and meat products are an important component of the diet in developed countries. This
17 type of food has **repeatedly been** reported to contain biogenic amines [16]. The most prevalent
18 BAs in these products are putrescine, tyramine, cadaverine, and also histamine. The only
19 amines present at significant levels in fresh meat are spermidine and spermine. Some amines
20 such as tyramine, putrescine and cadaverine can be formed during storage of meat [36]. It is
21 reported that tyramine concentrations in stored beef was highest on the meat surface,
22 however, it can be reduced effectively by washing [37]. Generally, fermented meat products
23 are an example of products which considerable amounts of BAs can be found as a
24 consequence of the use of poor quality raw materials, contamination and inappropriate
25 conditions during processing and storage [16]. Moreover, the microorganisms responsible for
26 the fermentation process may contribute to BAs accumulation. In fact, the non-protein
27 nitrogen fraction which increases during fermentation includes the presence of free amino
28 acids, precursors of BAs. The major protease activity is derived from endogenous meat
29 enzymes. Proteolysis is favored by the denaturation of proteins as a consequence of acidity
30 increase, dehydration and action of sodium chloride [16]. Fermented products with
31 comparable microbiological profiles may differ in their BAs content, indicating that the
32 production of such compounds depends on a complex interaction of factors [16]. Raw meat
33 material is the natural source of the substrate from which BAs are produced. It also is the

1 largest component of the matrix in which the decarboxylation reactions take place and any
2 conditions that alter its nature and characteristics will influence the formation of biogenic
3 amines.

4 The highest concentration of BAs in meat and meat products occurred in meat sausages from
5 Greece. Papavergou et al., 2012 [7] reported the occurrence of cadaverine, putrescine and
6 histamine in concentrations up to 689.89 mg/kg in fermented sausages, in contrast to dry meat
7 ripened products with spermine to be the most frequent detected BA with concentration range
8 from 11.69 ± 0.77 to 46.32 ± 0.39 mg/kg. Lower concentrations were detected in sausages
9 from China and Poland, with the most dominant BAs being spermine, histamine and
10 tryptamine ranging up to 104.28 mg/kg (China) [38] and 2-phenylethylamine, tyramine and
11 putrescine ranging up to 17.1 mg/kg (Poland) [4]. Moreover, Lazaro et al., 2015 [39] detected
12 tyramine up to 356.8 mg/kg, followed by putrescine, cadaverine, spermine and spermidine
13 with concentrations up to 54.8 mg/kg in chicken and quail samples from Brazil. Furthermore,
14 Lazaro et al., 2015 [39] supported that the correlation between the BAs and bacterial growth
15 does not present a specific profile for the BAs but depends on the meat sample. In salami
16 from Germany, putrescine and tyramine were the most detected BAs (up to 77.14 mg/kg) [5]
17 in contrast to salami from Italy, agmatine and spermine appeared in lower concentrations up
18 to 8.3 mg/kg [9]. Slightly higher concentrations were presented in 4 different meat samples
19 (fresh beef, chicken, lamb, rabbit) from Italy, with the presence of spermine not exceeding
20 22.22 mg/kg [6].

21 **2.3. Biogenic amines in dairy products**

22 Dairy products are important components in the human diet. Their current consumption is
23 relatively high and is expected to increase steadily during the next few decades [40]. Thus, the
24 provision of wholesome and safe dairy products to consumers is expected to be more
25 challenging with the anticipated increased consumption, as the risk increases with the
26 exposure to hazards, such as biogenic amines (BAs), potentially present in the product [40].
27 Together with wine, dairy products can accumulate high levels of BAs. Biogenic amines
28 continue to raise concern due to their frequent detection at high levels in various types of
29 dairy products and to increased awareness of their actual or potential adverse health effects
30 [40]. Also, the fact that BAs are produced not only by microbial dairy contaminants of
31 different origins but also by the technological microbiota used in the fermentation and/or
32 ripening of dairy products, including **lactic acid bacteria (LAB)**, yeasts, and molds,
33 complicates their control by conventional means.

1 In the raw material (milk) polyamines are the most abundant; however, also in the final
2 product such amines as cadaverine, histamine, putrescine, tyramine, β -phenylethylamine and
3 tryptamine are all detected. The content of BAs in different types of cheese is different.
4 Moreover, these differences can also appear within the same type of cheese and even between
5 different sections of the same cheese.

6 As was previously mentioned, the occurrence and amount of BAs in food depends on many
7 factors among which the availability of the precursor amino acid(s) is a limiting factor. It is
8 noted that the precursor amino acids may be naturally present in milk in a free state or be
9 released from milk proteins by hydrolysis. Proteolytic activities impact on the formation of
10 precursor amino acids in dairy products may result from different sources acting
11 independently or in combination, including proteolytic strains of micro-organisms present in
12 dairy products, proteases used for coagulating milk in cheese-making, the milk-native heat-
13 stable protease plasmin, and other proteases liberated from somatic cells. Subsequently, BA-
14 producing microorganisms will continue the formation process of BAs, which are then
15 released into the matrix of dairy products [41].

16 It is reported that Gram-positive bacteria are the main BA producers in cheese. Several strains
17 of such genera as *Enterococcus*, *Streptococcus*, *Leuconostoc* and *Lactobacillus* are indicated
18 as BAs producers, and can be present in microbiota of milk or introduced through
19 contamination before, during or after the dairy products processing. In fact, BA⁺-LAB may
20 even form part of the starters or adjunct cultures, thus, including the inability to produce BAs
21 as an indispensable condition of strains intended to be used as starters is of high importance.
22 This information was the basis to introduce a system for a pre-market safety assessment of
23 selected taxonomic groups of microorganisms leading to a 'Qualified Presumption of Safety'
24 (QPS) by the European Food Safety Agency (EFSA) [42]. And thus, several bacteria
25 associated with food e.g. *Lactobacillus*, including *L. buchneri*, *L. brevis*, *L. hilgardii*, have
26 obtained a QPS status [42], although some strains of these species have been indicated as BAs
27 producers.

28 The presence of BAs in different types of cheese has been described in a lot of surveys. More
29 than 15 BAs have been analyzed [5, 9, 37, 43-47]. Among different types of cheese;
30 cadaverine was found to be more dominant than other BAs. In 7 different types of cheese in
31 Austria, cadaverine ranged from 2 to 748.2 mg/kg [5]. The occurrence of cadaverine in
32 Formaggio di Fossa ranged up to 1303 ± 5.02 mg/kg [45] and in Cabrales 774.51 mg/kg from
33 Italy [44]. The highest concentration presented in Otlu peynior cheese from Turkey (1844.5
34 mg/kg) [43]. Moreover, histamine presented up to 1159.7 mg/kg [3], tyramine up to 1125.2

1 mg/kg [43] in Turkey and up to 2519.98 mg/kg in cabrales cheese from Italy [44], while
2 slightly lower concentration were observed for other cheese types and regions with BAs
3 concentration not exceeding 847 mg/kg [43].

4 Regarding BAs, in all the other dairy products [15] yogurt [5, 38], milk (cow and goat), kefir,
5 fermented cream and buttermilk [46], only putrescine, histamine and agmatine has been
6 detected in dairy products from USA with maximum concentration up to 3.2 mg/L, while
7 tyramine has been detected in cow and goat milk from Brazil at concentrations up to 337.11
8 mg/kg [47]. Lower concentrations observed for all the other regions with BAs maximum
9 concentrations of BAs up to 26.1 mg/kg in yogurt, 5 mg/kg in buttermilk, 15.4 mg/kg in
10 fermented cream, 14.3 mg/kg in kefir from Czech Republic [46].

11 **2.4. Biogenic amines in chocolate and coffee**

12 Chocolate contains many pharmacological agents that separately or as a group, could evoke
13 physiological sensations and may be the driving force behind chocolate cravings. In the past
14 few years, the psychopharmacological effects of chocolate have been a topic of increasing
15 interest among nutrition neuroscientists as evidence continues to build for the localization of
16 chocolate's actions and the precise biomolecules involved.

17 One of the groups of compounds that occur in chocolate and may impact negatively on human
18 body is biogenic amines. Several endogenous biogenic amines are found in chocolate, most
19 notably, tyramine and phenylethylamine, tryptamine, clovamide, and serotonin. It is reported
20 that chocolate has the highest level of phenylethylamine among tested foods. This compound
21 is produced by brain tissue and is rapidly metabolized by monoamine oxidase- β and aldehyde
22 dehydrogenase to phenylacetic acid, the major metabolite of this compound in the brain.
23 When consumed at high levels, effect such as blushing, headaches and increase blood
24 pressure can occur. Consequently, Mayr et al., 2012 [5] reported that the dominant BAs were
25 spermidine, ethanolamine, tyramine, and 2-phenylethylamine with maximum concentration
26 up to 7.40 ± 3.4 mg/kg in chocolate from Germany. Sparse information exists for all the other
27 regions.

28 Coffee is one of the most common beverages and composed of carbohydrates, fiber, proteins,
29 free amino acids, lipids, minerals, organic acids, chlorogenic acid, trigonelline and caffeine.
30 Three different extraction techniques, decoction, infusion and pressure methods were used for
31 coffee brewing. Many factors influence the process of brewing, such as ground roast coffee
32 composition, grid, brewing method, coffee/water ratio, water hardness and temperature,
33 duration of the coffee–water contact, and filter material [48]. Putrescine appeared to be the

1 most dominant BAs in coffee beans and in coffee beverage followed by spermidine, spermine,
2 and serotonin, while cadaverine and tyramine are generally present in smaller amounts.
3 Ground coffee samples from Turkey and Brazil were analyzed. Higher concentrations
4 occurred for serotonin (170.8 mg/kg), tyramine (83.94 mg/kg), cadaverine (75.08 mg/kg)
5 and tryptamine (37.85 mg/kg) in Turkey ground coffee [49], while different pattern observed
6 in Brazil [50]. The highest concentration observed for putrescine (61.5 mg/kg), followed by
7 spermidine (8.2 mg/kg) and spermine (7.2 mg/kg). Moreover, in brewed coffee from Turkey
8 [49] were detected higher concentrations of tyramine (19.7 mg/L) and serotonin (13.55
9 mg/L), followed by tryptamine (9.185 mg/L), cadaverine (9.059 mg/L) and 2-
10 phenylethylamine (4.944 mg/L) compared with the brewed coffee from Italy (up to 1.95
11 mg/L) [48].

12 **2.5. Biogenic amines in fruits, vegetables and its products**

13 Fresh fruits, vegetables and their products like juices and sauces are a group, common added
14 in the daily dietary habits, expresses the culture, history and lifestyle of every country.
15 Harvesting processes, storage conditions and further management of the fruits and vegetables
16 (mashing, mixing, fermentation) varies greatly between countries. Fresh food and vegetables
17 contain BAs as endogenous components and due to uncontrolled microbial enzymatic activity
18 they can be accumulated [4]. Until now, in fresh fruit and vegetables, in their fermented
19 products and juices have been detected 22 BAs. The most detected BAs for this group are
20 tyramine, putrescine, cadaverine, histamine, spermine and spermidine, while serotonin and
21 agmatine has not detected in any of the analyzed samples. Also, the highest concentration of
22 BAs found in fresh fruits instead of juices. Among this group apple, banana, cabbage (raw
23 and fermented), olives, pineapples, pomelo, red grapes, white grapes and grape, apple and
24 plum, apricot, black and red currant, cherry grape, grapefruit, litchi, mango, orange, peach,
25 pear, pineapple juices have been analyzed. In fresh fruits and vegetables, higher
26 concentrations were observed for cadaverine (36.2 mg/kg) and tyramine (23.5 mg/kg) in
27 bananas from Poland [4], followed by spermidine (22.3 mg/kg) in raw cabbage from Spain
28 and putrescine in olives (14.63 mg/kg) from Italy [9]. Regarding the fermented cabbage,
29 higher concentrations were noted with putrescine (108.9 mg/kg), tyramine (60.66 mg/kg) and
30 histamine (37.01 mg/kg) from Germany [5]. The only high levels in juices was the
31 concentration of cadaverine in apricot, peach and pear (up to 17.22 mg/kg) from Italy [51] and
32 putrescine in peach (7.22 mg/kg) and pineapple (5.02 mg/kg) from Italy and Poland [4],
33 respectively .

2.6. Biogenic amines in soybean products

Soybean products are a diverse group of food products including tofu, soya sauce, sufu, doubanjiang, natto, soymilk, soy sprouts, tempeh, miso, tamari, soybean paste, soya bean, bean curd used in Chinese cuisine in Europe, America and Asia .

Different profile of BAs presented in different products. The differences in BAs profile between the soybean products may be attributed to different processes or hygienic conditions in the manufacture [52] and distribution. However, other factors in the variation of BA content could be the quantity of raw soybean product used, the fermentation processes or other technological processes, the proteolytic activity from bacteria [53] or other microorganism contaminants with potential activity [54].

In sufu the most dominant BAs were putrescine (316.9 mg/kg) and tyramine 446.6 mg/kg [55], while another profile of BAs observed in sufu products from China, with cadaverine (up to 883.7 mg/kg), putrescine (177.6 mg/kg) and spermidine (154.8 mg/kg), higher concentrations were detected in Spain up to 1730 mg/kg for tyramine and histamine [54]. Also, Yang et al., 2014 [56] reported the presence of six out of eight BAs in white sufu from China and the detection of unsafe level in 8 samples, although the authors conclude that further investigation is needed. Additionally, Kim et al., 2012 [57] detected 2-phenylethylamine, spermidine and tyramine in higher concentrations from safe level of human health in some natto products from Korea, while lower concentrations of biogenic amines were detected in natto products from Spain (spermidine up to 75.21 mg/kg). Among the other soybean products only soybean paste from Korea was presented remarkable concentrations in all of the nine analyzed BAs [58]. Lower concentrations were observed in soybean paste from Spain [54].

2.7. Biogenic amines in beer and other alcoholic beverages

Alcoholic beverages are a major category, including beers (all types), liqueurs, gin, rum, brandy, whiskey and ciders. Beer is produced mainly by mixing malted barley and hops and selected yeast strains, such as *Saccharomyces cerevisiae* (top fermenting), *Saccharomyces carlsbergensis* with wild yeast and lactic acid bacteria. It was observed that the high concentration of histamine and tyramine linked with microbial contamination during brewing. On the other hand, putrescine, agmatine, spermidine, spermine and 2-phenylethylamine could be natural constituents either from malt or hop.

1 Ciders also produced from apple juice with indigenous yeast and LAB. A lot of strains have
2 been isolated and identified as BA producers. The other alcohol beverage, liqueurs is a
3 mixture of ethyl alcohol (e.g. cognac, rum, or whiskey) or a neutral distillate of agricultural
4 origin flavored with fruit, cream, herbs, spices, flowers or nuts and bottled with added sugar,
5 honey, or high-fructose corn syrup, produced either by heat, infusion, cold or maceration
6 process or distillation [59].

7 Besides the extended consumption worldwide of beer and other alcoholic beverages, scarce
8 data exists concerning the detected BAs. Almeida et al., 2012 reported the detection and
9 analysis of eighteen BAs in beer samples from Portugal [59]. The most dominant ones were
10 putrescine, tyramine and dimethylamine with concentrations up to 12.777mg/L, which are in
11 agreement with published data from Iran and Brazil [17]. Aflaki et al., 2014 [17] observed
12 very low concentrations for non-alcohol beers from Iran with concentrations below 1.17
13 mg/L for the analyzed BAs. For all the other alcoholic beverages have been conducted only
14 one survey, so further investigation is needed. Among, rum, gin, whiskey and brandy were
15 highlighted only the BAs in rume. On the other hand, in liqueurs were detected very low
16 concentrations in contrast to the other beverages.

17 **2.7.1. Biogenic amines in wine**

18 Literature data reports that more than 15 amines have been identified in wine and their total
19 concentration has been reported to range from a few ng/L to about 50 mg/L, depending on the
20 quality of the wine. Several factors impact on the type of BA that could be found in wine
21 including differences in the wine-making process, time and storage conditions, raw material
22 quality and possible microbial contamination during winery operations. Generally, they are
23 two different sources of BAs in wine: raw materials and fermentation processes. It has been
24 shown that some amines occur in grapes, namely, histamine and tyramine, as well as several
25 polyamines and volatile amines. Although, histamine, putrescine and tyramine are present in
26 higher concentration level in wine, other compounds including phenylethylamine, cadaverine
27 and isoamylamine are also present in smaller amounts. Putrescine and cadaverine are
28 normally associated with poor sanitary conditions of grapes.

29 Generally, lactic acid bacteria [10] can produce metabolic energy and/or increase their acid
30 resistance by using catabolic pathways that convert amino acids into amine-containing
31 compounds including BAs. Therefore, many researchers are focused on studies of correlation
32 of BAs production in wine with species of LAB involved in the wine-making process. It is
33 widely known that several bacteria are implicated in BAs production in wine including

1 *Lactobacillus*, *Pediococcus*, *Oenococcus* spp. and *Leuconostoc* [17]. It is reported that
2 *Leuconostoc mesenteroides* has a high potential to produce tyramine or histamine in wine
3 [17], while *Oenococcus oeni* is able to significantly contribute to the overall BA content of
4 wines, mainly producing histamine, however, the ability of each bacteria type to produce BAs
5 varies among strains [17]. Moreover, LAB strains have the ability to simultaneously produce
6 different amines, suggesting that some strains might possess more than one amino acid
7 decarboxylase activity under specific culture conditions.

8 According to the literature, in white wines the range of BAs ranged from n.d. to 12.8 mg/L.
9 High concentrations were found in Italy for histamine, putrescine, tyramine and ethylamine
10 while in Portugal only histamine presented in 8.94 mg/L. 15 out of 16 BAs occurred in red
11 wines worldwide. Higher concentrations were detected for histamine 23.1 ± 2.2 mg/L in
12 Portugal [60], in Italy 10.8 mg/L [61], in France 14.05 mg/L [62] and in different EU countries
13 (Italy, France, Germany, Switzerland, Austria and Spain) 16.2 mg/L [63]. Also, putrescine
14 presented the highest concentration in three different surveys in Italy with 31.8, 11.13 and
15 16.2 mg/L respectively [51, 61, 63] and in France 48.72 mg/L [62]. Lower concentrations
16 were detected for the above BAs in Brazil and China. Slightly lower concentration of
17 tyramine were present and ranged up to 18.8 mg/L [61]. Ethylamine and methylamine
18 presented the highest concentrations in France up to 10.46 and 36.64 mg/L, respectively [62].
19 Ethanolamine was analyzed and detected in concentrations up to 17.44 μ g/L in China [64] and
20 serotonin was absent from the analyzed samples in Italy and in China [51,64]. Moreover, the
21 most persistent BAs in rose wines were histamine in Portugal with concentrations ranged up
22 to 15.1 mg/L [60] and tyramine (10.8 mg/L) in Italy [61], while histamine and spermine
23 detected in China in concentrations up to 18.35 mg/L in rice wine [38].

24 However, studies have shown that higher concentrations of BAs occurred in red wine samples
25 instead of white, rose, rice and Porto wines. Comuzzo et al., 2013 [63] supported that climatic
26 conditions could be connected with these variations but also winemaking technologies could
27 play a key role in the production of BAs.

28 **2.7.2. Biogenic amines in vinegar**

29 Vinegar constituted after the bacteria conversion of ethanol to acetic acid. Every alcoholic
30 mixture, with ratio alcohol-water to wine can produce vinegar [65]. Although these two food
31 products are of great importance, data concerning the occurrence of BAs is limited. However,
32 spermine and tyramine were detected in both black and green tea from Asia with
33 concentrations up to 0.336 mg/L. While higher concentrations of 3- aminopropionic acid, 4-

1 aminobutanoic acid and agmatine were detected in herbal tea from USA [15], so further
2 investigation should be consider. Furthermore putrescine was detected in vinegars from USA
3 (up to 3.2 mg/L) and Spain (0.525), while histamine presented slightly lower concentration in
4 Spanish vinegars (0.309 mg/L) [65].

5 **2.8. Biogenic amines in tea**

6 Tea is a widespread product worldwide and is available and consumed regularly in large
7 amounts. The leaves and buds of *Camellia sinensis* mixed with water constitute the tea extract.
8 Different varieties, quantities, qualities of the plant and processes applied in every country.
9 Two different categories are well known, green tea after heat or steam treatment and fast
10 drying of young leaves and buds of the plant and black tea after procedures such as
11 weathering, destruction of plant tissues by various rolling, crushing and/or tearing and finally
12 drying. After these processes, the enzymes which are responsible for oxidation and
13 degradation released and form polyphenols and the color compounds.

14

15 **3. Physiological and Toxicological Aspects of Biogenic Amines**

16 Many BA's are important for normal function of biological systems. For example in
17 eukaryote cells they are important precursors for a variety of precursors, some play an
18 important roles as neurotransmitters and others such as putrescene and spermidine are
19 involved in critical biological functions. However, in larger concentrations, usually from an
20 accumulation in a food source, these compounds can be toxic.

21 Biogenic amines may be a constituent of many foods and consumption can be problematic for
22 human health. High BA concentrations can cause flushes, headache, nausea, palpitations of
23 the heart and changes in blood pressure and many other physiological problems. Important
24 BA's found in food include histamine, tyramine, putrescene, cadaverine and
25 phenylethylamine. Polyamines, such as putrescine, cadaverine, agmatine, spermine, and
26 spermidine, are naturally present in food and are involved in growth and cell proliferation
27 [66].

28 The toxicological effects of many of these compounds has been reported for many reasons
29 including the effect they can have on human health.

30 Many of these amines in the presence of nitrites can be potential carcinogens when converted
31 to nitrosamines [66], but nitrosamines formed from the polyamines only become a health risk

1 as toxicity is reached after consumption of large amounts, and more than expected in a daily
2 meal.

3 In general, there is little research on the toxicology of BA's, but that which exists is
4 predominately on histamine. Consuming large amounts of histamine (greater than 500 ppm)
5 can lead to poisoning which may manifest as an allergen reaction with symptoms including
6 breathing, itching, rash, vomiting, fever, and hypertension. An intake of 5—10 mg of
7 histamine may be considered as having some effect to some sensitive people while 10 mg is
8 generally considered as tolerable limit, 100 mg can induce a medium toxicity and 1000 mg is
9 highly toxic [25]. In fact histamine and tyramine are considered most toxic and particularly
10 relevant for food safety, with putrescine and cadaverine potentiating the effects by inhibition
11 of histamine detoxifying enzymes [25].

12 BA's ingested with food are detoxified by amine oxidases in the GI tract, and particularly the
13 intestinal mucosa. Under normal conditions, amines ingested are metabolized by conjugation
14 or oxidation reactions with amine oxi-dase enzymes such as monoamine oxidase (MAO), di-
15 amine oxidase (DAO), polyamine oxidases (PAO) and N-methyl transferase [67].

16 Therefore, it can be seen that MOA or DOA inhibitor medication (antihistamines, antimalarial
17 agents, anti -depressant drugs), alcohol or genetics (enzymes not properly functioning) may
18 affect BA metabolism. In addition, people with GI tract diseases may be poor metabolisers of
19 BA's [25]. Under these circumstances the BA's enter the systematic circulation where they
20 may promote release of adrenaline and noradrenaline, leading to many of the well
21 documented problems (increased cardiac output), tachycardia, increased blood sugar and
22 higher blood pressure.

23 In terms of toxicity via Oral absorption levels for putrescine, spermine, and spermidine are
24 2000, 600, and 600 ppm, respectively. The acute toxicity level for tyramine and cadaverine is
25 greater than 2000 ppm. The no observed adverse effect level (NOAEL) is 2000 ppm for
26 tyramine, putrescine, and cadaverine; 1000 ppm for spermidine; and 200 ppm for spermine
27 [68].

28

29 **4. Regulations Policy**

30 Without doubt, the toxicity of BAs is a very important parameter, however, determination of
31 the exact toxicity threshold of BAs in an appropriate product of food is a difficult task, due to
32 the fact that their effect does not depend only on BAs presence alone, but is influenced by
33 other compounds. In addition, toxic effect of BAs on organism is also dependent by on the

1 specific efficiency of the detoxifying mechanisms in different individuals [16]. Therefore it
2 can be stated that the BAs toxicity will depend on two factors associated with the food itself
3 (quantitative and qualitative) and related to the consumer (individual susceptibility and state
4 of health).

5 Due to the fact that there is still lack of information on toxic doses for each biogenic amine,
6 not for all amines occurred in food legal limits are established. In fact, concentration level of
7 histamine is regulated by law in some type of food product (fish food).

8 The European Food Safety Authority confirmed histamine and tyramine as the most toxic and
9 particularly relevant for food safety [69]. Taking into account the data from food intoxication
10 outbreaks a legal upper limit of 100 mg histamine·kg⁻¹ food and 2 mg·L⁻¹ of ethanol has been
11 suggested. In Brazil, the Regulation of Industrial and Sanitary Inspection of Animal Products
12 does not mention the amine maximum level allowed in products of animal origin [67].
13 However, MERCOSUR Resolution and the Technical Regulation on the Identity and Quality
14 of Fresh Fish (whole and gutted) establish a maximum level of 10 mg/100g of histamine in
15 the muscles of species of the Scombridae, Scomberesocidae, Clupeidae, Coryphaenidae and
16 Pomatomidae families [67]. The maximum acceptable histamine levels in fish were also
17 established in other countries. For example, the European Union has established regulations
18 according to which histamine level should be below 100 mg·kg⁻¹ in raw fish, and below 200
19 mg·kg⁻¹ in salted fish, however, this is obligatory for species belonging to the Scombridae,
20 Engraulidae, Coryphenidae, Pomatomidae and Clupeidae families [69]. In USA, the Food and
21 Drug Administration, established a maximum limit of 5 mg histamine/ 100 g product at the
22 port and 10 mg histamine/ 100g product in pickled fish for species susceptible to form
23 histamine [67]. The Nutritional codex of the Slovak Republic had determined the maximal
24 tolerable limit for the following two BAs: histamine (20 mg·kg⁻¹ in beer and 200 mg·kg⁻¹ in
25 fish and fish products) and tyramine (200 mg·kg⁻¹ in cheese)[70]. A recommended upper limit
26 of 100 to 200 mg kg⁻¹ for histamine in meat products has been proposed by the Netherlands
27 Institute of Dairy Research and by the Czech Republic.

28 There are no established standards for cadaverine, putrescine or other BAs, only some
29 recommendation are given, for instance, the recommended maximum level of tyramine has
30 been proposed variously to be in the range of 100-800 mg·kg⁻¹ of food. Value of 30 mg·kg⁻¹
31 for β-phenylethylamine has been reported as toxic dose in food.

32

33

5. Presence of biogenic amines as an indicator of food products quality

1 Due to the fact that the level of concentration of BAs can increase (cadaverine, putrescine and
2 tyramine), decrease (spermine and spermidine or remain constant during the processing and
3 storage of some food products (eg. meat, meat products), their amounts and ratios have been
4 proposed as an index of the hygienic conditions of raw material and/or manufacturing
5 practices [16]. However, the usefulness of BAs as a quality index depend on the nature of the
6 product what impact on the tendency to be more satisfactory in fresh meat as well as heat-
7 treated products than in fermented products.

8 The Chemical Quality Index (CQI) was introduced in 1977 [71] for seafood and fish and was
9 calculated using following equation:

$$CQI = \frac{cHIM + cPUT + cCAD}{1 + cSPD + cSPM}$$

11
12 where HIM – histamine, PUT – putrescine, CAD – cadaverine, SPD – spermidine, SPM –
13 spermine and c – concentration [$\text{mg}\cdot\text{kg}^{-1}$].

14 Food freshness should be evaluated by considering an amine index, which includes all the
15 BAs related to meat spoilage, and thus, considering the fact that tyramine increases during
16 meat storage, this BA should also be included in a Biogenic Amine Index (BAI). This
17 knowledge was used in BAI proposed in 1982. However, it needs to be remember, that not all
18 spoilage or starter microorganisms can decarboxylate free amino acids. Even within the same
19 species, not all strains develop the same decarboxylating capacity, so that a low concentration
20 of BA does not always signal good microbiological quality [16].Therefore, there is no simple
21 way to establish a biogenic amine index that reliably predicts quality for products of this kind.

23 **6. Analytical challenges and strategies of biogenic amines determination**

24 Due to the fact that two reasons for importance of BAs determination in food exist which are
25 potential toxicity and possibility of using them as food quality markers, the development of
26 analytical methodologies for laboratory examining of BAs content is of high importance.

27 Undoubtedly, BAs identification remains one of the greatest challenges in food analysis.
28 From the analytical point of view, bioactive amine detection in food is not simple due to
29 reasons including strong polar character of the compounds, which results in a greater
30 solubility in water rather than in the organic solvents frequently used; complexity of the
31 matrix sample; variable concentration range which mainly is very low; the presence of

1 potentially interfering compounds; absence of intrinsic properties of the compounds, which
2 could enable their detection by usual physico-chemical methods as spectrophotometric,
3 fluorometric or electrochemical methods; and the occurrence of several biogenic amines
4 simultaneously. However, to solve these problems the developed analytical methods are
5 generally based on amine extraction and derivatization followed by separation and quantification.
6 The extraction of amines represents the critical step of the process and it affects negatively the
7 analytical recoveries, while derivatization also is not desirable process because it is additional
8 step of analytical procedure, what brings further errors and losses in determined analyte
9 concentration. Recently, extraction and derivatization processes are often performed
10 simultaneously. After extraction (and derivatization if required), the determination of BAs is
11 most commonly performed by means of chromatographic methods: high-performance liquid
12 chromatography (HPLC), gas chromatography (GC) and capillary electrophoresis (CE).

13 **6.1. Liquid Chromatography**

14 The most commonly popular technique for the determination of BAs in food products is the
15 HPLC with Reversed-Phase separation, using C18 columns, however, other solutions are
16 proposed. Table 1 summarizes the chromatographic methods used to quantify BAs in the food
17 matrices, in the last decade.

18 Generally, the most common resolution to sample preparation prior to final separation is
19 application of solvent extraction and derivatization process, not only to remove compounds
20 that may interfere with the analysis but also to concentrate the analytes. In some cases, a
21 simple treatment with polyvinylpolypyrrolidone (PVPP) to remove some phenolic compounds
22 is used. Considering derivatization processes, pre-column or post-column modes are usually
23 performed, since BAs do not have enough absorption in the UV-Vis or FLD wavelength
24 ranges. This step is also applied to improve the separation in the RP columns, reducing the
25 polarity of the original compounds. Several derivatization reagents have been reported,
26 however, dansyl chloride (DNS-Cl) has been commonly applied in the last years, since that its
27 derivatives can be detected using DAD, FLD and MS. Taking into account this three type of
28 detection type, FLD revealed better sensitivity to detect dansylated amines. DNS-Cl is very
29 often used as pre-column derivatizing reagent in the determination of BAs in food products,
30 mainly because it produces stable derivatized compounds. From the other hand, the
31 dansylation reaction is a time consuming process (10-60 min) and it requires the application
32 of external temperature (40 to 70 °C). However, a new method to perform the dansylation at
33 room temperature, during 20 min, using ionic liquids as media for the derivatization of BAs in

1 wines was introduced [72]. Another important reagent for derivatization of BAs is *ortho*-
2 phthalaldehyde (OPA) compound. Although, OPA derivatives are less stable, the process can
3 be performed at room temperature in a short time. OPA reagent can be used without using any
4 preliminary separation or clean-up. Moreover, it can be used for post column derivatization
5 [73].

6 **6.2. Capillary Electrophoresis**

7 The second most commonly performed technique applied to the determination of biogenic
8 amines in foods is capillary electrophoresis (CE), despite its low sensitivity when compared
9 with other methods. CE has several advantages: it is simple, rapid, and reliable, making it a
10 very useful tool for screening a large number of samples in a short period of time [26].
11 Moreover, CE is efficient, as well as inexpensive in terms of reagent consumption, and
12 presents a lower reproducibility of migration times than LC. Therefore, the usefulness of this
13 technique will depend on the expected BAs levels in food samples. Several approaches are
14 used to solve the problem of BA determination in food samples using this technique: i)
15 application of derivatization process, ii) application of selected buffer system without
16 derivatization, iii) application of specific kits. Off-line pre-column derivatization is most
17 commonly used, with the resulting derivatives being injected into the CE. Derivatization
18 processes can also be coupled with some innovative on-line pre-treatment procedures,
19 contributing to enhanced sensitivity of these methods. Different type of derivatizing reagents
20 are used, and these depend on the detection technique coupled to CE. Fluorometric methods
21 are used owing to fluorescence of BAs at some pH range and reaction of BAs with suitable
22 agents. This is achieved mainly by reaction with *o*-phthalaldehyde, dansylchloride or
23 dabsylchloride and β -naphthol [26]. *o*-phthalaldehyde has the disadvantages that it reacts only
24 with primary amines and the instability of its fluorescent derivatives, while dabsyl- and
25 dansylchloride react with both primary and secondary amino groups and provide stable
26 derivatives. Dabsyl derivatives are coloured, so they absorb in the visible region, while dansyl
27 derivatives combine a unique feature of being both fluorescent and detectable in the UV-
28 region [74]. Indirect detection or electrochemical detection has also been used after CE
29 separation of BAs [74]. In indirect methods, a previous step involving clean-up, such as added
30 polyvinylpyrrolidone (PVP) followed by filtration, is usually performed. As a detection
31 technique, UV, photometric detection and MS (or MS/MS) are usually applied. Information
32 on the latest developments in determination of BAs in food samples by CE techniques are
33 presented in Table 2.

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6.3. Gas Chromatography

Gas chromatography is not as commonly used as liquid chromatography or capillary electrophoresis for determination of BAs in food samples. However, some studies are reported, mainly with the application of mass spectrometer as a detection technique. Gas chromatography has been specifically applied in fermented beverages by some authors in order to offer alternative methods to LC. Before analysis, derivatization of analytes need to be performed to change the properties of analytes, typically to increase volatile properties and to decrease polarities of BAs. Depending on the detection technique used for final determination, different type of derivatizing reagents can be applied, e.g. pentafluorobenzoyl chloride, however, the most popular are alkylated chloroformates. The fact that the derivatization reaction can be performed in an aqueous basic solution is one advantage of using these compounds. In addition, the derivatization process occurred at room temperature in a short time and can be coupled with extraction procedure. Moreover, the derivatives obtained are characterized by such properties which are useful for application of analytical procedures based on GC techniques at the mixture separation, detection, and quantitative determination stages.

Recently, several works focused on determination of BAs in food samples such as fish or alcoholic beverages by using isobutyl chloroformate coupled with solid phase microextraction (SPME) [75] or dispersive liquid-liquid microextraction (DLLME) [24, 59]. Reported methods were efficient and highly reproducible, allowing the accurate identification and quantification of a higher number of biogenic amines. Furthermore, the derivatization procedure and the overall analysis time were faster than in some LC methods, reaching LODs of the same order.

6.4. Non-chromatographic approaches for determination of biogenic amines

Chromatographic techniques such as GC, LC or CE are among the most important instrumental methods for precise quantitative analysis of BAs. From the other site, these methods are often time-consuming as well as they require considerable skill [76]. In addition, a disadvantage of the HPLC, CE and GC-MS analyses in general is the long and tedious sample pretreatment. A further principal drawback of these methods is the requirement of (sometimes harmful) organic solvents of HPLC grade quality, whereby the cost for their purchase and disposal has to be taken into consideration. Enzymatic as well as immuno-

1 enzymatic methods such as commercially available test kits designed to histamine
2 determination can also be applied for routine analysis with semiquantitative and quantitative
3 determination of biogenic amines.

4 Disposable screen-printed electrode biosensors with enzymes have been shown as a step
5 forward to reduced sample pretreatment. Biosensors combines biological recognition through
6 enzyme specificity with construction simplicity and they are a good and cheap alternative for
7 the traditional methods of analytes determination. In biosensors used for BA determination,
8 amine oxidases (AO) based electrodes, which catalyze the oxidative deamination of primary
9 amines, diamines and substituted amines to produce aldehyde, ammonia and hydrogen
10 peroxide, have been reported [77]. AO-sensors can base on platinum sreen-printed electrodes
11 (SPEs), using a glutaraldehyde – bovine serum albumin cross-linking immobilization
12 procedure [78]. The procedure involves the measurement of the H₂O₂ produced by applying
13 a potential higher than 600 mV. Monoamine oxidase (MAO)/horseradish peroxidase (HRP)
14 and diamine oxidase (DAO)/horseradish peroxidase (HRP) based biosensors using screen-
15 printed carbon electrodes for the determination of BAs in fish samples was also reported. The
16 enzymes have been covalently immobilized onto the carbon working electrode, previously
17 modified by an aryl diazonium salt, using hydroxysuccinimide and carbodiimide. The
18 detection has been performed by measuring the cathodic current due to the reduction of the
19 mediator hydroxymethylferrocene at a low potential. A linear response range from 0.2 up to
20 1.6_μM and from 0.4 to 2.4_μM of histamine was obtained for DAO/HRP and MAO/HRP based
21 biosensors, respectively.

22 An interesting idea of application of polymer layers with different changes in absorption due
23 to interaction with aromatic, aliphatic, and polyamines was reported [79]. Several colorimetric
24 methods using test spots are also known and many times applied for routine analysis of food
25 samples [80]. These can be semiquantitatively evaluated by visual readout of the originated
26 color in comparison to a reference color scale [76]. Colorimetric sensor arrays consisting
27 either of several amine sensitive dyes [81] or organic liquid crystals [82] also have been
28 applied for the determination of volatile amines in food and beverage samples.

29 Nowadays, an amperometric sensors are also many often used for BAs determination mainly
30 in food products. An example of this type of biosensor composed with pea seedling AO and
31 creen printed carbon electrode modified with MnO₂ for determining selected BAs was
32 designed in 2007 [83]. The bio-component was immobilized with Nafion solution. The
33 enzymatically produce hydrogen peroxide was determined to quantify BAs. The limits of
34 detection were determined to be 0.3 μM for cadaverine and putrescine and 3.0 μM for

1 tyramine and histamine. The sensor was used to quantify BAs in chicken meat samples.
2 Enzymatic sensors reduce the time needed for analysis as well as offer a rapid screening
3 method for industrial food quality testing. The use of disposable transducers, such as SPEs,
4 boosts the intrinsic characteristics of enzymatic sensors. Screen-printing technology, which
5 offers design flexibility, proces automatization and good reproducibility in the transducers
6 fabrication, had been shown as a method for mass production of biosensors at low cost [77].
7 In 2010, a new chromogenic and fluorogenic dry chemistry sensing spots based on filter paper
8 containing an amine-reactive chromogenic probe and fluorescein as a green fluorescent (but
9 amine insensitive) reference dye incorporated in a hydrogel matrix was presented [76]. These
10 test spots can quantitate BAs upon dipping into the sample. The test spots were evaluated with
11 six different biogenic amines at concentrations between 0.01 and 10 mM using the RGB
12 readout option of a digital camera. This sensor spots represent an attractive alternative to
13 existing schemes for sensing biogenic amines. Its digital read-out makes it more robust, and
14 the use of conventional cameras goes along current trends toward simplified methods for
15 absorption-based and emission-based detection schemes. In addition, the method also may
16 enable high-throughput analysis and in-field examinations and does not require sophisticated
17 instrumentation or trained personel.

Table 1. Information on analytical methodologies based on gas and liquid chromatography developed for BAs determination in food samples.

Matrice	Analyte	Sample preparation	Derivatization	LOD/LOQ	Recovery	Separation technique	Detection	Ref.
wine	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL LOQ: 3.5–26.1 ng/mL	91.2–108.3 %	HPLC (column: Hypersil C18)	FLD	[38]
	PUT, CAD, 2-PE, SPR, SPRE, HIS, TYR	Addition of PVPP	YES: dansyl chloride	LOD: 0.09–0.30 mg/L LOQ: 0.30–1.00 mg/L	>78 %	HPLC (column: C ₁₈ YMC-Pack ODS-A)	UV	[84]
	HIS, TYR, 2-PE, SER, TRYP, OCT, DOP, CAD, PUT, AGM, SPR, SPRE	Solvent extraction	YES: OPA (post column derivatization)	LOD: 0.05–0.2 mg/L LOQ: 0.1–0.3 mg/L	93.56–103.28 %	UHPLC (column: Acquity UPLC BEH C18)	FLD	[85]
	PROP, DMET, DET, MET, TRYP, CAD, SPR, 2-PE, TYR, PUT, HIS, BUT, HEX, IPENT, IBUT, SPRE, AGM	Dilution with water	YES: <i>p</i> -toluenesulfonyl chloride	LOD: 0.023–83 µg/dm ³ LOQ: 0.075–270 µg/dm ³	-	HPLC (column: Gemini C-18)	MS/MS	[86]
	BUT, CAD, DET, DMET, ET, MET, HIS, PROP, PUT, SPR, TRYP, TYR, 2-PE	DLLME	YES: IBCF	LOD: 1.1–4.1 µg/L LOQ: 3.3–12.3 µg/L	77–105 %	GC (column: ZB-5MS, 0.25 µm)	MS	[24]
	MET, DMET, ET, DET, PROP, IPROP, BUT, IBUT, AM, IAM, 2-MBUT, HEX, PYR, PIP, MOR, PUT, CAD, 2-PE, HIS, TYR	DLLME	YES: IBCF	LOD: 1.8–36.8 µg/L	85–111 %	GC (column: HP-5MS, 0.25 µm)	MS	[87]
beer	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL LOQ: 3.5–26.1 ng/mL	91.2–108.3 %	HPLC (column: Hypersil C18)	FLD	[39]

	PUT,HIS, CAD, 2-PE, HEX, TYR, SPRE, SPR	Solvent extraction	YES: EAC	LOD: 0.27–0.69 ng/mL	94.18-104.02 %	HPLC (column: Hypersil BDS C ₁₈)	FLD	[88]
	PROP, DMET, DET, MET, TRYP, CAD, SPR, 2-PE, TYR, PUT, HIS, BUT, HEX, IPENT, IBUT, SPRE, AGM	Dilution with water	YES: <i>p</i> -toluenesulfonyl chloride	LOD: 0.023-83 µg/dm ³ LOQ: 0.075-270 µg/dm ³	-	HPLC (column: Gemini C-18)	MS/MS	[86]
	TYR, MET, DMET, ET, IPROP, DET, IBUT, 2MBUT, PYR, IAM, MOR, PIP, AM, 2-PE, PUT, CAD, HIS	DLLME	YES: IBCF	LOD: 0.3-2.9 µg/L LOQ: 1.0-9.5 µg/L	72-113 %	GC (column: DB-5MS, 0.18 µm)	MS	[59]
cheese	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL LOQ: 3.5–26.1 ng/mL	91.2–108.3 %	HPLC (column: Hypersil C18)	FLD	[38]
	PUT,HIS, CAD, 2-PE, HEX, TYR, SPRE, SPR	Solvent extraction	YES: EAC	LOD: 0.27–0.69 ng/mL	94.98-101.38 %	HPLC (column: Hypersil BDS C ₁₈)	FLD	[88]
	ETH, MET, AGM, HIS, DMET, ET, OCT, PYR, DOP, IPROP, PROP, TYR, PUT, BUT, CAD, TRYP, 2-PE, 3-METBUT, SPRE, SPR	Solvent extraction	YES: AQC	LOD: 4-162 mg/g	-	ULPC (column: Nova-Pak™ C ₁₈)	FLD	[3]
	HIS, TYR, 2-PE, SER, TRYP, OCT, DOP, CAD, PUT, AGM, SPR, SPRE	Solvent extraction	YES: OPA (post column derivatization)	LOD: 0.05-0.2 mg/L LOQ: 0.1-0.3 mg/L	79.10-103.00 %	UHPLC (column: Acquity UPLC BEH C18)	FLD	[73]
	PUT, CAD, SPRE, SPR, 2-PE, HIS, TYR, TRYP	Solvent extraction	YES: dansyl chloride	LOD: 0.032-0.098 µg/L LOQ: 0.11-0.32 µg/L	-	UHPLC (column: Zorbax Eclipse XDB – C18 column)	UV	[89]
yogurt	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL LOQ: 3.5–26.1 ng/mL	91.2–108.3 %	HPLC (column: Hypersil C18)	FLD	[38]
sausage	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL	91.2–108.3 %	HPLC (column: Hypersil	FLD	[38]

				LOQ: 3.5–26.1 ng/mL		C18)		
	PUT,HIS, CAD, 2-PE, HEX, TYR, SPRE, SPR	Solvent extraction	YES: EAC	LOD: 0.27–0.69 ng/mL	96.37-101.30 %	HPLC (column: Hypersil BDS C ₁₈)	FLD	[35]
	HIS, TYR, 2-PE, SER, TRYP, OCT, DOP, CAD, PUT, AGM, SPR, SPRE	Solvent extraction	YES: OPA (post column derivatization)	LOD: 0.05-0.2 mg/L LOQ: 0.1-0.3 mg/L	87.33-100.24	UHPLC (column: Acquity UPLC BEH C18)	FLD	[73]
rice wine	TRYP, HIS, CAD, 2-PE, HEX, TYR, SPR	UA-DLLME	YES: BCEC-Cl	LOD: 1.1–7.8 ng/mL LOQ: 3.5–26.1 ng/mL	91.2–108.3 %	HPLC (column: Hypersil C18)	FLD	[38]
Corn oil	HIS, 2-PE, PUT, TYR, CAD, TRYP, SPR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 0.01-0.10 mg/kg LOQ: 0.02-0.31 mg/kg	94.51-106.72 %	HPLC (column: Nova-Pak C ₁₈ 4 μm)	UV-VIS	[90]
Fresh fish	MET, HIS, ET, TYR, PROP, TRYP, 2-PE, ISM, HEP, PUT, PUT, CAD	UA-LLE	YES: naphthalene-2,3-dicarboxaldehyde	LOD: 2.5 and 330 mg/kg	81.0-102.5 %	HPLC (column: Inertsil ODS-3)	FLD	[85]
	PUT,HIS, CAD, 2-PE, HEX, TYR, SPRE, SPR	Solvent extraction	YES: EAC	LOD: 0.27–0.69 ng/mL	95.81-103.47 %	HPLC (column: Hypersil BDS C ₁₈)	FLD	[88]
	HIS, TYR, 2-PE, SER, TRYP, OCT, DOP, CAD, PUT, AGM, SPR, SPRE	Solvent extraction	YES: OPA (post column derivatization)	LOD: 0.05-0.2 mg/L LOQ: 0.1-0.3 mg/L	83.08-98.81 %	UHPLC (column: Acquity UPLC BEH C18)	FLD	[73]
	PUT, CAD, SPRE, SPR, 2-PE, HIS, TYR, TRYP	Solvent extraction	YES: dansyl chloride	LOD: 0.032-0.098 μg/L LOQ: 0.11-0.32 μg/L	-	UHPLC (column: Zorbax Eclipse XDB – C18 column)	UV	[88]
Canned fish	MET, HIS, ET, TYR, PROP, TRYP, 2-PE, ISM, HEP, PUT, PUT, CAD	UA-LLE	YES: naphthalene-2,3-dicarboxaldehyde	LOD: 2.5 and 330 mg/kg	81.0-102.5 %	HPLC (column: Inertsil ODS-3)	FLD	[85]
		Solvent extraction	YES: dansyl chloride	LOD: 4.43-7.34 μg/L LOQ: 14.76-24.45 μg/L	90.9–106.3%	HPLC (column: Waters Spherisorb 5 μm ODS2)	UV-VIS	[91]
	HIS, TYR, PUT, CAD	DI-SPME	YES: IBCF	LOD: 2.98–	78.9–110 %	GC (column: RXi-	MS	[75]

				45.3 µg/kg LOQ: .83–149 µg/kg		5MS, 0.25 µm)		
shrimp sauce	TRYP, PUT, CAD, HIS, TYR, SPRE	HF-LPME	YES: dansyl chloride	LOD: 0.0075- 0.030 µg/mL LOQ: 0.03- 0.10 µg/mL	88.6-103 %	HPLC: (column: Waters Spherisorb 5 µm ODS2)	UV	[35]
		Solvent extraction	YES: dansyl chloride	LOD: 4.43- 7.34 µg/L LOQ: 14.76- 24.45 µg/L	90.9–106.3%	HPLC (column: Waters Spherisorb 5 µm ODS2)	UV-VIS	[91]
tomato ketchup	TRYP, PUT, CAD, HIS, TYR, SPRE	HF-LPME	YES: dansyl chloride	LOD: 0.0075- 0.030 µg/mL LOQ: 0.03- 0.10 µg/mL	86.7-104 %	HPLC: (column: Waters Spherisorb 5 µm ODS2)	UV	[35]
Meat	TRYP, PUT, CAD, HIS, TYR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 4.43- 7.34 µg/L LOQ: 14.76- 24.45 µg/L	90.9–106.3%	HPLC (column: Waters Spherisorb 5 µm ODS2)	UV-VIS	[91]
	TYR, PUT, CAD, SPR, SPRE	Solvent extraction	YES: benzoyl chloride	LOD: 0.03– 1.25 µg/L LOQ: 0.15– 5.00 µg/L	64.40-112.22 %	HPLC (column: Tracer Extrasil ODS2)	UV-VIS	[92]
	PUT, CAD, SPRE, SPR, 2-PE, HIS, TYR, TRYP	Solvent extraction	YES: dansyl chloride	LOD: 0.032- 0.098 µg/L LOQ: 0.11- 0.32 µg/L	-	UHPLC (column: Zorbax Eclipse XDB – C18 column)	UV	[89]
Rice porridge	HIS, 2-PE, PUT, TYR, CAD, TRYP, SPR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 0.01- 0.10 mg/kg LOQ: 0.02- 0.31 mg/kg	86.63-106.23	HPLC (column: Nova-Pak C ₁₈ 4 µm)	UV-VIS	[90]
soy bean products	TRYP, PUT, CAD, HIS, TYR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 4.43- 7.34 µg/L LOQ: 14.76- 24.45 µg/L	90.9–106.3%	HPLC (column: Waters Spherisorb 5 µm ODS2)	UV-VIS	[91]
juice	TRYP, PUT, CAD, HIS, TYR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 4.43- 7.34 µg/L LOQ: 14.76-	90.9–106.3%	HPLC (column: Waters Spherisorb 5 µm ODS2)	UV-VIS	[91]

				24.45 µg/L				
	HIS, 2-PE, PUT, TYR, CAD, TRYP, SPR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 0.01-0.10 mg/kg LOQ: 0.02-0.31 mg/kg	92.35-107.01 %	HPLC (column: Nova-Pak C ₁₈ 4 µm)	UV-VIS	[90]
	MET, DMET, ET, DET, PROP, IPROP, BUT, IBUT, AM, IAM, 2-MBUT, HEX, PYR, PIP, MOR, PUT, CAD, 2-PE, HIS, TYR	DLLME	YES: IBCF	LOD: 1.8-36.8 µg/L	92-112 %	GC (column: HP-5MS, 0.25 µm)	MS	[87]
shrimp	PUT, HIS, CAD, 2-PE, HEX, TYR, SPRE, SPR	Solvent extraction	YES: EAC	LOD: 0.27–0.69 ng/mL	93.74-103.40 %	HPLC (column: Hypersil BDS C ₁₈)	FLD	[88]
Chocolate, vegetables, and fruits	TYR	Solvent extraction	NO	LOD: 10 ng/mL LOQ: 30 ng/mL	72.0-85.8 %	HPLC (column: LiChrospher 100 RP-18e)	FLD-DAD	[93]
fermented cow's and goat's milks	TYR, CAD, PUT, HIS, SPRE	Solvent extraction	YES: benzoyl chloride	LOD: 0.03-1.30 mg/L LOQ: 20-5.00 mg/L	91-107%	HPLC (column: Extrasil Tracer ODS2)	DAD	[47]
peanut butter	HIS, 2-PE, PUT, TYR, CAD, TRYP, SPR, SPRE	Solvent extraction	YES: dansyl chloride	LOD: 0.01-0.10 mg/kg LOQ: 0.02-0.31 mg/kg	93.90-107.74 %	HPLC (column: Nova-Pak C ₁₈ 4 µm)	UV-VIS	[90]
mushrooms	PUT, CAD, SPRE, SPR, 2-PE, HIS, TYR, TRYP	Solvent extraction	YES: dansyl chloride	LOD: 0.032-0.098 µg/L LOQ: 0.11-0.32 µg/L	-	UHPLC (column: Zorbax Eclipse XDB – C18 column)	UV	[89]
<p>AGM: agmatine; AM: amylamine; AQC: 6-aminoquinolyl-N-hydroxy-succinimidyl carbamate; BCEC-Cl: 2-(11H-benzo[a]carbazol-11-yl) ethyl carbonochloridate; BUT: butylamine; CAD: cadaverine; DET: diethylamine; DI-SPME: direct immersion solid phase microextraction; DLLME: dispersive liquide liquide microextraction; DMET: dimethylamine; DOP: dopamine; EAC: ethyl-acridine-sulfonyl chloride; ET: Ethylamine; ETH: ethanolamine; FLD: fluorescence detection; HEP: heptylamine; HEX: 1,6-hexamethylenediamine; HIS: histamine; HPLC: high-performance liquid chromatography; HS-SPME: head space solid phase microextraction; IAM: Isoamylamine; IBCF: isobutyl chloroformate; IBUT: isobutylamine; IPENT: isopentylamine; IPROP: isopropylamine; ISM: Isoamylamine; LLE: liquid-liquid extraction; 2-MBUT: 2-Methylbutylamine; MET: Methylamine; 3-METBUT: 3-methylbutylamine; MOR: morfoline; OCT: octopamine; 2-PE: 2-phenylethylamine; PIP: piperidine; PROP: propylamine; PUT: putrescine; PVPP: Polyvinylpyrrolidone; PYR: pyrrolidine; SER, serotonin; SPR: spermine; SPRE: spermidine; TRYP: Tryptamine ;TYR: tyramine; UA-DLLME: ultrasound-assisted dispersive liquid–liquid microextraction; UA-LLE: ultrasound-assisted liquid–liquid microextraction; ULPC: ultra-performance liquid chromatography; UV: ultraiolet</p>								

Table 2. Information on analytical methodologies based on electrophoresis techniques developed for BAs determination in food samples.

Matrice	Analyte	Electrophoretic method	Sample preparation	Derivatization	Conditions	LOD/LOQ	Recovery	Detection	Ref.
Meat	TMA, PUT, CAD, SPR, TRYP, SPRE, 2-PE, TYR	Capillary zone electrophoresis	Homogenization, SPE	YES: dansyl chloride	Running buffer: 6 mM copper sulphate + 6 mM 18-crown-6-ether + 4 mM formic acid – pH 2.7 – in water	LOD: 0.2-0.6 µg/ml LOQ: 0.7-1.9 µg/m	-	Photometric detection	[74]
Beer	ETH, TRYP, TRPH	Microchip capillary electrophoresis	Degassed, Phosphate buffer	NO	Glass microchannel chips, model MC-BF4-001. Running buffer: 20 mM phosphate (pH 2.5) and a high voltage of 2.5 kV	LOD: 1.4 -6.8 mg/L	-	Electrochemical detection	[94]
	HIS, TYR, PUT, CAD, SPR, SPRE, TRYP, 2-PE	Capillary electrophoresis	Degassed, filtration, addition of PVP	NO	PVA-coated silica capillary 700 mm, 50 µm. Background electrolyte: 0.5 M acetic acid (pH 2.5)	LOD: 1-2 µg/L LOQ: 3-8 µg/L	83-110 %	MS/MS	[95]
		Capillary isotachopheresis	Degassed	NO	PTFE analytical capillary 160 mm, 300 µm. Leading electrolyte: 5 mM Ba(OH) ₂ +15 mM valine + 1% hydroxyethylcellulose (pH 8.5). Terminating electrolyte: 0.02 M TRIS + 0.1 M HCl (pH 8.3).	LOD: 0.2-0.48 mg/L	90-101 %	Conductometric detector	[96]
Sousage	TMA, PUT, CAD, SPR, TRYP, SPRE, 2-PE, TYR	Capillary zone electrophoresis	Homogenization, SPE	YES: dansyl chloride	Running buffer: 6 mM copper sulphate + 6 mM 18-crown-6-ether + 4 mM formic acid – pH 2.7 – in water	LOD: 0.2-0.6 µg/ml LOQ: 0.7-1.9 µg/m	-	Photometric detection	[74]
Wine	HIS, TYR, PUT, CAD, SPR, SPRE,	Capillary electrophoresis	Filtration, addition of PVP	NO	PVA-coated silica capillary 700 mm, 50 µm.	LOD: 1-2 µg/L LOQ: 3-8 µg/L	90-113 %	MS/MS	[95]

	TRYP, 2-PE				Background electrolyte: 0.5 M acetic acid (pH 2.5)				
	Capillary isotachopheresis	Filtration	NO	PTFE analytical capillary 160 mm, 300 µm; Leading electrolyte: 5 mM Ba(OH) ₂ +15 mM valine + 1% hydroxyethylcellulose (pH 8.5). Terminating electrolyte: 0.02 M TRIS + 0.1 M HCl (pH 8.3).	LOD: 0.2-0.48 mg/L	90-101 %	Conductometric detector	[96]	
	HIS, TYR, PUT, CAD, SPRE, TRYP, 2-PE	MECK	Filtration	YES: FITC	Silica capillary 580 mm, 50 µm. Running buffer: Brij 35, borate buffer (pH 9.6)	LOD: 0.06 - 0.11 µg/L	93-104 %	LIF	[97]
	HIS, TRYP, TYR, 2-PE	MECK	Direct analysis	NO	Fused silica capillary 645 mm, 50 µm. Electrophoresis buffer of 20 mM borate (pH 9.3) containing 30 mM SDS and 5% (v/v) methanol	-	-	UV	[98]
	2-PE, SPR, SPRE, CAD, PUT	MECK	Homogenization (6% trichloroacetic acid), filtration, dilution with water	YES: FBQCA	Running buffer: 25 mM pH 9.5 boric acid, 25 mM SDS, and 27% ACN. U: 22.5 kV	LOD: 0.4 – 12 nM	-	LIF	[99]
Fish	2-PE, SPR, SPRE, CAD, PUT	MECK	Homogenization (6% trichloroacetic acid), filtration, dilution with water	YES: FBQCA	Running buffer: 25 mM pH 9.5 boric acid, 25 mM SDS, and 27% ACN. U: 22.5 kV	LOD: 0.4 – 12 nM	-	LIF	[99]
	TMA, PUT, CAD, SPR, TRYP, SPRE, 2-PE, TYR	Capillary zone electrophoresis	Homogenization, SPE	YES: dansyl chloride	Running buffer: 6 mM copper sulphate + 6 mM 18-crown-6-ether + 4 mM formic acid – pH 2.7 – in water	LOD: 0.2-0.6 µg/ml LOQ: 0.7-1.9 µg/m	-	Photometric detection	[74]

Soy sauce	2-PE, SPR, SPRE, CAD, PUT	MECK	Homogenization (6% trichloroacetic acid), filtration, dilution with water	YES: FBQCA	Running buffer: 25 mM pH 9.5 boric acid, 25 mM SDS, and 27% ACN. U: 22.5 kV	LOD: 0.4 – 12 nM	-	LIF	[99]
Oysters	HIS, TYR, 2-PE, PUT, SPR	Capillary electrophoresis	Homogenization (6% perchloric acid)	NO	Phosphate buffer at pH 7.00 in the detection cell, 5 mmol/L Ru(bpy) ₃ ²⁺ and 50 mmol/L phosphate buffer at pH 7.00 as the separation buffer	LOD: 6.0x10 ⁻⁴ - 9.6 x 10 ⁻² µg/mL	92.5–104.2%.	electrochemiluminescence	[100]

AGM: agmatine; AM: amylamine; BUT: butylamine; CAD: cadaverine; DET: diethylamine; DI-SPME: direct immersion solid phase microextraction; DLLME: dispersive liquid-liquid microextraction; DMET: dimethylamine; DOP: dopamine; EAC: ethyl-acridine-sulfonyl chloride; ET: Ethylamine; ETH: ethanolamine; FBQCA: 3-(4-fluorobenzoyl)-2-quinolinecarboxaldehyde; FLD: fluorescence detection; FITC: Fluorescein isothiocyanate isomer; HEP: heptylamine; HEX: 1,6-hexamethylenediamine; HIS: histamine; HPLC: high-performance liquid chromatography; HS-SPME: head space solid phase microextraction; IAM: Isoamylamine; IBCF: isobutyl chloroformate; IBUT: isobutylamine; IPENT: isopentylamine; IPROP: isopropylamine; ISM: Isoamylamine; LIF: Laser-induced fluorescence detector; LLE: liquid-liquid extraction; 2-MBUT: 2-Methylbutylamine; MECK: micellar electrokinetic capillary chromatography; MET: Methylamine; 3-METBUT: 3-methylbutylamine; MOR: morfoline; OCT: octopamine; 2-PE: 2-phenylethylamine; PIP: piperidine; PROP: propylamine; PUT: putrescine; PVPP: Polyvinylpyrrolidone; PYR: pyrrolidine; SER, serotonin; SPR: spermine; SPRE: spermidine; TMA: trimethylamine; TRYP: Tryptamine ; TRPH, tryptohane TYR: tyramine; UA-DLLME: ultrasound-assisted dispersive liquid-liquid microextraction; UA-LLE: ultrasound-assisted liquid-liquid microextraction; ULPC: ultra-performance liquid chromatography; UV: ultrafiolet

6.5. Green Assessment of selected analytical procedures applied for determination of BAs in wine and fish samples

Green Analytical Chemistry (GAC) is an ideology concerned with the development of analytical procedures that minimize consumption of hazardous reagents and solvents as well as maximize safety for operators and the environment. Recently, there have been significant developments in methodological and technological tools to prevent and reduce the deleterious effects of analytical activities. And although, there are numerous examples of analytical procedures reported in the literature that are claimed to be green by their authors, these statements are not supported by any evidence, in the form of applied greenness metrics, and comparisons with previously developed analytical or standard procedures. Therefore, calculations that give an answer for question whether an analytical procedure can be regarded green, should be performed utilizing the tools that serve such assessment.

In this section several analytical procedures used for biogenic amines determination in wine [24, 87, 86, 98] and fish samples [75, 85, 91, 99] by application of different type of methods (GC, LC and CE), that are mentioned in this paper are assessed in respect to the green character. To evaluate these selected protocols, Analytical Eco-Scale was used.

Considering the penalty points (PPs) calculated for each procedure used for wine analysis (Table 3), it can be concluded, that Procedure 4 (CE-DAD) can be assigned as green (Score: 85). However, this is not quantitative analysis. Also Procedure 3 gives satisfied results (Score: 73). The worst procedure in term of “green” profile is Procedure 1 which apply DLLME extraction type coupled with derivatization process (Score: 62), and although Procedure 2 (Score: 69) is based on the same techniques, it consume much less reagents.

Considering the PPs calculated for each procedure used for fish analysis, it can be stated that Procedure 8 (CE-LIF) can be assigned as green (Score: 77). Procedures: 6 and 7 are similar taking into account its “green” character, while Procedure 5 (Score: 48) is far from being green.

Without a doubt, this Analytical Eco-Scale is a good semi-quantitative tool for laboratory practice and educational purposes. It is simple and fast to use, has well-defined criteria of evaluation and can be applied to any known and new methodologies.

Table 3. Calculated PPs for evaluated analytical procedures for biogenic amines determination in wine (Procedures 1-4) and fish samples (Procedures 5-8)

Wine analysis: PROCEDURE 1 [87]		Wine analysis: PROCEDURE 2 [24]		Wine analysis: PROCEDURE 3 [86]		Wine analysis: PROCEDURE 4 [98]	
Reagents	PPs	Reagents	PPs	Reagents	PPs	Reagents	PPs
NaOH	1	Pyridine	1	Water	0	Methanol	6
Phosphate buffer 0.5 M	0	Internal standard	4	Formic acid (0.1 %)	2	Internal standard	4
Internal standard	4	HCl	3	Acetonitrile	8	Borate buffer (20 mM)	0
HCl	4	Chloroform	2	Borate buffer (0.5 M)	0	Sodium dodecyl sulfate	0
Sodium azide	1	Isobutyl chloroformate	8	Tosyl chloride	8		
Toluene	6	MeOH	6				
Isobutyl chloroformate	8						
MeOH	6						
	Σ 30		Σ 24		Σ 18		Σ 10
Instruments	PPs	Instruments	PPs	Instruments	PPs	Instruments	PPs
Transport	1	Transport	1	Transport	1	Transport	1
GC-MS	2	GC-MS	2	HPLC-MS/MS	4	CE-DAD	2
Occupational hazard	0	Occupational hazard	0	Occupational hazard	2	Waste	2
Centrifugation	1	Waste	1	Waste	2		
Temperature storage	1						
Waste	3						
	Σ 8		Σ 4		Σ 9		Σ 5
Total PPs: 38		Total PPs: 31		Total PPs: 27		Total PPs: 15	
Score: 62		Score: 69		Score: 73		Score: 85	
Fish analysis: PROCEDURE 5 [85]		Fish analysis: PROCEDURE 6 [91]		Fish analysis: PROCEDURE 7 [75]		Fish analysis: PROCEDURE 8 [99]	
Reagents	PPs	Reagents	PPs	Reagents	PPs	Reagents	PPs
Methanol	8	HCl (0.1M)	3	n-hexane	8	HCl	3
Internal standard	4	NaHCO ₃	0	Internal standard	4	Water	0
Borate buffer	0	NaOH (2 M)	1	Isobutyl chloroformate	8	NaOH (1M)	1
Acetonitrile	8	Dansyl chloride	8	Trichloroacetic acid (5 %)	2	Sodium dodecyl sulfate	0
Acetone	4	Acetone	4	Iso-octane	4	Boric acid	1
HCl	3	Water	0	NaCl (25 %)	0	Acetonitrile	4
Trichloroacetic acid	2	Acetonitrile	8			FBQCA	4
Hexane	8	Glutamic acid	4			Methanol	4
NaOH (1M)	1					Trichloroacetic acid	2
Potassium cyanide	2						
	Σ 40		Σ 28		Σ 26		Σ 19

Instruments	PPs	Instruments	PPs	Instruments	PPs	Instruments	PPs
Transport	1	Transport	1	Transport	1	CE-LIF	2
HPLC-FLD	2	HPLC-UV-VIS	2	GC-MS	2	Homogenization	1
Occupational hazard	1	Occupational hazard	1	Occupational hazard	0	Occupational hazard	0
Centrifugation	1	Centrifugation	1	Centrifugation	1	Waste	1
Temperature storage	1	Temperature storage	1	Temperature storage	1		
Sonification	1	Waste	3	Homogenization	1		
Waste	5			Waste	3		
	Σ 12		Σ 9		Σ 9		Σ 4
Total PPs: 52		Total PPs: 37		Total PPs: 35		Total PPs: 23	
Score: 48		Score: 63		Score: 65		Score: 77	

7. Conclusions

To protect the health of consumers, there is a requirement for more stringent regulations and more diligent monitoring of foods by regulators, vendors and producers. New green analytical extraction procedures are needed for monitoring of BAs in the food matrices and should be fast, inexpensive and easily adopted within analytical laboratories worldwide.

Considering the quality control as well as research requirements, a more precise identification of analytes is needed, hence the requirement for sensitive methods to detect slight changes in BAs profile.

The quantitation of BAs can be highly problematic due to several factors. Biogenic amines are small, polar compounds and these issues can make the separation challenging when using reverse phase chromatography. Thus, the assortment of chromatographic column is very important as some specific reverse phase columns can separate selected classes of BAs, and moreover, can add additional cost to whole analysis because are more expensive. Due to the fact that biogenic amines have highly similar structures to the compounds in the same subgroup as well similar chemical and physical properties to other compounds presented in food samples. This brings problem in providing effective separation by isocratic chromatography which is required for certain quantitative methods and is problematic when quantitating a number of different BAs simultaneously.

Additional problem in quantitation of biogenic amines is that they occur at very low concentration level (sub-ng/mL range), what means that a highly sensitive method is needed to accurately quantitate the analytes. This issue is even more problematic when working with low volume of the samples which means the absolute quantities of BAs in the total sample are low. Moreover, the method usually require time consuming and expensive sample preparation before analysis in order to achieve the high level of sensitivity required to quantitate the low concentration in food samples.

The food matrix in which BAs are commonly examined is often complex. Even aqueous matrixes such as wine, beer, dairy fermented products are problematic because usually contain interfering compounds such as polyphenols, lipids, proteins (depending on the sample). Hence, the sample preparation and extraction of these compounds is time consuming. It also means that these compounds need efficient separation and retention away from interfering compounds which can cause further problems with detection. Moreover, many of BAs do not strong absorbance when using UV detection, thus, derivatization step is required when using gas chromatography as a means of separation.

Due to increased sensitivity and the specific structural information that MS or MS/MS detectors can provide, they are the most adequate detection technique for low concentrations of metabolites. However, matrix effects remains one of the main problematic issues when quantifying BAs in food samples which are composed of complex matrices. Therefore, the sample preparation step has been commonly used to minimize these matrix interferences. Isotopically labeled internal standards are also used to minimize the matrix effect, allowing the quantification of ultratrace quantities.

Reducing the time of analysis, being able to use a lower concentration of derivatizing agent and increasing sensitivity are the current challenges facing the BA research community. Thus, in the context of future regulations of BA in fermented products, fast and robust methods of analysis will be required.

Following previous considerations it should be helpful to actively promote the production of functional beverages and foods, having a modified balance between amines and polyphenols, using different agricultural management practices and processing methods.

In order to assess human exposure and the risk associated with biogenic amines, there is a strong need to carry out comprehensive food surveys and related studies, such as gastrointestinal uptake studies, which are urgently required for a better understanding of the contribution of food pathway to consumer exposure to BAs.

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