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Review

Accumulation of Biogenic Amines in Wine: Role of Alcoholic and Malolactic Fermentation

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Abstract: Biogenic amines (BAs) are detrimental to health and originate in foods mainly from decarboxylation of the corresponding amino acid by the activity of exogenous enzymes released by various microorganisms. BAs can be generated at different stages of the wine production. Some of them are formed in the vineyard and are normal constituents of grapes with amounts varying with variety, soil type and composition, fertilization and climatic conditions during growth and degree of maturation. BAs can be also formed by the yeasts during the alcoholic fermentation (AF), as well as by the action of bacteria involved in the malolactic fermentation (MLF). As aminogenesis is a complex and multifactorial phenomenon, the studies carried out to identify the main vinification stage of BAs production yielded contradictory results. In particular, there is not a general consensus yet on which fermentation supports mostly the accumulation of BAs in wine. In this context, the aim of the present paper deals with the most recent results related with the influence of alcoholic and malolactic fermentation parameters on BAs-producer microorganism in wine.

Keywords: biogenic amines; wine; alcoholic fermentation; malolactic fermentation

1. Introduction

BAs are nitrogenous compounds that, if ingested at high concentrations, can represent an health hazard for humans. They can be formed in foods by the activity of exogenous enzymes released by several microorganisms able to decarboxylate the precursor amino acid and by transamination of aldehydes and ketones. Natural polyamines, such as putrescine (PUT), spermine (SPE), spermidine (SPD) and agmatine (AGM), are present at low levels in microorganisms, plant, animal and human cells where they are involved in important physiological functions. In foods, the decarboxylation process can be related to the activity of decarboxylase enzymes, present both in spoilage and in other microorganisms (i.e., naturally occurring and/or artificially added lactic acid bacteria involved in food fermentation) [1,2]. BAs generally originate in wine by microbial decarboxylation of amino acids and, while the latter directly contribute to wine smell, taste and appearance [3], high concentrations of the former can cause undesirable physiological effects in sensitive humans such as nausea, tachycardia etc. [4], especially when alcohol and acetaldehyde are present. Among BAs, histamine (HIS) is the most important, not only because is the most toxic but also because ethanol and other amines (AGM, cadaverine (CAD), tyramine (TYR), phenylethylamine (PHE), tryptamine (TRY), PUT) enhance its toxicity by inhibiting the enzymes (methyl transferase, diamine oxidase and monoamine oxidase) involved in HIS detoxification in humans [1]. In addition, wines containing high histamine levels risk being rejected in markets with high quality and safety standards [5,6] It follows that the presence of BAs in wines has been studied extensively for 30 years and particularly over the last 10 years, as a consequence of the increasing attention to consumer protection. Even though there are no accurate regulations, several countries like Canada, Switzerland or South Africa are requiring BAs analysis. For

instance, the recommended upper limit for HIS is 10 mg L^{-1} in Australia and Switzerland, 8 mg L^{-1} in France, 3.5 mg L^{-1} in Netherlands, 6 mg L^{-1} in Belgium and 2 mg L^{-1} in Germany [6–11]. The only country that established an official maximum limit of 10 mg L^{-1} for the presence of HIS in wines, Switzerland, removed it in imported wines in 2011.

Some authors reported the presence of BAs in different wine products [12,13]. A wide range of concentrations were observed, starting from not-detected up to 130 mg L^{-1} [14,15], with the main amines being PUT, HIS, TYR and CAD. These are mainly the products of microbial decarboxylation of ornithine, histidine, tyrosine and lysine, respectively [4], although PUT can also be formed via the arginine deiminase pathway from arginine [16], as well as via the agmatine deiminase pathway [17]. Some BAs, including PUT, SPE and SPD, are also formed by the metabolisms of plants; however, many other biogenic amines such as PHE, AGM, TRY, isoamylamine (ISA), methylamine (MET) and ethylamine (ETH) have also been found in wine [14].

BAs can be produced at any stage of the winemaking. Some of them can be already present in grapes, although many parameters affect their levels and distributions (soil type and composition, fertilization and climatic conditions during growth and degree of maturation). Moreover, it has been found that the storage of grapes prior to crushing under non-sterile conditions can also influence BA concentrations [18], suggesting these compounds as indicators of a lack of hygiene during the winemaking process or associated with poor sanitary conditions of grapes [19].

During winemaking, yeasts and bacteria involved in AF and MLF can contribute to BAs accumulation as well. Moreover, many oenological parameters (i.e., must treatment, length of fermentation in the presence of pulp and skin, alcohol content, sulphur dioxide concentration, added nutrients, pH, temperature and quantity and type of finings and clarification agents), have been also reported to influence the concentration of BAs in wines [20] by increasing the concentration of precursor amino acids or by favoring the development of BAs-producing microorganisms. Ageing or storage of wine can contribute as well [15]. In any case, it is necessary to fulfill the conditions supporting the growth of decarboxylase positive microorganisms or the activity and/or the relevant decarboxylase enzymes [21,22].

It follows that, the evolution and presence of BAs in wines, both qualitative and quantitative, is a complex and multifactorial phenomenon still not well defined as it depends on many different related aspects (agronomic, microbiological, technological, hygienic, storage, etc.). This produces a lack of agreement among published results, in relation to the different parameters considered in each study. In particular, researches carried out to identify the kind fermentation mainly responsible of the BAs production and/or accumulation, yielded contradictory results. Some authors reported that amines were formed at the end of the AF, while, most authors underlined an increased amine production at the end of MLF; finally, other studies found no significant increase in amine production at the end of AF or MLF [20].

In this context, the aim of the proposed paper deals with the most recent results related with the influence of AF and MLF on the concentration of BAs in wine.

2. Analytical Determination of BAs in Wine

The analytical determination of BAs in the medical, biological and food samples is an important and difficult mission. In the last years, several hundred Science Citation Index journal articles have directly dealt with BAs analysis in foods [21,23]. This growing interest can be related to the toxicity of BAs, as well as the possibility to use these species as good indicators of spoilage [24].

Reverse Phase liquid Chromatography (RP-LC) represents the official method of analysis indicated for the determination of BAs in foods. Considering its costs and performances, it can be regarded as a good methodology [7]. Due to the fact that BAs have highly similar structures, as well as chemical and physical properties to other compounds found in foods, usually in the separation procedure the assortment of chromatographic column is very important. To this regard, some specific columns can separate selected classes of BAs. However, the use of such columns generally increases the costs of the analysis, as they are generally quite expensive. In addition, the quantitation of BAs is made difficult due to very low concentration level (sub-ng/mL range), requiring a highly sensitive methodology.

Finally, the complexity of the food matrix, should be considered. In fact, the presence of interfering compounds such as polyphenols, lipids and proteins requires a severe pre-treatment of the sample.

Considering the determination of BAs in wines, this analysis is important for the quality control of the products. The levels of BAs, in fact, can be regarded as quality and safety indicators, related either to raw materials or to production process, packaging, storage and distribution. As previously underlined, different factors influence the total amounts and profiles of BAs in wines, also for sample with very similar characteristics. In particular, agronomic, technological, hygienic conditions and microbiological parameters applied during fermentations, play a crucial role in BAs changeability. On the contrary, the different analytical approaches, which are generally validated and showing suitable analytical performances, can be surely considered as secondary sources of variability, although not to be disregarded.

Various methods of separation, identification and determination of BAs have been described during the last years [13] and many analytical methods have been developed to quantify these compounds in wines [25], including capillary electrophoresis [26], gas-chromatography [27] and enzymatic methods and immunoassays [28]. Nevertheless, the most employed technique for the determination of BAs in wine samples was the LC, coupled with different detector systems, such as fluorescence or ultraviolet [29,30]. This methodology allows to get high sensitivity, resolution and versatility, ensuring excellent performances with cost quite reduced. Unfortunately, presence of interfering substances, strong polarity of BAs, their low concentration in food matrix and sample complexity, sometimes get complicated the analytical determination of BAs.

In addition, the absence of predominant functional groups in the chemical structures of the most widespread BAs required a derivatization step before their determination. Derivatization can be accomplished by pre-column or post-column methods, although the first methodologies are usually preferred, despite the matrix effect was more remarkable than post-column strategies [31]. Method of analysis, selectivity, compatibility with the required reaction conditions and possibility of working in the pre-column mode represent the many criteria in the choice of the suitable derivatization agent. These features begin fundamental in the analysis of wine, where high amounts of amino acids and organic acids were also detected [31]. Therefore, the elaboration of the appropriate derivatization procedures is still relevant, permitting chromatographic separation with satisfactory selectivity and accuracy. Among various reagents used for this purpose, the most popular were dabsyl chloride [32], dansyl chloride [33], benzyl chloride [34], 9-fluorenylmethoxycarbonyl chloride [35], *o*-phthaldialdehyde [36], fluorescein isothiocyanate [37], 1,2-naphthoquinone-4-sulfonate [38], 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate [29] and diethyl ethoxy methylene malonate [39]. However, the use of a derivatization agent is often affected by restrictions or disadvantages, e.g., the reaction with dansyl-chloride is slow and not specific, *o*-phthaldialdehyde reacts only with primary amines, 1,2-naphthoquinone-4-sulphonate requires reaction conditions characterized by high pH and temperature and other reagents exhibit short detection wavelengths and low stability [20]. Finally, it should be considered the optimum pH of the derivatization reaction (higher than 7.5), [29] that could affect the concentration of the organic acids, such as tartaric and malic acids, usually detected in the wine matrix [31]. This drawback is usually overcome by using suitable buffer solutions, although samples with very low pH may influence the derivatization procedure [31].

Moreover, additional problems were caused by the interaction between BAs during their determination in the biological matrices [29]. Derivatization agents react with amine groups of amino acids and BAs present in the food matrix [40], however, in fermented products the amino acids are usually several orders of magnitude higher than BAs, thus hindering their analytical detection. The use of more concentrated reagent solutions could overcome this drawback, even if interferences or degradation of the excess of derivatization agent could cause new problems [31]. Therefore, elaboration of a suitable and selective procedure for BAs derivatization prior to LC separation is the main problem, which must be solved.

In the determination of BAs, the time of analysis of the separation step was widely variable and mainly related to the number of analytes under consideration, ranging between 5 and 85 min, while

if the methods involved the simultaneous determination of amino acids and BAs lasted, in all cases, more than 30 min. Lately, reduced run time and solvent consumption were performed by Ultrahigh Pressure Liquid Chromatography (UPLC) that offers many advantages over LC in the determination of BAs in complex food matrix [41].

Recently, liquid chromatography coupled with tandem mass spectrometry and ultra-performance liquid chromatography coupled to a quadrupole-time of light mass spectrometry have been shown to be very powerful techniques to increase the performance of BAs analysis, also without derivatization [41]. Unfortunately, in the BAs identification the limits of detection (LODs) obtained were not significantly lower than those reached by fluorescence detection and this fact explains its widespread use [42]. Ultra-trace analysis was accomplished by a new method recently performed and involved the use of isotopically labeled internal standard, to minimize matrix interferences and employing tandem mass spectrometry detector, able to provide specific structural information and a more sensitive detection capability [42].

An alternative to LC could be represented by thin-layer chromatography, that could simultaneously analyze several samples and does not need special equipment [43]. Recently, this technique was employed to determine BAs in wine samples, previously treated with poly-vinylpyrrolidone to avoid interferences and were derivatized with dansyl chloride [44]. Semi-quantitative methodology, poor sensitivity, as well as, long analyses time represent the main disadvantages of this technique.

In order to offer alternative methods to LC, gas chromatography methods were recently developed and validated for the determination of BAs in fermented beverages [45], also if this methodology not so often was applied to determine BAs in food matrices. To increase volatile properties of BAs and to decrease their polarities a previous derivatization step, using isobutyl chloroformate as derivatizing agent, was required. The proposed method showed to be efficient and highly reproducible, allowing the accurate identification and quantification of a higher number of BAs, than LC methods. In addition, time of analysis and derivatization reaction were faster compared to the LC methodologies, with LODs of the same order of magnitude.

Finally, capillary electrophoresis coupled to mass spectrometry has been proposed for the quantitative determination of BAs in wine samples [46]. The method is fast due to the short migration time (<10 min) and sensitivity, while the use of a poly-vinyl alcohol-coated silica capillary allows to suppress the electroosmotic flow, increasing the separation efficiency.

3. BAs and Alcoholic Fermentation

It has been reported that amines can be formed at the end of the AF as consequence of the normal metabolic processes of yeast. During AF, amino acid precursors can accumulate in musts in relation to several routes. In fact, besides the amino acids present in grapes being partially or totally metabolized by yeasts, some can be secreted by yeasts at the end of fermentation, other can be released by proteolysis during the autolysis of dead yeasts and other can be produced by enzymatic degradation of the grape proteins. Moreover, the amount of available amino acids is the consequence of several technological factors including the length of skin maceration. Lower concentrations of HIS, TYR and PUT, were detected in Spanish Tempranillo red wines manufactured with less than 10 days of skin maceration. Values higher than 2 or 4-time higher were revealed in wines elaborated with longer macerations [47]. Anyway, even if there is no consensus about correlation between the concentration of the amino acid precursor and the corresponding amine amount, as well as between the amino acids in the medium and the total BAs levels, this aspect should not be neglected [48].

The contribution of yeast to BAs production in wine is controversial [49]. Among yeasts, those generally present in wines such as *Saccharomyces cerevisiae*, *Saccharomyces bayanus*, *Brettanomycesbruxellensis* and *Kloeckeraapiculata*, have been shown to produce HIS, TYR, SPD, ethanolamine (ETN), AGM, PHE and CAD [50–53]. TYR can be also released in musts as a consequence of the hydrolysis of hydroxycinnamic amide compounds in grapes by the action of yeast [48]. However, Marcobal et al. showed the absence of significative increase in BAs content in commercial red wine during alcoholic fermentation, were yeasts are predominant [54]. The formation of HIS and TYR during alcoholic fermentation was evidenced also

by Vidal-Carau [55]. Differently, López-Rituerto et al. evidenced by using NMR experiments with labelled and no labelled histidine that the production of HIS in wine is the consequence of MLF and not of AF [56].

A decrease in BAs content especially PUT was found by Granchi et al. [57]. Caruso et al. [52] investigate the BAs production by 50 different yeast strains and *Brettanomyces bruxellensis* and *Saccharomyces cerevisiae* were the two highest producers. No toxic level of putrescine PUT, CAD and SPD were found in wines inoculated with Dekkera/*B. bruxellensis* by Vigentini et al. [58]. In general, it is agreed that BAS formation by yeast during alcoholic fermentation is much less significant than that the contribution of LAB during MLF [59]. Del Prete et al. [19] investigated the evolution of BAs content in must and wines of Merlot, Syrah, Cabernet Franc., Montepulciano, Sangiovese, Carmenere and Cesanesed'Affile. In all investigated must only ETN, ETH and PUT were found with total BAs content ranging from 8.41 to 26.11 mg/L for Montepulciano and Carmenere must year 2004 and from 36.53 to 53.61 mg/L for Cabernet Franc. and Carmenere must year 2005, respectively. The content of BAs was investigated also in wines after 72 h of alcoholic fermentation. PUT content was drastically reduced since it was used by yeast for polyamines biosynthesis. TYR was detected only in Montepulciano, Sangiovese and Cesanesed'Affile wines with values of 1.70, 1.78 and 1.56 mg/L, respectively. Interestingly, AGM was absent from wines from year 2004 but its value is ranging from 0.33 to 1.72 mg/L for Sangiovese and Cesanesed'Affile, respectively. In general, the total BAS content of wine is lower than that reported for wines measured after 72 h of alcoholic fermentation. A similar result was found also by Marques et al. that investigated 82 Portuguese wines [60]. At the end of alcoholic fermentation, a lower content of ISA and TYR in comparison with must was found. These data are probably due the co-precipitation with fine less. ETN was the predominant BAs with a concentration ranging from 21 to 24 mg/L in Montepulciano d'Abruzzo fermented with autochthonous *S. cerevisiae* SRS1 and RT73 [61]. Investigation of BAs content in must and wine from Calabrian (Italy) autochthonous cultivar undergoing spontaneous AF and MLF, was reported by Restuccia et al. [62]. Grapevines included Arvino, Gaglioppo, Greco Nero, Magliocco Canino, Magliocco Dolce and Nocera. In most, the total BAs content ranging from 23.7 to 63.1 mg/L for Arvino and Magliocco Canino, respectively. SPM showed highest value in all sample except Arvino must. A higher total BAs content was observed in wines in comparison to their must. In fact, the total BAs ranging from 30.0 to 74.1 mg/L for Arvino and Magliocco Canino, respectively. PHE was detected in all samples except in both Magliocco Dolce must and wine. BAs were mostly formed during spontaneous alcoholic fermentation. In fact, total BAs concentrations raised ranging from 1.65 (Greco Nero) to 2.9 (Arvino) and accounting for no less than 79% of the final BAs amounts in wines [63]. This indicates that in the considered samples, the presence of BAs was linked to AF more than to MLF, as already reported by Wang et al. [53]. The BAs profile in Rioja red wines made with the red minority varieties *Vitisvinifera* cv. Tempranillo, Monastel and Maturana Tinta de Navarrete in two different years after AF was monitored by Martínez-Pinilla et al. [48]. No significative differences were recorded among wines in relation to the concentration of BAs. Generally, wines from vintage 2010 showed a lower total BAs content. AGM was the most abundant particularly in Monastel wine (8.7 and 2.4 mg/L in vintage 2009 and 2010, respectively) followed by PUT (2.4 and 5.7 mg/L in Tempranillo and Maturana Tinta de Navarrete, respectively). TRY was not detected in samples from vintage 2010. Benito et al. [63] describes a new red winemaking approach as an alternative to the traditional malolactic fermentation by using *Schizosaccharomycs pombe* and *Lachanceathermo tolerans*. Wines obtained by this technique showed BAs levels lower than 2 mg/L. In particular, the combined use of two no *Saccharomyces* strain allow to reduce the value of all measured BAs in comparison with the use of *Saccharomyces* + malolactic fermentation with particular reference to HIS and PUT (0.44 vs. 1.46 mg/L and 1.71 vs. 2.18 mg/L, respectively). No significant differences were recorded in BAs levels when different *Schizosaccharomyces pombe* strains (JB899/Y470, JB917/CBS1057, JB873/NCYC3422 and V1) were tested [64]. These differences should be attributed to the ability of *Schizosaccharomyces pombe* to metabolize urea [65].

The main results dealing with BAs and AF, are summarized in Table 1.

Table 1. BAs determination in wines after alcoholic fermentation.

Sample	BAs	Microorganism/Spontaneous	Analytical Method	Total BAs Content (mg/L) (Harvest Year)	Reference
Tempranillo	HIS; MET; ETH; TYR; PHE; PUT; CAD	Spontaneous	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	22.37 (2004)	[47]
Merlot	AGM; ETA; ETH; PUT; TYR	*S. cerevisiae* (10^6 cells/mL)	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	6.69 (2004) 25.87 (2005)	[19]
Syrah				9.70 (2004) 23.67 (2005)	
Cabernet Franc.				9.65 (2004) 14.02 (2005)	
Montepulciano				12.01 (2004) 21.31 (2005)	
Sangiovese				10.96 (2004) 18.11 (2005)	
Carmenere				8.94 (2004) 20.59 (2005)	
Cesanese d'Affile				15.62 (2004) 27.53 (2005)	
Montepulciano d'Abruzzo	CAD; TRY; PHE; TYR; HIS; ETA; ETH; PUT	*S. cerevisiae* SRS1 (10^6 cells/mL)	Derivatization with dansyl chloride and separation by HPLC coupled with PDA detector.	21–24 (2011)	[61]
Arvino	PHE; PUT; HIS; TYR; SPD; SPM	Spontaneous	Derivatization with dansyl chloride and separation with RP-LC-UV with gradient elution (solvents water and acetonitrile).	23.7 (2016)	[62]
Gaglioppo				41.9 (2016)	
Greco Nero				44.0 (2016)	
Magliocco Canino				63.1 (2016)	
Magliocco Dolce				36.6 (2016)	
Nocera				46.8 (2016)	

Table 1. *Cont.*

Sample	BAs	Microorganism/Spontaneous	Analytical Method	Total BAs Content (mg/L) (Harvest Year)	Reference
Tempranillo	HIS; AGM; SPD; TYR; PUT; TRY; CAD; PHE	Spontaneous	Derivatization with diethyl ethoxy methylene malonate and separation by RP-LC-UV with gradient elution.	14.6 (2009) 6.9 (2010)	[48]
Monastel				14.3 (2009) 10.2 (2010)	
Maturana Tinta de Navarrete				13.9 (2009) 9.6 (2010)	
Aglianico of Vulture	ETA; MET; AGM; TRY; PHE; PUT; CAD; HIS	*Dekkera/B. bruxellensis* (5%)	Derivatization with dansyl chloride and separation with RP-LC-UV with gradient elution (solvents water and acetonitrile).	15.01 (2000)	[52]
		S. cerevisiae (5%)		12.4 (2000)	
		Kloeckeraapiculata (5%)		6.21 (2000)	
		Candida stellata (5%)		6.73 (2000)	
		Metschnikowiapulcherrima (5%)		9.60 (2000)	
Italian red wine	PUT; CAD; SPM	*Dekkera/B. bruxellensis* (CBS2336 and CBS4601)	Derivatization with dabsyl-chloride and separation with separation with RP-LC-UV with gradient elution (Water and acetonitrile).	0.40 (2006)	[58]
Tempranillo	HIS; TYR; PHE; PUT; CAD	*Kluyveromycesthermotolerans/ Schizosaccharomyces pombe V2*	UHPLC coupled to fluorescence detector and separation with separation gradient elution (A: methanol/acetonitrile—B: sodium acetate/tetrahydrofuran).	2.89 (NR)	[63]
		Selected S. pombe (JB899/Y470)		1.47 (NR)	[64]
		Selected S. pombe (JB917/CBS1057)		1.55 (NR)	
		Selected S. pombe (JB873/NCYC3422)		1.39 (NR)	
		Selected S. pombe V1		1.47 (NR)	
		Non-Selected S. pombe (936/CECT12774)		1.50 (NR)	
		Non-Selected S. pombe (935/CECT12774)		1.51 (NR)	

HIS = Histamine; MET = Metionine; ETH = Ethylamine; TYR = Tyramine; PHE = β-Phenylamine; PUT = Putrescine; CAD = Cadaverine; AGM = Agmatine; ETA = Etanolamine; TRY = Tryptamine; SPD = Spermidine; SPM = Spermine; NR: Not reported.

4. BAs and Malolactic Fermentation

At present, the tendency is to consider the MLF as one of the most important factors that determine the presence of BAs in wines. As the majority of white wines do not undergo MLF, together with the fact that, consequently, their pH is generally lower than that of red wines, it is widely accepted that the content of BAs of white wines is smaller than that of red wines. Although there is not a general consensus on which fermentation mostly contributes to the final BAs level, a general increase in BAs total concentration is normally observed in red wines after MLF, although each amine can show a different behavior.

There are two mechanisms by which wine MLF can occur: (i) natural fermentation due to the growth of indigenous strains, or (ii) controlled fermentation after inoculation with selected starter cultures, mainly *Oenococcusoeni*.

During spontaneous MLF, microorganisms that are present on healthy grapes can be transferred to winery equipment, where they can remain present in significant numbers. As the metabolic characteristics of the indigenous bacteria are usually unknown, they may possess decarboxylase activities, leading to BAs production [59]. In this sense, indigenous flora generally increases the risk of BAs formation and species belonging to all four genera LAB are considered the main BAs producers. After AF, they find a different amino acid composition in comparison with the initial medium. Yeasts, in fact, already changed the composition of the initial must in nitrogen compounds by using some amino acids and secreting others during AF. Moreover, extended lees contact seems to be responsible of higher BAs concentrations in wines as LAB can hydrolyze and decarboxylate higher levels of peptides and free amino acids released by yeasts [66].

The nature of the LAB responsible for MLF exerts a major influence on BAs formation and thus, the levels observed are highly dependent on their aminogenic capacity [15,67,68]. Anyway, contradictory results are widely present in literature about the role of MLF on BAs levels and profiles found in wines. This can be explained considering that: (i) the BA production is associated with specific strains rather than particular species [69] and (ii) the histidine decarboxylase genes might be located in unstable plasmid being lost during bacterial cultures [70].

Among LAB, both in spontaneous and guided MLF, the most observed species is *Oenococcusoeni*. It is capable of proliferating in the harsh wine environment, i.e., high alcohol content (14% *v*/*v*), high concentration of SO_2 (50–80 mg L^{-1}), low temperature (18–20 °C) and low pH (ca. 3.5) [71]. This last aspect should not be disregarded and is not rare to find. In fact, to meet the market demand, wines are generally less acid than the past. The ripening of the grape tends to be prolonged to the maximum possible, for increasing the extractability of the phenolic compounds and the concentration of the aroma precursors. For the same reason, grape skins or grapes are all processed in winery, producing higher levels of precursor amino acids that, after decarboxylation, allow the formation of BAs.

However, its role in the production of BAs, HIS in particular, is not yet clarified [72]. Coton et al. [73] and Landete et al. [74] found *O. oeni* strains with histamine-forming capacity, in contrast, Moreno-Arribas et al. [75] and Garai et al. [69], isolated strains without this capacity. More recently, Barbegal et al. demonstrated that a non-commercial selected autochthonous *O. oeni* strain could be used to conduct MLF while lowering histamine formation in the same winery [75]. LAB were isolated and only *O. oeni* were present and both histamine producer and non-producers. Among non-producing strains, one was considered suitable to become a starter in Tempranillo red wine owing to its genetic features, prevalence in the produced wines, compatibility with alcoholic degree and high polyphenolic content, inability to form HIS, growth kinetics and malolactic activity. The inoculated vat showed much lower HIS concentration than the non-inoculated control vat, also after 1 year aging. As reported by Garcia-Moruno & Muñoz [72], conflicting results can be explained by: (i) the absence of validated controls histamine-producer *O. oeni* strains; (ii) analytical errors affecting the published results; (iii) the very low reported HIS concentration produced by *O. oeni* strains; and (iv) the presence of contradictory data for the same strain or method.

Lactobacillus with particular reference to *Lactobacillus buchneri*, *Lactobacillus brevis*, *Lactobacillus hilgardii* and *Lactobacillus mali* and *Leuconostoc* spp., *L. mesenteroides* in particular, are frequently linked with BAs production in wine [21,51,75–77]. BAs could be produced by LAB strains simultaneously, suggesting that some strains might possess more than one amino acid decarboxylase activity under specific culture conditions [73,77]. Moreover, the specificity of LAB populations could explain the differences in BA contents found in regional wines. For example, Marcobal et al. [78] and Manfroi et al. [79] reported that *L. brevis*, *L. hilgardii* are responsible of BA production less than *Lactobacillus plantarum*. Arena et al. [80] reported the ability of *L. hilgardii* strain X1B isolated from wine to produce PUT from arginine via two different enzymatic pathways. More recently and for the first time, *Lactobacillus rhamnosus* was found to be the predominant species in Chilean Cabernet Sauvignon wines during MLF [81]. Moreover, *L. rhamnosus* showed the highest aminogenic capacity (10.97–28.61 mg L^{-1}), as well as a HIS-forming capacity, thus being the principal species responsible for BAs formation in the five wineries studied.

Other microorganism in natural MLF are *Pediococcus* that are often components of wine microflora generally associated with spoilage. Several studies showed that *Pediococcus* strains such as *P. damnosus* and *P. parvulus* are responsible of HIS production [51,82]. In addition, several strains of *Enterococcus faecium* and enterobacteria BA producing specie, have been reported in wine, grape and musts [72,83,84]. The presence of *G. oxydans*, *A. siamensis*, *Serratia* sp. and *Enterobacter* sp., capable of producing HIS, was also observed during MLF [85].

Amino biogenic potential is not a widely distributed property among *Staphylococcus* [86]. However, Benavent-Gil et al. [87] reported in Tempranillo red wines from Ribera de Duero D.O. (Denomination of origin) the presence of two strains of *Staphylococcus epidermidis* as a natural component of the indigenous microbiota associated with wine, with four strains of *Oenococcusoeni*. None of the *O. oeni* strains produced HIS, CAD or PUT but one of the *S. epidermidis* strains was able to produce all three in synthetic medium and grape must, while in wine it was able to produce HIS (>10 mg L^{-1}).

Considering controlled MLF, commercial preparations of starter cultures are said to be selected for the absence of amino acid decarboxylases and are therefore unable to produce BAs. Many studies comparing spontaneous and controlled MLF using existing and potential commercial starter cultures, showed a reduced BAs concentration (HIS, PUT and TYR in particular) when applying selected bacteria during winemaking [46,56,60,71,75,79,88–90].

More recently, Smit et al. evaluated the impact of the addition of complex commercial yeast and bacterial nutrients as well as different MLF inoculation times on the production of BAs (HIS, PUT, TYR and CAD) in Pinotage and Shiraz [91]. Conflicting results were obtained. In the Shiraz, co-inoculation resulted in lower BAs concentrations after MLF (total BAs never exceeding 7 mg L^{-1}), while the opposite was found in Pinotage (total BAs never exceeding 13 mg L^{-1}), probably in relation with differences in vintage, geographical region, grape varieties, vinification methods, availability of amino acid precursors, etc. However, authors concluded that for both wines, the production of BAs was affected more by the presence of decarboxylase positive LAB than by the addition of complex nutrients or the inoculation scenario. The same authors confirmed later that co-inoculation of Cabernet Sauvignon and Pinotage (vintage 2006 and 2007) with a commercial MLF starter culture of *O. oeni* was even more effective than conventional inoculation in reducing the incidence of PUT, HIS and CAD in comparison with spontaneous MLF [91]. Authors demonstrated in both cultivars and vintages, that co-inoculation of the starter cultures at the beginning of AF simultaneously with yeast, exerted this effect by domination of indigenous bacteria producing at the same time a limited contact between amino acid precursors and spoilage LAB. *O. oeni* cells. To this regard, it has been found that co-inoculation successfully took place with AF and that MLF was mainly performed and completed by this species.

Anyway, it should be kept in mind that contaminant bacteria other than *O. oeni*, may produce HIS during and after MLF as well, also when using commercial starters, as previously suggested by Buteau et al. [92] and later confirmed by Costantini et al. [93]. In the latter study, it was shown by cultural methods that the commercial preparations were contaminated with *Lactobacillus rossiae* and *L. buchneri*, which produced HIS. This aspect was investigated by Del Prete et al. [19]. Besides the use

of selected yeasts (*S. cerevisiae*) and bacteria (*O. oeni*) unable to produce BAs, to exclude interferences due to uncontrolled contaminating microorganisms present in grapes and/or in the environment, authors evaluated the evolution of BAs from musts to wines under aseptic conditions. Data showed that the amines ETN, ETH and PUT were already present in grapes of all varieties investigated. On the contrary, HIS and CAD were never detected. Moreover, ETN, was mainly produced in wine by *S. cerevisiae* while AGM and TYR, as probable consequences of hydrolysis of hydroxycinnamic amide compounds in grapes by the action of yeast and bacteria. To avoid the risks in wines undergoing MLF, Benito et al. [63] evaluated the combination of two non-Saccharomyces yeast strains in order to replace the traditional MLF in Tempranillo wines. It was found, that malic acid was totally metabolized by *Schizosaccharomyces pombe,* while *Lachancea thermotolerans* produced lactic to produce sufficient acidity also in wines deriving from low acidity musts. The comparison among control wines undergoing classical MLF and alternatively fermented wines showed that the latter were fruitier also containing less acetic acid and BAs. More recently, the same authors characterized many *S. pombe* strains by evaluating biochemical parameters of oenological interest [64]. Three genetically different *S. pombe* strains appeared suitable for winemaking. In comparison with *Saccharomyces cerevisiae*, these strains were able to exert effective malic acid de-acidification at the same time reducing BAs concentrations and ethyl carbamate precursors without performing MLF.

The main results dealing with BAs and MLF, are summarized in Table 2.

Table 2. BAs determination in wines after malolactic fermentation.

Sample	BAs	Microorganisms	Analytical Method	Total BAs Content (mg/L) (Harvest Year)	Reference
Periquita	TYR; PUT; HIS	Spontaneous	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	27.6 (2006) 7.0 (TYR) (2006)	[60]
		CMS2 (inducer of MLF)		2.0 (TYR) (2006)	
Merlot	AGM; ETA; ETH; PUT; TYR	*O. oeni* (5×10^6 cells/mL)	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	6.59 (2004) 37.55 (2005)	[19]
Syrah				8.73 (2004) 47.59 (2005)	
Cabernet Franc.				6.88 (2004) 31.26 (2005)	
Montepulciano				8.43 (2004) 33.85 (2005)	
Sangiovese				8.16 (2004) 34.09 (2005)	
Carmenere				8.63 (2004) 29.71 (2005)	
Cesanese d'Affile				13.64 (2004) 37.80 (2005)	
Tempranillo	HIS; AGM; SPD; TYR; PUT; TRY; CAD; PHE	Spontaneous	Derivatization with diethyl ethoxy methylene malonate and separation by RP-LC-UV with gradient elution.	2.227 (2009) 1.313 (2010)	[48]
Monastel				3.772 (2009) 2.236 (2010)	
Maturana Tinta de Navarrete				5.019 (2009) 1.646 (2010)	
Merlot	PUT; SPD; SPM; AGM; CAD; SRT; HIS; TYR; TRY; PHE	Spontaneous *	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	<0.40 (2008)	[79]
		O. oeni DSM 7008 (6 mg/L) *		1.93	
		O. oeni DSM 12923 (6 mg/L) *		15.5	
		L. plantarum DSM 4361 (200 mg/L) *		14.3	
		Yeast *		7.94	
		Spontaneous **		12.4	

Table 2. *Cont.*

Sample	BAs	Microorganisms	Analytical Method	Total BAs Content (mg/L) (Harvest Year)	Reference
		O. oeni DSM 7008 (6 mg/L) **		7.4	
		O. oeni DSM 12923 (6 mg/L) **		7.7	
		L. plantarum DSM 4361 (200 mg/L) **		24.1	
		Yeast **		12.9	
		Spontaneous *		6.88	
		O. oeni DSM 7008 (6 mg/L) ***		9.08	
		O. oeni DSM 12923 (6 mg/L) ***		6.23	
		L. plantarum DSM 4361 (200 mg/L) ***		14.6	
		Yeast ***		9.20	
		Spontaneous †		6.43	
		O. oeni DSM 7008 (6 mg/L) †		6.13	
		O. oeni DSM 12923 (6 mg/L) †		9.81	
		L. plantarum DSM 4361 (200 mg/L) †		17.7	
Arvino	PHE; PUT; HIS; TYR; SPD; SPM	Spontaneous	Derivatization with dansyl chloride and separation with RP-LC-UV with gradient elution (solvents water and acetonitrile).	30.0 (2015)	[62]
Gaglioppo				50.3 (2015)	
Greco Nero				54.4 (2015)	
Magliocco Canino				74.1 (2015)	
Magliocco Dolce				43.3 (2015)	
Nocera				54.5 (2015)	
Tempranillo	HIS; MET; ETH; TYR; PHE; PUT; CAD	Spontaneous	Derivatization with *o*-phthaldialdehyde and separation with HPLC coupled to fluorescence detector.	22.37 (2004)	[47]
		Commercial malolacticbacteria		14.75 (2004)	

HIS = Histamine; MET = Metionine; ETH = Ethylamine; TYR = Tyramine; PHE = β-Phenylamine; PUT = Putrescine; CAD = Cadaverine; AGM = Agmatine; ETA = Etanolamine; TRY = Tryptamine; SPD = Spermidine; SPM = Spermine; SRT = Serotonine. *: Spontaneous AF fermentation; **: *Saccharomyces bayanus* (250 mg/L); ***: *Saccharomyces cerevisiae* (250 mg/L); †: *Bacteria.*

5. Conclusions

The presence of BAs in wine gained a global attention because of their importance for human health and food safety. BAs in wine can take origin from raw materials and processing practices as the content and types of BAs are reported to have regional variability and related to several agricultural and oenological factors. All these parameters are interconnected and influence each other. It follows that the goal to identify the main phase during grape cultivation and winemaking, which mostly contributes to the BAs formation/accumulation, is virtually impossible. Also restricting the evaluation only to the processing phases, it should be underlined that all winemaking practices have the potential, when not controlled, to induce BAs production. Focusing the study only on the fermentation phases, it can be concluded that BAs can be formed from their respective amino acid precursors by various microorganisms present in the wine, at any stage of production, ageing or storage. This because the distribution of BAs producers amongst wine microorganisms seems to be random and not a specific feature of a specie. In addition, a direct overlapping of the data arising from different studies is not easy to accomplish and sometimes meaningless, as samples considered are always very different under the agricultural and oenological point of view. These aspects, associated with the complexity of the phenomenon under investigation, surely account for the lack of agreement and controversial results.

Anyway, it can be stated that the contribution of yeast to BAs production was found to be indirect (by amino acid secretion and autolysis) or direct, as strains of *B. bruxellensis* and *S. cerevisiae* were reported to produce significant concentrations of BAs. Moreover, it is generally agreed that LAB of the genera *Lactobacillus*, *Leuconostoc*, *Pediococcus* and *Oenococcus* during MLF, can be considered the wine microorganisms mainly associated with amino acid decarboxylation and BAs formation, especially if spontaneous MLF occur in high pH wines fermented on lees. It follows that BAs accumulation in wines should be primarily controlled by the use of selected non-BAs producing starters to carry out MLF, although some attempts have been accomplished to completely avoid MLF using combination of non-Saccharomyces yeast strains. On the contrary, if starter strains are recognized to not produce BAs, prevention should focus on the strict selection of the winemaking conditions. In particular, special attention should be paid to: (i) the control of commercial yeast starters to avoid bacterial contaminants able to produce BAs; (ii) the wine pH not exceeding the value of 3.5 thus preventing the growth Lactobacillus and Pediococcus spp which are of BAs producers; (iii) the concentration of SO_2 which have to be suitable to inhibit the growth of undesirable bacteria after MLF; (iv) the time of contact with the lees which promotes the accumulation of BAs producing bacteria after MLF by nutrients release in the medium.

Finally, monitoring the BA content during wine fermentation with reliable and sensitive analytical techniques, is a worthwhile goal in order to identify problems related to wine fermentation or wine spoilage microorganisms and thus providing solutions to avoid BA accumulation in wine. To this regard, the official technique for the determination of BAs is the LC coupled with UV detector and, considering the costs and the performances this methodology can be considered as a good procedure. Other techniques were proposed as alternative and, in some cases, better performances were obtained in terms of resolution and time of analysis but usually these procedures require higher costs.

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