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Review

An Overview on Biogenic Amines in Wine

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Abstract: Biogenic amines (BAs) are low molecular weight compounds formed from precursor amino acids, mainly by microbial decarboxylation. The presence of these compounds is important in the food and beverage industry because, in high amounts, they can lead to negative effects on consumers. In this review, we illustrate the critical aspects needed to control the formation of BAs during winemaking and their presence in the final product. Recent biotechnological approaches related to microorganisms and their ability to reduce BAs are illustrated. The current methods used for BA detection and quantification are also presented. These methods are very important to consider, as BAs can serve as markers for the quality assessment of products. The information presented here offers an overview useful for identifying specific parameters and conditions which should be controlled to minimise BA content in wine; knowledge about BAs in foods and beverages has been accumulating in recent years, not only to ensure and improve quality (since BAs have been used as an indicator of spoilage) but especially to guarantee consumer safety due to the potential toxic effects of BAs on humans.

Keywords: biogenic amines; wine; detection; control; microorganisms

1. Introduction

Biogenic amines (BAs) are commonly found in many foods: high concentrations have been reported in fish, chocolate, cheese, soybean products, sausages and processed meat [1–6], as well as in fermented foods and beverages.

Several investigations have reported the presence of BAs in wine, the most important of which are histamine, tyramine and putrescine. BAs can be present in all types of wines. In white wines, the BA content is smaller than in red wines, i.e., 0–10 mg/L for white wines and 0–30 mg/L for red wines [7].

The literature has reported that different countries have established upper limits of histamine in wine: 2 mg/L in Germany, 5mg/L in Finland, 10 mg/L in Australia and Switzerland, 8 mg/L in France, 3.5 mg/L in Netherlands and 6 mg/L in Belgium [8]. However, to our knowledge, no legal limits for BA content in wine have been established.

A person's sensitivity to BAs depends on his or her capacity for detoxification [9], which is also affected by the presence of ethanol in beverages and/or the assumption of determined medicines. It is difficult to establish maximum limits for these compounds in foodstuffs, because complex interactions occur between BAs and other substances.

Regarding the dose–response relationship, the European Food Safety Authority (EFSA) reported [10] that in healthy volunteers, no symptoms occurred after consuming 25–50 mg of histamine assumed from fishery products or non-alcoholic beverages; however, headache and flushing occurred after consuming 75–300 mg of histamine.

In a study of wine-intolerant subjects, Kanny et al. [11] did not find a relationship between the amine content of tested wines and the frequency and severity of symptoms caused by these wines. This finding suggests that wine intolerance and the generation of adverse reactions to wines may be due to the participation of a substance other than histamine or BAs.

Histamine has been detected in wines from different countries for example, in Portugal, 23.1 mg/L [12]; in Italy, 10.8 mg/L [13]; and in France, 14.05 mg/L [14]. Comuzzo et al. [15] also found 11.1 mg/L, 14.8 mg/L and 12.1 mg/L of histamine in Spanish, German and Austrian wines, respectively. Also, putrescine was found in wines at different concentrations in three surveys in Italy (31.8, 11.13 and 16.2 mg/L) [13,15,16] and in one survey in France (48.72 mg/L) [14].

Glória et al. [17] observed that in Cabernet Sauvignon wines from Oregon, USA, putrescine was the prevalent amine (63.5%), followed by histamine (16.8%) and spermidine (9.8%). The prevalence of these amines was also observed in Rioja wines [18] and red wines from Tarragona [19]. Bach et al. [14] reported concentrations of ethylamine and methylamine up to 10.46 mg/L and 36.64 mg/L, respectively, in French wines.

BA amounts depend on several factors. On the one hand, winemaking conditions, vinification techniques, ageing, agricultural practices and climatic conditions can affect BA amounts [20]; on the other, BA amounts are also affected by the species of microorganisms responsible for their production in wine with decarboxylase enzymes, the abundance of amino acid precursors in the medium and wine parameters, such as pH, alcohol and sulphur dioxide, that influence bacterial growth [8,21].

The presence of these compounds represents a critical aspect in oenology; recently, BA content has been considered as an important indicator of the quality and safety of wine [13]. In addition, some authors have reported regional differences in the quantities of BAs in wine [22].

The aim of this review is to summarise the state of the art regarding the main aspects involved in the presence of BAs in wine. A good knowledge of these aspects would be helpful for actively promoting the production of wine without BAs by correctly managing practices and processing methods.

2. Biogenic Amines and Microorganisms

In the winemaking process, both yeasts and bacteria may participate in amine production. There is general agreement that yeasts make a less significant contribution than lactic acid bacteria (LAB) to the final BA content in wine, a finding which has been supported by the greater quantity of data regarding the biochemistry, genetics and regulation of amine production by LAB compared with the data available for yeasts.

Few studies have been conducted on the formation of BAs by yeasts, and most of them only compared different yeast species and only quantified histamine [23].

According to Caruso et al. [24], *Saccharomyces cerevisiae* can produce significant amounts of ethanolamine and agmatine; these authors also tested non-*Saccharomyces* yeasts: *Kloeckera apiculata*, *Candida stellata*, *Metschnikowia pulcherrima*, *Brettanomyces bruxellensis* and the fungus *Botrytis cinerea*. They found that the highest concentration of total BAs was formed by *B. bruxellensis*, with an average value of 15 mg/L, followed by *S. cerevisiae*, with an average value of 12.14 mg/L. The other species formed less than 10 mg/L of total BAs. Two amines seemed to be species-specific, phenylethylamine and ethanolamine, and were produced in more considerable amounts by *B. bruxellensis* and *S. cerevisiae*, respectively. The same results were confirmed by Granchi et al. [25].

Torrea and Ancín-Azpilicueta [26] found slight BA production by *S. cerevisiae* depending on the strain, but the concentrations were very low. Tristezza et al. [27] demonstrated the ability of yeast species of oenological provenience to produce histamine during grape must fermentation. In particular, they found an isolate of *Issatchenkia terricola*, one strain of *M. pulcherrima* and two isolates of *Pichia manshurica* that were able to synthesise histamine.

Contrary to these authors, Landete et al. [28] did not find BA production in any of the 36 strains of different wine yeast genera screened: *Aureobasidum, Candida, Hanseniaspora, Hansenula, Kloeckera, Metschnikowia, Pichia* or strains of the species *S. cerevisiae.*

Marcobal et al. [29] demonstrated that some amines can be produced in grape or in grape must as putrescine, cadaverine or phenylethylamine, or they can be formed by yeasts during alcoholic fermentation (AF), as ethylamine and phenylethylamine, although only very low concentrations were reached during these early stages.

These results lead, therefore, to the conclusion that yeasts do not appear to be the main cause of most of the amines found in wines.

Usually, BA production results from the presence of bacteria that are capable of decarboxylating amino acids [30,31] (Figure 1); in particular, histamine is formed from histidine by histidine decarboxylase (*hdc*); ornithine decarboxylase (*odc*) catalyses the decarboxylation of ornithine to putrescine; and tyrosine is the precursor of tyramine produced by tyrosine decarboxylase (*tdc*).

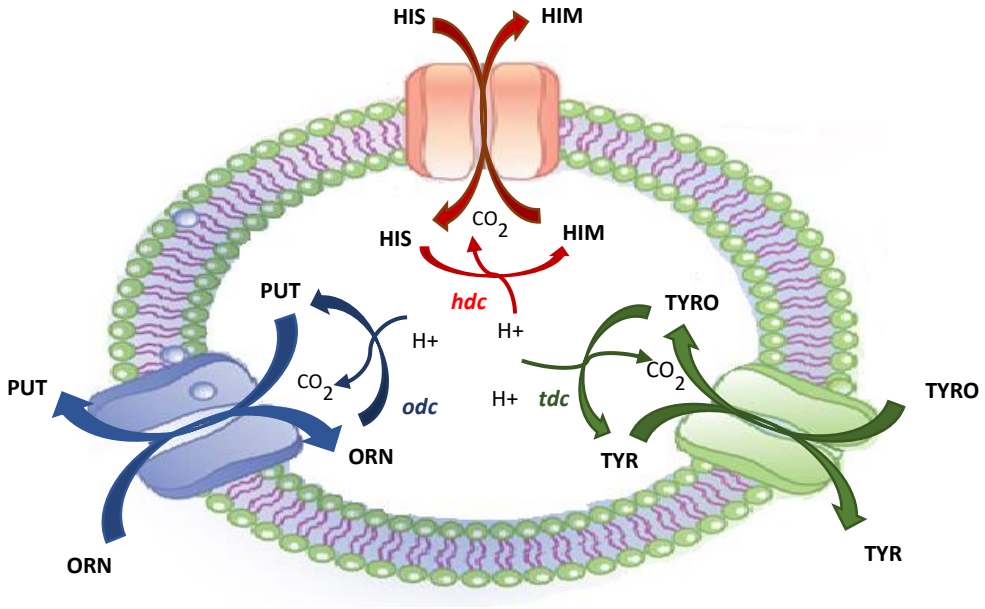

Figure 1. Biogenic amine formation from their precursor amino acids and their intake/uptake by the transmembrane antiporter.

Decarboxylase genes are contained in cassettes constituted by four genes, one of which encodes for a transmembrane amino acid/amine antiporter; this has been demonstrated for the tyrosine/tyramine antiporter by Lucas et al. [32] in *Lactobacillus brevis*; for the ornithine/putrescine antiporter by Romano et al. [33] in *L. brevis*; and for the histidine/histamine antiporter in *Lactobacillus buchneri* by Molenaar et al. [34] and Cruz Martin et al. [35].

This operon has particular importance since it generates a proton motive force and regulates cellular pH, thereby contributing to energy production; therefore, the production of BAs can be considered a defence mechanism used by bacteria to better survive in an acidic medium [36].

Amino acid decarboxylase activity depends on several factors: pH, temperature, sugars and amino acid precursors. Pessione et al. [37] reported that in LAB, pH can regulate decarboxylase enzymes by catalytic activation and biosynthetic overexpression. In a different work, it was demonstrated that decarboxylase biosynthesis is maximal during the stationary phase when the pH is low due to lactic acid accumulation [38]; this aspect is consistent with the hypothesis that BAs constitute a protective mechanism against a low pH. For histidine decarboxylase (HDC), the optimum pH is 4.8 [39]; for tyrosine decarboxylase (TDC), the optimum pH is 5.0 [40]; while for ornithine decarboxylase, (ODC), the optimum pH is 5.8 [41].

Temperature is also an important factor. Moderate temperatures increase enzyme activity, as shown by Marcobal et al. [42], who found that in *Enterococcus faecium* and *L. brevis*, the optimum temperature for tyramine production under aerobic conditions was 32 °C; whereas under anaerobic conditions, the maximum tyramine production was obtained at 22.0–24.5 °C.

The sugar concentration of the medium can influence decarboxylase activity; in particular, the lack of sugars has often been associated with higher BA production. This association can be explained by the fact that the decarboxylative pathway transport system provides metabolic energy [43]. Landete et al. [44] observed that in the oenological LAB (*Lactobacillus hilgardii, Pediococcus parvulus* and *Oenococcus oeni*), an increasing concentration of fructose and glucose progressively inhibited histamine formation; moreover, *hdc* gene expression was also reduced by malic acid and citric acid, whereas ethanol enhanced HDC enzyme activity.

Finally, HDC and ODC biosynthesis were shown to be closely dependent on the presence of high concentrations of free amino acids in the growth medium [38].

Among LAB, *O. oeni* is the main species present in wine and is the best adapted one for carrying out malolactic fermentation (MLF) to the stressful conditions of wine [45]. If BA formation is associated with MLF, then *O. oeni* would be expected to be mainly responsible.

Some authors have found that *O. oeni* significantly contributes to the overall content of histamine in wines, but that the ability of the species to produce this amine varies among strains [46,47]. Contrarily, Costantini et al. [48] and Moreno Arribas et al. [30] did not find *O. oeni* to be capable of producing histamine, a finding also confirmed by Garcia-Moruno and Munoz [49].

Marcobal et al. [50] isolated and identified a strain of *O. oeni* that produces putrescine, and they further studied this ability in another 42 strains of this species by molecular methods (*odc* gene detection). Additionally, they found that the *odc* gene was not present in any of the strains.

Regarding *Lactobacillus*, different strains have been found to be capable of producing BAs: *Lactobacillus hilgardii*, *Lactobacillus buchneri*, *Lactobacillus rossiae*, *Lactobacillus sakei* and *Lactobacillus mali* have all been found capable of producing histamine [48,51–53]

Tyramine-producing LAB in wine that has undergone MLF were identified and isolated by Moreno-Arribas et al. [54], all of which belong to the *Lactobacillus* genera; in particular, they found *L. brevis* and one strain of *L. hilgardii*. Costantini et al. [48] also found that *L. brevis* was able to produce tyramine. This finding was confirmed by Sebastian et al. [55], who tested 57 strains of *L. brevis* and observed the formation of BAs in all of them. Lastly, the ability of wine *Lactobacillus plantarum* strains to form tyramine was analysed by Arena et al. [56]. They found one *L. plantarum* strain harbouring the *tdc* gene, but tyramine production was occasional because tyrosine decarboxylase activity was negatively affected by sugars, such as glucose and fructose, and by L-malic acid. As the literature suggests, only one strain (*O. oeni* DSM 2025) was shown capable of producing tyramine in a defined growth medium [57].

Regarding the *odc* gene, it was detected only in *O. oeni* RM83 by Marcobal et al. [50].

From this description, we could conclude that the ability to produce BAs is mostly distributed among species that usually do not perform MLF, which is mainly carried out by *O. oeni*. These species are contaminants that can spoil wine and are therefore indicative of poor winemaking and bad sanitisation practices.

3. Biogenic Amines and the Type of Grape/Wine and Winemaking Stages

Cultivar-related differences in BA content have been observed in many studies of wines worldwide—for instance, in Italian, Spanish, Greek, Chinese and Chilean grapes and wines—and are summarised in Table 1.

Table 1. Biogenic amines found in different grape and wine.

Wine	Type of Wine	Biogenic Amine	Reference
Cabernet Franc	red	Eth,Ety, Put, Agm	[58]
Carmenere	red	Eth,Ety, Put, Agm	
Cesanese d'Affile	red	Eth,Ety, Put, Agm	
Merlot	red	Eth,Ety, Put, Agm	
Montepulciano	red	Eth,Ety, Put, Agm	
Sangiovese	red	Eth,Ety, Put, Agm	
Syrah	red	Eth,Ety, Put, Agm	
Aglianico (13)	red	Met, Eth, Agm, Pea, Put, Cad, Him, Spd, Tym	[22]
Primitivo di Manduria (15)	red	Eth, Agm, Pea, Put, Cad, Him, Spd, Tym	
Syrah (15)	red	Met, Eth, Agm, Pea, Put, Cad, Him, Spd, Tym	
Etna Rosso (13)	red	Met, Eth, Agm, Pea, Put, Cad, Him, Spd, Tym	
Chinese red wines from Shandong	red	Phe, Put, Cad, Him, Tyr, Spd and Spm	[59]
Chinese red wines from Beijing	red	Phe, Put, Cad, Him, Tyr, Spd and Spm	
Chinese red wines from Tianjin	red	Phe, Put, Cad, Him, Tyr, Spd and Spm	
Chinese red wines from Hebei	red	Phe, Put, Cad, Him, Tyr, Spd and Spm	
Chinese red wines from Xinjiang	red	Phe, Put, Cad, Him, Tyr	
Tempranillo from La Rioja,	red	Him, Tyr, Put, Phe	[60]
Tempranillo from Utiel-Requena	red	Him, Tyr, Put, Phe	
Tempranillo from Tarragona	red	Him, Tyr, Put, Phe	
Bobal	red	Him, Tyr, Put, Phe	
Garnacha	red	Him, Tyr, Put, Phe	
Xinomavro	red		[61] Note: amines >1 mg/L are indicated
Roditis	white	Phe	
Agiorgitiko	red	Phe, Put	
Cabernet Sauvignon	red		
Mantilaria	red	Ism, Him, Tym, Spd, Put	
Syrah	red	Put	
Merlot	red	Ism	
Debina	white	Cad	
Moshofilero	white	Put	
Malagouzia	white		
Asyrtiko	red	Put, Cad	
Grenache rouge	red	Put	
Chardonnay	white		
Muscat white	white	Ism, Put	
Muscat Hamburg	red		
Muscat d'Alexandrie	white	Put, Cad, Him	
Limnio	red	Cad	
Chilean young wines: Cabernet Sauvignon (9)	red	Put, Him, Tyr, Spd	[62]
Merlot (8)	red		
Carménère (10)	red		

The sanitary state of the grape also influences the amount of BAs, as demonstrated by Cecchini et al. [63] and in agreement with Leitao et al. [64], who associated putrescine and cadaverine in musts with poor sanitary conditions of grapes.

Moreover, during winemaking, AF and MLF may influence BA accumulation.

Del Prete et al. [58] conducted a study on different grape varieties—Merlot, Syrah, Sangiovese, Cesanese d'Affile, Carmenere, Montepulciano and Cabernet Franc—and monitored BA content during the different stages of vinification. The cultivars were grown in the same pedoclimatic conditions and with the same training system in order to reduce variability. In Table 2, the results obtained from analysing BAs in different winemaking phases are shown. Ethanolamine, ethylamine and putrescine were present in the grapes, while tyramine, cadaverine and agmatine were not found. These findings are in agreement with those of other authors: Ough et al. [65] found ethanolamine and ethylamine in grapes, while Broquedis et al. [66] detected putrescine in Cabernet Sauvignon and Ugni blanc.

Table 2. Individual biogenic amines during winemaking (from Del Prete et al. [58]).

Biogenic Amines (mg/L)	Must	Must 72h	Wine/AF	Wine/MLF
Ethanolamine	7.91 ^{a}	8.73 ^{a}	11.54 ^{b}	11.65 ^{b}
Agmatime	nd ^{a}	nd ^{a}	0.51 ^{a}	6.4 ^{b}
Ethylamine	9.83 ^{b}	10.07 ^{b}	1.87 ^{a}	1.96 ^{a}
Tyramine	nd ^{a}	nd ^{a}	0.36 ^{b}	0.069 ^{a}
Putrescine	11.23 ^{d}	3.76 ^{c}	1.76 ^{a}	2.26 ^{ab}

Mean concentration of individual BA in all cultivars in years 2004–2005; Mean values with the same superscript letters in the same line, do not significantly differ ($p < 0.05$, LSD, *Least Significant Difference*, test); Letters $^{a, b}$ indicates the statistically significant differences; AF: Alcoholic fermentation; MLF: Malolactic fermentation; nd: not detected.

During AF [58], ethanolamine and tyramine content increased, while the quantity of ethylamine and putrescine decreased. During MLF, agmatine increased, while tyramine decreased to nearly zero. The authors [58] explained that these differences were due to the normal metabolic processes of yeast and bacteria: ethanolamine is an intermediate in phospholipid synthesis that is released in wine by *S. cerevisiae*; agmatine and tyramine may likely be formed as a consequence of the hydrolysis of hydroxycinnamic amide compounds in grapes by the action of yeast and bacteria.

Generally, MLF is considered one of the most crucial factors for BA production: several authors have presented evidence that, in winemaking, BAs are mainly formed during the MLF phase [29,60,67,68].

Landete et al. [60] reported that MLF was the main source of tyramine, histamine and putrescine for red wines, while cadaverine and tryptamine concentrations were not affected. Conversely, Bauza et al. [69] observed an increase in putrescine levels during fermentation from must to AF to MLF, in agreement with Soufleros et al. [70].

About this matter, the data available in the literature are contradictory, since Soufleros et al. [70] found a significant correlation between the levels of tyramine and histamine during fermentation processes, while Herbert et al. [68] reported no significant changes in the levels of histamine during either alcoholic or malolactic fermentative processes, yet both putrescine and tyramine increased in red wines immediately after MLF. On the other hand, Del Prete et al. [58] reported that during MLF, tyramine disappeared, whereas the concentration of putrescine remained nearly unchanged; in addition, the level of agmatine increased during MLF.

Garcia-Marino et al. [71] observed that in high-quality wines, the greatest increase in BAs corresponded to AF—no new amines were observed after MLF. In contrast, in organic wines, MLF increased BA levels, particularly histamine, tyramine, tryptamine and phenylethylamine. Ethanolamine and putrescine had a different evolution: They reached their highest levels in both high-quality wines and organic wines; after AF and during MLF, putrescine further increased in organic wines.

During wine ageing and storage, concentrations of BAs have been reported to increase [60,72]. In the case of histamine, a consistent increase was noticed only several months after the end of MLF. Conversely, putrescine and tyramine concentrations increased immediately after MLF had finished [68].

Henriquez-Aedo et al. [73] analysed BAs in five different wineries during Cabernet Sauvignon vinification, as shown in Table 3. They observed that only one winery (B) showed the highest formation of BAs during MLF, whereas the others showed the highest formation during AF and in bottled wines. Therefore, it seems that the critical point for BA formation is bottled wine, which could be related to a lack of sanitation during bottling or to an insufficient SO_2 concentration to microbiologically stabilise the wine.

Table 3. Quantification of biogenic amines (BAs) levels (mg/L) during vinification (from Henriquez-Aedo et al. [73]).

Winery	Sample	Phe	Put	Cad	Him	Tyr	Spd	Spm	Total
A	grapes	nd	nd	nd	nd	nd	tr	tr	tr
	AF	nd	29.2	tr	nd	nd	tr	tr	29.2
	MLF	tr	11	tr	nd	nd	tr	tr	11
	Wine	nd	36.7	tr	nd	nd	1.6	tr	38.3
B	grapes	nd	nd	nd	nd	tr	tr	tr	tr
	AF	nd	4	tr	nd	tr	tr	tr	5
	MLF	tr	9.2	tr	nd	tr	tr	tr	9.2
	Wine	nd	5.5	tr	nd	tr	tr	tr	5.5
C	grapes	tr	1.2	tr	1.9	nd	2.2	2.5	7.8
	AF	nd	9.3	tr	nd	tr	1.3	tr	10.7
	MLF	nd	14.1	tr	nd	nd	tr	tr	14.2
	Wine	10	142.1	tr	8.4	8.1	tr	tr	168.6
D	grapes	nd	8.9	nd	nd	tr	2.9	tr	11.8
	AF	nd	38.6	tr	tr	tr	1.6	tr	40.2
	MLF	nd	11.7	1.3	1.3	tr	2.2	tr	13.9
	Wine	tr	8.5	3.5	3.5	1.5	2.7	tr	16.2
E	grapes	nd	9.8	tr	nd	tr	4.1	1.2	15.1
	AF	nd	14.7	tr	nd	tr	1.1	tr	15.8
	MLF	nd	12.9	tr	nd	tr	1.3	tr	14.2
	Wine	nd	14.3	tr	nd	tr	1.5	tr	15.8

nd: not detected; tr: traces, amount below calibration range; AF: Alcoholic fermentation; MLF: malolactic fermentation.

A similar study was conducted on Portuguese wines by Herbert et al. [68]. They showed that histamine, tyramine, tryptamine, phenylethylamine, putrescine and cadaverine did not vary during AF—particularly histamine, whose levels were close to the values found in the musts (average 1.2 mg/L for red musts). Nevertheless, samples taken about 18 months after the end of MLF in red wines presented higher levels of histamine (11.1 mg/L for red and 12.5 mg/L for white wines) than in the corresponding musts. Therefore, they identified the storage period as the critical stage.

Ordonez et al. [74] studied the effect of storage conditions on the BA profile in open bottles. They did not find significant changes in BA content, which remained similar to the initial concentration. However, after Principal component analysis (PCA), the authors observed that BA content could be useful for separating the different types of wines, particularly high-quality wines from standard wines and young white wines: Sandard wines were placed in the PC quadrant dominated by putrescine, while high-quality wines were placed in the quadrant described by agmatine and phenylethylamine.

These data lead to the conclusion that, in order to reduce BA levels, it is necessary to control every stage of the vinification. By identifying the critical point of BA formation, it is possible to carry out corrective actions to reduce or prevent their presence, developing or modifying some oenological and/or technological practices.

4. Agricultural and Oenological Practices

BA content can also be influenced by agricultural and oenological factors.

Regarding agricultural practices, Smit et al. [75] demonstrated that the use of nitrogen fertilisation can increase BAs in musts and wines. In particular, the total amine content increased significantly in musts; whereas in wines, the fertilisation effect had a lower impact on amine content with respect to the activity of microorganisms.

Other factors which can influence BA content are the degrees of vintage and maturity of grapes as well as irrigation. Martínez-Pinilla et al. [76] showed that in red wines from cv Monastel, Tempranillo and Maturana Tinta de Navarrete, the BA content varied between vintages. They observed that wines of vintage 2009 showed more total BA content than wines of vintage 2010, leading to a change in their amine profile; these results agree with those of other studies [58,77]. The authors explained that differences in amine content may be due to the diversity of wine microorganisms, which are naturally differently selected each year, probably due to climatic conditions.

Ortega-Heras et al. [20] observed that the amino acid content in grapes was affected by climatic conditions and vintages. Amino acid content also depended on the degree of maturity; in fact, in grapes or musts, the content increased from the veraison to the harvest. During ripening, a deceleration of berry growth and reduced protein synthesis occurs, and this may explain the accumulation of free amino acids [78]. The same authors observed that irrigation did not affect the evolution of nitrogen compounds during the AF process, but the degree of maturity in some of the amino acids tested was affected. No direct relationship could be established between irrigation or maturity degree and BAs.

Conflicting results regarding the correlation between grape skin maceration practices and the BA levels in wines have been reported in the literature. Soleas et al. [79] affirmed that skin contact time and BA concentration are not correlated. However, other authors have stated that the duration of skin maceration can affect the BA content in wine: a long skin contact time can potentially increase the production of BAs [80,81]. With regard to the influence of commercial enzymes on BAs, Martín-Álvarez et al. [81] concluded that the addition of pectolytic enzymes to grapes did not promote BA accumulation in their wine.

Pogorzelski [82], Ancín-Azpilicueta et al. [83] and Smit et al. [75] observed that in Cabernet Sauvignon and Syrah, the absence of skin contact resulted in a higher content of BAs; this can be explained by the absence of a phenolic compound, which can affect BA content. Galgano et al. [84] reported that phenolic compounds seem to be a natural mechanism for reducing putrescine formation because they can protect the cell against oxidative stress.

Finally, some studies have focused on the effect of organic or conventional agriculture on the BA content of wines. Tassoni et al. [85] analysed BA content in Lambrusco (red wine) and Albana (white wine), and they compared conventional, organic and biodynamic agricultural and oenological practices. In Figure 2A, the BA levels determined by HPLC are shown. In all the samples, putrescine was the most abundant polyamine, but its content was lower in biodynamic samples than in conventional samples. Cadaverine was totally absent in the Albana samples, while tryptamine was present in both grapes. Spermidine and spermine were higher in the biodynamic samples. In general, the total amount of BAs was on average 4.2-fold higher in Lambrusco than in Albana (Figure 2A). Figure 2B shows the BA levels found in wines. Samples AO and LB contained the highest BA amounts, respectively, for white and red wines. Histamine and tryptamine were the most abundant amines in both white and red wines, with average quantities 1.7- and 1.3-fold higher in red than in white wines. On the contrary, tyramine was on average 2.6-times more abundant in Albana than in Lambrusco wines. In Lambrusco, spermidine was present in organic and biodynamic samples, but it was absent in conventional samples; in Albana, this amine was present in the same amount in all the samples (Figure 2B).

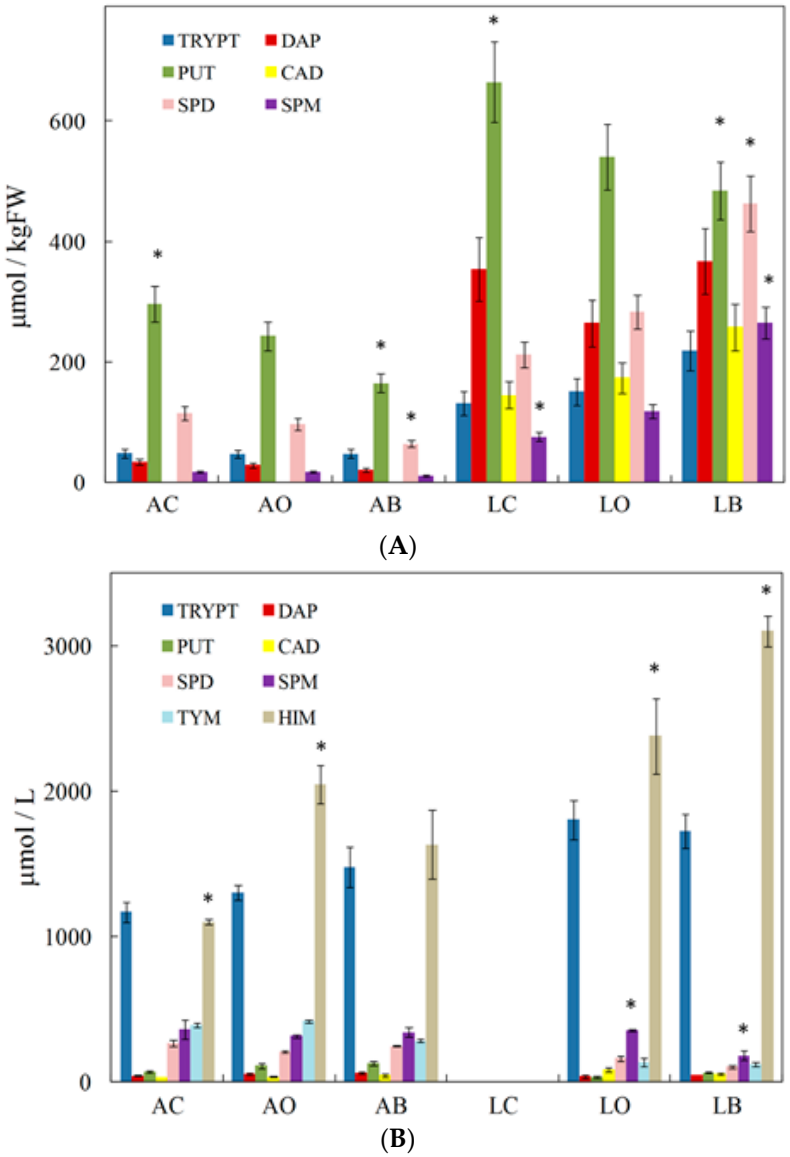

Figure 2. (**A**) Biogenic amine levels (µmol/kg) measured in Albana and Lambrusco berries grown following conventional (AC and LC), organic (AO and LO) and biodynamic (AB and LB) agricultural practices. (**B**) Biogenic amine levels (µmol/L) measured in Albana and Lambrusco wines obtained following conventional (AC), organic (AO and LO) and biodynamic (AB and LB) oenological practices. The star symbol indicates the statistically significant differences (Student's *t*-test, $p < 0.05$) among single compounds of the same group. Data are the mean ± SE ($n = 4$). (from Tassoni et al. [85]).

Tassoni et al. [86] conducted the same study on Pignoletto and Sangiovese wines and observed a major concentration of BAs in Italian Pignoletto white wines compared to Sangiovese red wines; the authors hypothesised that the higher levels of BAs in Pignoletto may be due to the presence of higher levels of amino acids. Their data seem to indicate no significant differences between conventional, organic and biodynamic practices.

5. Detection and Quantification of BAs

5.1. Enzymatic Methods

Enzymatic methods for the quantification of histamine were first developed for fish; subsequently, they have been introduced for wine.

Marcobal et al. [87] applied the ELISA (enzyme-linked immunosorbent assay) method for histamine determination in wines. The proposed method was validated by comparison with HPLC, and a good correlation with HPLC analysis was found. The advantages of using ELISA include its simplicity, rapidity and low cost, and it can therefore be proposed as a tool for histamine determination in wines instead of HPLC.

There is also an enzymatic test used to quantify histamine in foods and beverages. It is based on the reaction of histamine-dehydrogenase, which catalyses the oxidation of histamine to imidacetaldehyde in the presence of an electron carrier and a dye. The formation of the dye is measured at 450 nm by a microplate reader and is proportional to the histamine concentration.

The presence of histamine in samples, including wine, can be accomplished using specific strips; this technology allows the visual detection of histamine in only four minutes. The strips contain an enzyme that reacts specifically with histamine and reduces a dye indicator, producing a colour change for easy visual interpretation of the results. When the strips are dipped into samples containing histamine, the pad rapidly changes from white to a colour designating the histamine concentration present in the food or drink. This technique does not require laboratory equipment and can thus be used anywhere.

5.2. Chromatographic Methods

Basic information on BAs in foods is very important for protecting consumer health and meeting industry standards. Therefore, it is necessary to have sensitive and effective methods for BA quantification. The most popular analytical technique applied to quantify amines is HPLC with C18 reverse-phase (RP) columns. The determination of BAs is a bit difficult due in part to the physicochemical properties of these compounds. Numerous analytical methods have been proposed, and most analyses have been performed with a previous derivatization of amines, although some researchers have also determined amines without derivatization.

Typically, wine samples are analysed either directly or after a simple treatment with polyvinylpolypyrolidone (PVPP) to remove some phenolic compounds [62,88]. BAs do not have enough absorption in the UV-Vis or FLD (fluorescence detector) wavelength ranges. Therefore, a pre-column or post-column derivatization is often needed for their detection. The derivatization step improves separation in the RP columns by decreasing the polarity of the original compounds [62,88–90].

Different derivatization reagents can be used for HPLC analysis; the main goal is to quickly obtain amino derivatives that do not require a high reaction temperature and yield derivatives that remain stable over time. The most commonly used derivatizing reagents are dansyl chloride (DNS-Cl) and o-phthalaldeyde (OPA). The determination of dansylated amines in wines has been the target of several studies [91,92]. Both DAD (diode array detector) and FLD can be used, but FLD has demonstrated better sensitivity for detecting dansylated amines [62,88]. For the quantification of BAs in wine, DNS-Cl has been largely used because it produces stable derivatized compounds. The disadvantage of using this reagent is the time required for the reaction together with the application of a high external temperature: 10 to 60 min at 40 to 70 °C [92]. Jiang et al. [93] improved the dansylation reaction by using ionic liquids as media for the derivatization at room temperature and reducing the time to around 20 min.

OPA is also often employed in HPLC analysis. OPA derivatives are less stable, but the reaction can occur at room temperature in a short amount of time [94,95]. Pereira et al. [90] proposed a pre-column derivatization with OPA without using any preliminary separation or clean-up; derivatization was performed in three minutes into the sample injection loop of the HPLC and allowed the determination of both BAs and amino acids in wine using an FLD detector.

Wang et al. [96] used diethyl ethoxymethylenemalonate (DEEM) as a pre-column derivatization method for the quantification of 10 BAs and 23 amino acids, with RP-HPLC-DAD: DEEM shortened the analysis time to 30 min. This pre-column derivatizing compound enables the quantification of secondary and primary amines, and its derivatives are stable at room temperature for several days

and can be detected by a UV detector. In the official OIV (Organization International de la Vigne et du Vin) method, DEEM is also proposed as a derivatizing reagent.

The labelling agent 1,2-naphthoquinone-4-sulfonate (NQS) has also been described in the literature. Its derivatization is conducted, in general, in a basic medium (pH 8.5–10.5) at temperatures from 50 to 80 °C with reaction times from 2 to 20 min. NQS has been used previously for the pre- and post-column derivatization of amino acids [97–99] in HPLC and in capillary electrophoresis (CE) methods.

Recently, Jastrzebska et al. [100] employed a new derivatization reagent, namely 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (FNBT), for the determination of histamine, tyramine, tryptamine and phenylethylamine in wines using RP-HPLC-DAD analysis. This compound was shown to be simple and less time-consuming when compared to other reagents.

Other than HPLC, other methods can be used to analyse BAs. Thin Layer Chromatography (TLC) is an economical method employed for BA semi-quantification, but it requires time for analysis. Samples must be derivatized with dansyl chloride, and amines must be visualised under a UV lamp. TLC was described by Garcia-Moruno et al. [101] and employed by Costantini et al. [48] and Sebastian et al. [55] to detect histamine, putrescine and tyramine produced by LAB. A TLC method coupled to a densitometer to quantify dansylated BAs was also developed [102], and it can be used for routine analysis of histamine, tyramine, putrescine and cadaverine in wine.

5.3. Capillary Electrophoresis

Capillary electrophoresis (CE) is an alternative separation technique for the analysis of BAs that offers some advantages: It is simple, has a high resolving power, and allows for the screening of a large number of samples with a small sample requirement [103]. However, its LOD (limit of detection) is higher when compared with HPLC and ion chromatography, mainly because of lower amounts of the injected sample and a shorter optical path length. Ginterova et al. [104] reported that the reproducibility of CE is usually not as high as that of HPLC. For this reason, its suitability depends on the expected level of BAs in the samples. However, Daniel et al. [105] reached an LOD of 1–2 μg/L, and Uzasci et al. [106] used non-ionic micellar electrokinetic chromatography (a specific type of CE) to obtain an LOD of 0.06–0.11 μg/L.

5.4. Biosensors

In recent years, the development of biosensors has attracted much interest in the scientific community, because these low-cost devices can give results in a few minutes without the need for any kind of sample pre-treatment and with the option to be used outside the laboratory [107]. Biosensors for BAs comprise various combinations of different enzymes for selective biorecognition and signal transduction systems and are based on different signal mechanisms. Several works have focused on the development and application of biosensors. In 2010, Alonso-Lomillo et al. [108] reported, for the first time, monoamine oxidase (MAO)/horseradish peroxidase (HRP) and diamine oxidase (DAO)/horseradish peroxidase (HRP)-based biosensors using screen-printed carbon electrodes for the determination of BAs, which were successfully applied for the quantification of BAs in fish. A DAO-based biosensor was applied by Di Fusco et al. [109]. In 2016, Henao-Escobar et al. [110] described a biosensor for the simultaneous detection of histamine and putrescine: This system consisted of two working electrodes connected in array mode. Histamine dehydrogenase and putrescine oxidase enzymes were respectively immobilised by crosslinking on each working screen-printed electrode and were simultaneously determined by measuring the oxidation current with an amperometer.

The fast response, minimal sample treatment and high sensitivity of the apparatus indicate that biosensors may conveniently be employed within production plants or wineries to provide a reliable estimate of the overall BA content—a parameter that is increasingly being required by food quality commissions worldwide [109].

5.5. Molecular Methods

Molecular methods are also employed to detect BAs that produce bacteria. The PCR technique, using specific primers, can detect the presence of the *hdc*, *odc* and *tdc* genes that code for the decarboxylase enzymes [46,48,50,111,112].

Landete et al. [28], in their review, listed all the primers described in the literature for *hdc*, *tdc* and *odc*, which are reported here in Table 4. Assays can be conducted as single or multiplex reactions. The multiplex PCR assay can be successfully used for the routine detection of strains that are potential producers of histamine, tyramine, putrescine and cadaverine in foods. The simultaneous amplification of all the genes targeting amines in the same PCR reaction reduces both reagent quantities and labour costs. A multiplex PCR assay for the detection of histamine-, tyramine- and putrescine-producing LAB was developed by Coton and Coton, Marcobal et al., de Las Rivas et al. and Costantini et al. [51,113–115].

Finally, qPCR protocols have been set up for the quantification of *hdc*, *odc* and *tdc* genes and consequently for the enumeration of bacteria producing histamine, tyramine and putrescine in wine [52,116].

Table 4. List of the primers described in literature for the detection of decarboxylase genes *(hdc, odc, tdc)*.

Primer	5′ → 3′Sequence	Coding for	Reference
CL1	CCWGGWAAWATWGGWAATGGWTA	hdc	[111]
CL2	GAWGCWGTWGTCATATTWATTTGWCC	hdc	[111]
JV16HC	AGATGGTATTGTTTCTTATG	hdc	[111]
JV17HC	AGACCATACACCATAACCTT	hdc	[111]
JV17	AGACCATACACCATAACCTTG	hdc	[46]
CL1mod	CCAGGWAACATTGGTAATGGATA	hdc	[60]
HDC3	GATGGTATTGTTTCKTATGA	hdc	[51]
HDC4	CAAACACCAGCATCTTC	hdc	[51]
PHDC1	CCGTGCGGAAACAAAGAAT	hdc	[48]
PHDC2	CCAAACACCAGCATCTTCA	hdc	[48]
HIS1-F	GGNATNGTNWSNTAYGAYMGNGCNGA	hdc	[114]
HIS1-R	ATNGCDATNGCNSWCCANACNCCRTA	hdc	[114]
Hdc1	TTGACCGTATCTCAGTGAGTCCAT	hdc	[117]
Hdc2	ACGGTCATACGAAACAATACCATC	hdc	[117]
3	GTNTTYAAYGCNGAYAARACNTAYTTYGT	odc	[50]
16	TACRCARAATACTCCNGGNGGRTANGG	odc	[50]
4	ATNGARTTNAGTTCRCAYTTYTCNGG	odc	[113]
15	GGTAYTGTTYGAYCGGAAWAAWCAYAA	odc	[113]
AODC1	GMTCGTGAAATYAARCKG	odc	[48]
AODC2	KGRGTTCMGCYGGRGTAT	odc	[48]
Put1-F	TWYMAYGCNGAYAARACNTAYYYTGT	odc	[114]
Put1-R	ACRCANAGNACNCCNGNGGRTANGG	odc	[114]
Put2-F	ATHWGNTWYGGNAAYACNATHAARAA	odc	[114]
Put2-R	GCNARNCCNCCRAAYTTNCCDARTC	odc	[114]
P2-for	GAYATIATIGGIATIGGIYTIGAYCARG	tdc	[112]
P1-rev	CCRTARTCIGGIATIGCRAARTCIGTRTG	tdc	[112]
41	CAYGTNGAYGCNGCNTAYGGNGG	tdc	[113]
42	AYRTANCCCATYTTRTGNGGRTC	tdc	[113]
Pt3	TACACGTAGATGCTGCATATG	tdc	[48]
Pt4	ATGGTTGACTATGTTTTAAAAGAA	tdc	[48]
p0303	CCACTGCTGCATCTGTTTG	tdc	[118]
TD5	CAAATGGAAGAAGAAGTAGG	tdc	[118]
TD2	ACATAGTCAACCATRTTGAA	tdc	[118]
57	ATGAGTGAATCATTGTCG	tdc	[119]
58	TTATTTTGCTTCGCTTGCC	tdc	[119]
TDC1	AACTATCGTATGGATATCAACG	tdc	[120]
TDC2	TAGTCAACCATATTGAAATCTGG	tdc	[120]
TDC-F	TGGYTNGTNCCNCARACNAARCAYTA	tdc	[114]
TDC-R	ACRTARTCNACCATRTTRAARTCNGG	tdc	[114]

K = G or T; R = A or G; W = A or T; Y = C or T; S = C or G; M = A or C; D = A, G, or T; N = A, G, C, or T.

The ability of microorganisms to decarboxylate amino acids is highly variable. It depends not only on the species but also on the strain and on environmental conditions. PCR methods can be useful for detecting BA-producing bacteria early, but the presence of the decarboxylase gene is not always related to effective production. Therefore, in our opinion, both molecular and chemical methods should be applied for amine detection to obtain complete information from each wine sample.

6. BA Degradation

Present knowledge indicates that the control of microbiota is a good strategy for reducing BA production. Consequently, the use of selected non-BA-producing starter cultures can be useful for reducing the growth of contaminating microorganisms [81]. Reduction can also be enhanced by using bacteria capable of degrading BAs.

A current topic concerning BAs is the use of BA-degrading microorganisms [121]. García-Ruiz et al. [122] examined the ability of 85 LAB strains isolated from wines and other related oenological sources to degrade histamine, tyramine and putrescine; they found that the greatest BA-degrading ability was exhibited by nine strains belonging to the *Lactobacillus* and *Pediococcus* groups, the best of which was *L. casei* IFI-CA 52.

Two strains of *L. plantarum* were found by Capozzi et al. [123] to degrade putrescine and tyramine. One interesting aspect of their research was that *L. plantarum* survived in stressful wine conditions and improved wine aroma compounds, which are useful factors for competing with spoilage LAB. These strains show promising technological properties, suggesting that the ability to degrade BAs could also serve as a criterion for selecting a new generation of starter cultures [123]. Recently, Callejon et al. [124] demonstrated that two enzymes isolated and purified from the *L. plantarum* J16 and *P. acidilactici* CECT 5930 strains, and identified as multicopper oxidases, were able to degrade histamine, tyramine and putrescine, relevant BAs in wine [125].

Some yeasts have also been found capable of degrading BAs. Recently, Bäumlisberger et al. [126] observed that some strains of *Debaryomyces hansenii* and *Yarrowia lipolytica* were also able to reduce such compounds. The most effective strain, *D. hanseniii* H525, was able to metabolise a broad spectrum of BAs. This property is likely due to peroxisomal amine oxidase activity.

Such a finding introduces a new perspective on the possibility of employing microorganisms or purified microbial enzymes to deal with the problem of high amine concentrations in wine [124], and further research should be performed to find new strains capable of degrading BA.

7. Conclusions

In conclusion, the uncontrolled growth of indigenous microorganisms, especially bacteria with decarboxylase capacity, is among the main causes of the increase of amines in wine, together with the high quantity of amino acid precursors.

Although BAs are generally present in wine in low concentrations, it should be noted that, in the daily diet, their negative effects on health could be enhanced by their simultaneous presence in many other fermented foods, such as cheese, fish and meat, and in the presence of ethanol.

It is therefore essential to reduce the risks of BA production in the wine industry by applying appropriate procedures in the cellar. From a microbiological point of view, it is important to correctly manage wine fermentation to prevent the growth of contaminating microorganisms. A reduction in BA formation might also be achievable by optimising winemaking parameters and manufacturing practices to prevent wine contamination and the growth of BA-producer microorganisms.

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Abbreviations

Him	Histamine
Tyr	Tyramine
Put	Putrescine
Cad	Cadaverine
Met	Methylamine
Agm	Agmatine
Phe	Phenylethylamine
Spm	Spermine
Spd	Spermidine
Try	Tryptamine
Ety	Ethylamine
Eth	Ethanolamine
Tea	Triethylamine
Tma	Trimethylamine
Dap	Diamine-propane
Ism	Isoamylamine

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