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Biogenic amines in red wine: The impact of technological processing of grape and wine

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ABSTRACT

The knowledge of the biogenic amines present in wine is important to consumers in terms of their potential threats of toxicity to human and to wine producers as a result of market impact. In the scientific field, biogenic amines have the potential to be applied as indicators of food spoilage. Biogenic amines are essential at low concentrations for metabolic and physiological functions in animals, plants, and microorganisms, but at high concentrations can induce adverse reactions in susceptible individuals. Despite the intensive research aimed at determining and reduction of biogenic amines, our current knowledge remains far from complete. However, a number of factors that influence the biogenic amines concentration in red wine have been already described. Most of them are related to the winemaking conditions in the cellars and some of them are environmental factors. During winemaking it is important to consider all factors beginning from viticulture practices, alcoholic and malolactic fermentation and physiochemical composition of wine, as well as, aging and storage of wine. This paper reviews changes of the concentration of biogenic amines depending on technological processing of grape and wine.

Key words: biogenic amines, red wine, winemaking conditions, fermentation, microbiological decarboxylation

IZVLEČEK

BIOGENI AMINI V RDEČEM VINU: VPLIV TEHNOLOŠKE PREDELAVE GROZDJA IN VINA

Poznavanje prisotnih biogenih aminov v vinu je pomembno za potrošnike in pridelovalce zaradi potencialne nevarnosti toksičnosti za človeka in posledično tržnih vplivih. Na znanstvenem področju imajo biogeni amini potencial, ki se uporablja kot pokazatelji kvarjenja hrane. Biogeni amini so v majhnih koncentracijah bistvenega pomena za normalne metabolne in fiziološke funkcije pri živalih, rastlinah in mikroorganizmih, lahko pa imajo škodljive učinke pri velikih koncentracijah ter predstavljajo tveganje za zdravje občutljivih posameznikov. Kljub intenzivnim raziskavam, usmerjenim v določanje in zmanjšanje vsebnosti biogenih aminov, naše sedanje znanje še zdaleč ni dokončno. Opisanih je več dejavnikov, ki vplivajo na vsebnost biogenih aminov v rdečih vinih. Večina od njih je povezanih z vinarskimi razmerami v kleti, od katerih so nekateri tudi okoljski dejavniki. V vinarstvu je pomembno upoštevati vse dejavnike, ki se začnejo z vinogradniških vplivi, alkoholno in jabolčno-mlečnokislinsko fermentacijo, fizikalno-kemijsko sestavo vina, kakor tudi staranjem in skladiščenjem vina. V tem članku so pregledno podane spremembe vsebnosti biogenih aminov glede na tehnološke postopke predelave grozdja in pridelave vina.

Ključne besede: biogeni amini, rdeče vino, pogoji med pridelavo vina, fermentacija, mikrobiološka dekarboksilacija

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1 INTRODUCTION

Biogenic amines (BA) are low molecular weight compounds, derived from aromatic or cationic amino acids and all of them have one or more positive charges and a hydrophobic skeleton. The chemical structure of BA can be aliphatic (putrescine, cadaverine, spermine, spermidine), aromatic (tyramine, phenylethylamine) or heterocyclic (histamine, tryptamine). The most frequently found BA in wine are histamine, cadaverine, putrescine, phenylethylamine and tyramine (Figure 1) (Smit et al., 2008; Čuš et al., 2013). Amines are mainly formed in foods in fermentative processes and during aging and storage by microbiological decarboxylation of the corresponding amino acid precursors, which is why they are referred to as biogenic. The non-volatile BA (histamine, putrescine, cadaverine, spermine, spermidine, agmatine, tyramine, tryptamine and volatile amine phenylethylamine are formed mainly by microbial decarboxylation of corresponding amino acids (Halász et al., 1994): histidine – histamine; tyrosine – tyramine; phenylalanine – phenylethylamine; arginine and/or ornithine – putrescine; arginine – agmatine; lysine – cadaverine (Buňka et al., 2012) . Volatile amines, except phenylethylamine, are believed to be formed by the reductive amination or transamination of the corresponding aldehyde or ketone (Smith, 1980; Ough et al., 1981). In spite of toxicological implications no legal limit has been defined for BA in wine. Because of these reasons, some countries have established regulations regarding either their content in various kinds of food or their maximum limit requirements (Lehtonen, 1996). In the wine industry, the occurrence of BA has been receiving increasingly attention. There are trade implications due to the recommended or suggested existing limits for histamine in wine in some European countries. Switzerland and Austria reject wines which contain more than 10 mg l^{-1}, and lower limits have been recommended in Germany (2 mg l^{-1}), Holland (3 mg l^{-1}), Finland (5 mg l^{-1})), Belgium (5-6 mg l^{-1}) and France (8 mg l^{-1}) (Lehtonen, 1996; Smit et al., 2008). Generally the toxic dose in alcoholic beverages is considered to be between 8 and 20 mg l^{-1} for histamine, 25 and 40 mg l^{-1} for tyramine, while as little as 3 mg l^{-1} of phenylethylamine can cause negative physiological effect (Soufleros et al., 1998).

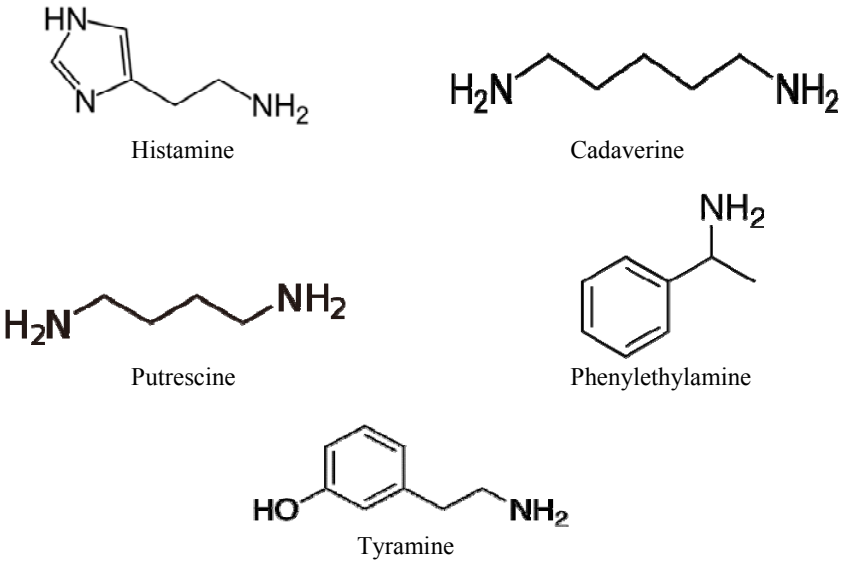

Figure 1.: Chemical structures of the biogenic amines most frequently found in wine.

Some studies have found that BA are formed by yeasts and their concentration is increased during alcoholic fermentation. BA formation in winemaking takes place predominantly during malolactic fermentation (MLF) by lactic acid bacteria (LAB) (García-Ruiz et al., 2011). Contamination may occur from poor sanitary conditions of both grape berries and processing cellar equipment (Moreno-Arribas and Polo,

2009). The results of some studies indicate that vintage can clearly influence the BA contents in wine (Martín-Álvarez et al., 2006). Many actions for increasing the complexity of wine, such as skin maceration and aging on lees, strongly influenced the final content of BA in wines. Some studies have shown significant correlation between some BA and the physico-chemical parameters of wine (pH, total acidity, alcohol and total SO_2 concentration) (Martín-Álvarez et al., 2006).

2 BIOGENIC AMINES (BA)

Bioactive or biologically active amines are low molecular weight organic bases, formed by biochemical processes and are involved in metabolic and physiologic functions in every living organism, playing several important roles (Halász et al., 1994). In humans, the BA involved in brain function, regulation of body temperature and the pH of the stomach, gastric acid secretion, and immune response, the cellular growth and differentiation, etc. The main BA associated with wine are putrescine, histamine, tyramine and cadaverine (Čuš et al., 2011; 2013), followed by phenylethylamine, spermidine, spermine, agmatine and tryptamine (Smit, 2008). Histamine, tyramine and especially putrescine were found in some wines by Buňka et al. (2012) and by Čuš et al. (2011; 2013), while the white wines showed lower content of BA in comparison to the red wines (Table 1) (Bodmer et al., 1999).

Table 1.: Comparison of biogenic amines concentration (mg l^{-1}) in red and white wine (Bodmer et al., 1999).

wine	tyramine	histamine	putrescine	cadaverine	phenylethylamine	spermidine
red	18.2	19.6	99.9	1.0	1.4	2.6
white	2.3	1.1	9.7	0.6	1.7	1.5

There are also recent studies which confirm the fact that histamine and tyramine are the most abundant BA produced by bacterial isolates from experimental wines (Sebastian et al., 2011), in contrast to the lower amounts found by Kaschak et al. (2009) in commercial wines of average quality. Literature data on the levels of biogenic amines in the Montenegrin red wine is not available, but we find more recent data for Slovenian wines (Baša Česnik et al., 2012; Čuš et al., 2011; 2013). The authors found out that the microbiological stability of the wines was poor and should be improved, but however, the levels of BA in the traded Cviček and Blaufränkisch wines were low (Čuš et al., 2013).

Spermine, spermidine and putrescine are involved in DNA, RNA and protein synthesis, growth, membrane stabilization and senescence prevention of organism (Souza et al., 2005). Histamine and serotonine are vaso- and neuroactive and can also protect plants from insects and predators (Smith, 1985). Some amines are frequent constituents of grapes with amounts varying with variety, soil type and composition, fertilization and climatic conditions during the grape growth and stage of maturation (Souza et al., 2005). Putrescine and spermidine are usually abundant in grapes, whereas agmatine, cadaverine, spermine, histamine, tyramine and phenylethylamine have been found in small amounts (Ough, 1971; Zee et al., 1983; Vidal-Carou et al., 1990; Glória et al., 1998; Hajos et al., 2000; Sass-Kiss et al., 2000).

BA can be produced during fermentation processes, aging or storage, when wine is exposed to the undesirable activity of decarboxylase-positive microorganisms. However, reports on development of BA are contradictory. There are reports indicating the possibility that amines are formed in wine by the action of contaminant microorganisms or by those not directly implicated in the fermentation process, for example enteric bacteria (Buteau et al., 1984). In this case, formation of amines was related to the lack of hygiene during winemaking. Based on this assumption, histamine alone or together with other amines could be an indicator of the quality of raw materials employed or poor sanitary conditions prevailing during wine production (Buteau et al., 1984; Vidal-Carou et al., 1990; Soufleros et al., 1998).

A number of studies have reported no remarkable rise in the content of BA during alcoholic fermentation, concluding that yeasts do not appear to be responsible for the production of most amines found in industrial commercial red wines (Herbert et al., 2005; Marcobal et al., 2005). Most researchers attribute the formation of amines, especially tyramine and histamine, to the action of bacteria involved in MLF (Buteau et al., 1984; Vidal-Carou et al., 1990; Soufleros et al., 1998; Sebastian et al., 2011; Buňka et al., 2012). According to Soufleros et al. (1998), during MLF carried out by indigenous LAB, amino acid contents decreased significantly, while content of bioactive amines increased. Lactic acid bacteria are present in low populations in healthy grapes and are transferred to the cellar equipment where they reproduce rapidly. These indigenous bacteria are responsible for spontaneous MLF. However, the metabolic characteristics of the microbiological flora are not well known and in some strains enzymatic decarboxylase activities could be involved in BA production (Soufleros et al., 1998; Arena and Manca de Nadra, 2001).

2.1 Toxicological effect of biogenic amines (BA) in wines

In alcoholic drinks, especially wine, BA received more attention, because ethanol can increase the toxic effects by directly or indirectly inhibiting the enzymes responsible for detoxification of these compounds (Maynard and Schenker, 1996; Smit et al., 2008). The human organism easily tolerates low contents of BA since these are efficiently broken down by mono- and diaminoxidase enzymes in the intestinal tract (Moreno-Arribas and Polo, 2009). Although there are differences in individual susceptibility to intoxication by BA, several pharmacological reactions can take place after excess intake of these compounds. The best known reactions are those caused by histamine. Histamine is known to cause rash, edema, headaches, hypotension, vomiting, palpitation, diarrhea, and heart problems (Ladero et al., 2010). Tyramine and phenylethylamine can produce hypertension through the release of noradrenalin and norepinephrine, respectively, which are vasoconstrictors. Putrescine and cadaverine although non-toxic themselves, aggravate the adverse effects of histamine, tyramine and phenylethylamine, as they interfere with the enzymes that metabolize them (Shalaby, 1996; Silla Santos, 1996). Moreover, putrescine and cadaverine can have negative effects on wine aroma, giving them flavors of putrefaction or rotting flesh, respectively (Moreno-Arribas and Polo, 2009).

Beside the toxic effect (Ladero et al., 2010), some BA also have other negative consequences, particularly regarding sensory characteristics of wine and thus economic implications. A study carried out by Rohn et al. (2005) showed that high contents of histamine in wines identify well-trained wine assessors. In that study to describe the feeling in the mouth (mouthfeel descriptors) used two, namely: "deep throat irritation" and "creep language." No special taste, it can not be attributed to histamine. Putrescine, which is the most common BA in wine, may reduce the sensory quality of wine at concentration of 15-20 mg l^{-1} in white and 20-30 mg l^{-1} in red wines, respectively (Arena and Manca de Nadra, 2001).

2.2 Microorganisms related to production of biogenic amines in the winemaking

In the winemaking process, all groups of wine microorganisms may participate in production of BA. There is general agreement that yeasts make a less significant contribution than LAB to the final content of BA in wine. There is also a fact that yeasts form different BA than LAB. On the other hand, there is much more data about the biochemistry, genetics and regulations of amine production by LAB, compared with the data available for yeasts. Beside yeasts and LAB, fungus *Botrytis cinerea* can cause biotic stress of grapevine and therefore can lead to a rise in the amine content of the grape berries (Hayos et al., 2000).

2.2.1 YEAST

A large species of indigenous yeasts can grow and perform alcoholic fermentation in wine, along with commercial *Saccharomyces cerevisiae* strains. Few studies have been conducted on the formation of BA by yeasts, and most of these only compared different yeast species and only quantified histamine (Torrea and Ancín, 2002). Somavilla et al. (1986), using six yeast strains, demonstrated that small amounts of histamine are produced during alcoholic fermentation and that the

association of yeasts and LAB can reduce the histamine content (Moreno-Arribas and Polo, 2009). The highest histamine concentrations (from 3.7 to 8.3 mg l^{-1}) were produced when histidine was added to the must (34 mg l^{-1}), in other experiments histamine concentrations were lower than 1.2 mg l^{-1}. Vidal-Carou et al. (1990) did not detect formation of histamine during alcoholic fermentation, although they detected tyramine formation, but at very low concentrations (0.60 mg l^{-1}). In contrast, other authors disagree with the hypothesis that BA are formed by LAB during MLF. Torrea-Goñi and Ancín-Azpilicueta (2001) found a slight BA production by *Saccharomyces cerevisiae* depending on the strain. Landete et al. (2007) screened 36 strains of different yeast genera isolated from must and wines for production of BA (*Aureobasidum, Candida, Hanseniaspora, Hansenula, Kloeckera, Metschnikowia, Pichia,* strains of the species *Saccharomyces cerevisiae*), and no BA were produced by any of these strains. These results are consistent with previous studies in which neither histamine, tyramine, nor putrescine production were detected in 50 yeasts strains isolated from grape and/or wine (Moreno-Arribas and Polo, 2009). These results, therefore, indicate that yeast does not appear to be directly involved in the direct origin of most amines found in wine.

2.2.2 LACTIC ACID BACTERIA (LAB) AND THE CONDITIONS FOR THEIR GROWTH IN MUST AND WINE

Usually BA production results from the presence of bacteria that are capable of decarboxylating amino acids (Gale, 1946). The LAB are a group of Gram positive bacteria, non-respiring, non-spore forming, cocci or rods, which produce lactic acid as the major end product of the fermentation of carbohydrates. Beside the positive aspects of LAB, they are also able to form redundant metabolites in wine (Bartowsky, 2009). Only few species of LAB can grow in media such as must and wine, which are very selective type of media. Bacteria from the genera *Lactobacillus, Pediococcus* and *Oenococcus* are the main strains involved in BA production. Different strains of *Lactobacillus hilgardii, L. brevis, L. buchneri* and *L. mali* have been found to be able to produce a variety of BA in wine (Moreno-Arribas and Lonvaud-Funel, 1999; Moreno-Arribas et al., 2000; Moreno-Arribas et al., 2003; Constantini et al., 2006; Landete et al., 2007).

Among LAB, *O. oeni* is the main species present in wine and the best adapted to carry out the MLF at low pH of wine (Wibowo et al., 1985). If BA formation is associated with MLF, it would be expected that *O. oeni* has the enzymes for breakdown of peptides and decarboxylation of amino acids present in wine at this stage (Leitão et al., 2000). Some authors found that *O. oeni* significantly contribute to the overall content of histamine in wines and that the ability of the species to produce this amine varies among strains (Coton et al., 1998; Guerrini et al., 2002). Marcobal et al. (2004) isolated and identified a strain of the *O. oeni* species, a producer of putrescine, and also studied the ability of another 42 strains of this species to produce putrescine at a molecular level. The gene that encodes biosynthesis of this amine was not present in any of them.

Other authors found that inoculation with commercial starter culture of LAB could reduce the incidence of BA in comparison with spontaneous MLF in wines (Martín-Álvarez et al., 2006; Schneider et al., 2011). Actually, starter cultures could inhibit indigenous bacteria, or possibly could decrease the production of BA by undesirable strains.

Amine build-up usually results from decarboxylation of free amino acids by enzymes of bacterial origin. Hystidine decarboxylase catalyzes decarboxylation of histidine to histamine. Tyramine decarboxylase is responsible for the production of tyramine from tyrosine. Number of tyramine-producing LAB in wine that had undergone MLF were identified and isolated by Moreno-Arribas et al. (2000) and all of them belong to *Lactobacilli*. As the literature suggest, no tyramine-producing *O. oeni* strain has yet been reported except of one strain (*O. oeni* DSM 2025) that was shown to be able to produce tyramine in a defined growth medium (Choudhury et al., 1990). This is confirmed by Sebastian et al. (2011) who observed formation of BA for all 57 strains of *Lactobacillus brevis.* The dominant BA found in this study was tyramine, which was formed by 96% of the strains, while histamine was produced by 19% of *Lactobacillus brevis* strains.

Lactobacillus paracasei formed histamine and ethylamine, while species such as *Lactobacillus delbrueckii* and the most important *Oenococcus oeni* did not show any production of BA (Sebastian et al., 2011).

There are a lot of factors affecting the activity of LAB in wine.

Sulphur dioxide: The antimicrobial activity of SO_2 is based on its ability to pass across cell membrane. Free forms of sulphur dioxide are inhibitorier than bound forms. Of the free forms, molecular SO_2 has the greatest antimicrobial activity. The pH has a marked influence on the toxicity of sulphur dioxide (Jackson, 2008). Therefore, maintaining low pH is helpful in making SO_2 the most effective tool to control LAB. In wine, SO_2 is bound to certain carbonyl compounds such as acetaldehyde. When LAB metabolize the carbonyl compound, the bound SO_2 is released. It is this liberated free form of SO_2 that prevents further growth of the bacteria. Different species and strains vary in their sensitivity to sulphur dioxide. In general, it appears that *O. oeni* is the most sensitive (Jackson, 2008). After MLF the wine is sulphited with the objective of eliminating the yeasts and residual bacteria, but due to the rise in pH and also to the fact that it is found in part combined with the polyphenols, the activity of the SO_2 decreases. Thus can give rise to some LAB remaining viable months after the winemaking and conserving certain biological activity, fundamentally that which helps their survival (García-Marino et al., 2010).

pH: Wine pH is one of the most important factors influencing the growth of LAB. It affects the initiation and duration of MLF, it influences the type of species of bacteria that may develop in wine and it also affects the metabolic behavior of the organism and thereby determines the kind of byproducts formed as the result of bacterial activity (Dharmadhikari, 1992). In the wine pH range mostly from 3.0 to 4.0, the time needed for the completion of MLF decreases with an increase of pH. Bousbouras and Kunkee (1971) reported that at pH 3.15 it took 23.4 weeks to complete MLF; whereas at pH 3.83, it was completed in just two weeks. Many researchers have noted the effect of pH on the species of bacteria that can grow in wine. Generally at pH below 3.5, the MLF is often dominated by *Oenococcus*; whereas, above pH 3.5, species of *Pediococcus* and *Lactobacillus* seem to flourish. It should be noted here that many strains of *Lactobacillus* are involved in wine spoilage. Another important pH effect not commonly realized is the effect of pH on the metabolic behavior of the organisms. For example at pH 3.5 and above, LAB are more likely to decompose sugars, tartaric acid and citric acid. As mentioned earlier, fermentation of sugars leads to higher content of volatile acids in wine (Dharmadhikari, 1992). Lopez et al. (2012) established that the elaboration of 'Tempranillo' grapes at lower pH did not prevent BA formation.

Ethanol: LAB are sensitive to ethanol at 8-10 %vol. Cocci are more sensitive than bacilli. There is some variation between various species regarding alcohol tolerance. The alcohol tolerance is influenced by pH and storage temperature (Bousbouras and Kunkee, 1971; Kelly et al., 1989).

Temperature of fermentation: LAB can normally grow in the range of 10-30 °C, out of this range their metabolism is reduced or stopped. The optimal temperature is 20-25 °C for *Oenococcus* and 25-30 °C (Kelly et al., 1989) for *Lactobacillus*. A growth of LAB can be stopped at 35 °C (Schieri, 1991). Temperature is influenced by ethanol; if the alcohol content is 13-14 % vol., the optimum temperature decreases (Ribéreau-Gayon et al., 1998). If MLF starts, LAB can complete it also at decreased temperature (Ribéreau-Gayon et al., 1998). The influence of temperature on LAB growth is also related to wine pH and SO_2 content.

Nutrition: The LAB need organic compounds for its growth: sugars, amino acids and organic acids. Sugars are the best nutrient for LAB because they provide energy and further stored in ATP molecules. Also citric acid and arginine provide energy to LAB. MLF and histidine decarboxylation are useful to conserve energy (Ribéreau-Gayon et al., 1998). LAB are not able to synthesize amino acids, to the contrary of yeasts (Schieri, 1991). Amino acids must be present in wine to induce LAB growth (Coton et al., 1999). The different strains have different needs: cocci are more exigent than bacilli. Normally, alanine, arginine, cysteine, glutamine, histidine, leucine, phenylalanine, serine, tryptamine, tyramine and valine are necessary all together or partly. Amino

acids are usually used to synthesize new proteins or to provide energy (arginine and histidine) (Ribéreau-Gayon et al., 1998). After alcoholic fermentation yeast lees undergo proteolysis and release amino acids and peptides in the medium.

Oxygen: LAB benefit from the increase of the oxidoreductive potential of wine in order to multiply or at least to improve their existence temporarily (Millet et al., 1995).

3 VITICULTURE AND WINEMAKING FACTORS AFFECTING PRODUCTION OF BIOGENIC AMINES (BA)

The contents of BA produced in wine largely depend on the abundance of amino acid precursors in the grape must, since on the whole, BA increase with an increase in amino acids contents. Amino acid content may be influenced by vinification methods, grapevine variety, geographical origin and vintage (Soufleros et al., 1998; Moreno-Arribas et al., 2000). While some factors increase the content of amino acid precursors, other factors influence the growth and the enzyme activity of microorganisms that can form BA.

3.1 Geographical origin, variety, viticultural practices and vintage year

Some amines, such as putrescine and spermidine, may already be present in grape berries (Solange et al., 2005). According to Broquedis et al. (1989) these amines are found in the pericarp of 'Cabernet sauvignon' berries. Del Prete et al. (2009) found some amines in grapes, such as ethanolamine, ethylamine and putrescine. Therefore, putrescine content in wine may be influenced more by geographical origin and grapevine variety than by winemaking practices (Landete et al., 2005). Potassium deficiency in the soil has been linked to an increase in putrescine content in plants (Adams, 1991); while water deficiency does not seem to influence the content of BA in grape berries and wines (Bover-Cid and Holzapfel, 1999). The stage of grape maturation and the soil type can also influence BA contents in the produced wine (Glória et al., 1998).

Glória et al. (1998) 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 (Vazquez-Lasa et al., 1998). Prevalence of other types of amines has also been reported in the literature, for example, 2-phenylethylamine in wines from Hungary (Hajos et al., 2000; Sass-Kiss et al., 2000). Histamine, tyramine and putrescine contents in Brazilian wines were lower compared to the red wines from other countries (Solange et al., 2005).

The mean contents of all BA, except for cadaverine, can vary significantly over vintages (Martín-Álvarez et al., 2006). In this study, results can be explained partially by the fact that the contents of most of the precursor amino acids varied between years. Moreover, differences in BA contents between vintages could also be due to the diversity of yeast and bacteria strains that are present on the grapes each year.

3.2 Alcoholic fermentation

During alcoholic fermentation, the duration of skin contact is the first factor that affects the extraction of some compounds present in grape skin, especially phenolic compounds and also of other components such as proteins, polysaccharides and amino acids which are precursors of BA. In most red wines alcoholic fermentation takes place in contact with the grape skin. During cold maceration, grape must is left in contact with the grape skins at a cold temperature prior to alcoholic fermentation. Extended maceration after alcoholic fermentation can also be applied at cool temperature to extent the extraction period. Pectolytic enzymes are added to grape musts to increase the yield of juice, to clarify the must or wine, to extract more grape derived compounds such as phenols and to facilitate pressing and filtration (Smit et al., 2008).

Soufleros et al. (1998), determined low content of BA (histamine, tyramine and putrescine) after alcoholic fermentation. Kovačević Ganić et al. (2009) found that cryomacerated wines have higher content of BA, then press wines or free-run wine. Soleas et al. (1999) found no correlation between duration of skin contact and content of

BA. On the other hand, Martín-Álvarez et al. (2006) and Bauza et al. (1995) found that duration of skin maceration is a very important variable which affects the content of BA in wine, and that longer maceration time could favor increased production of BA. These authors noted that the mean content of phenylethylamine and cadaverine were affected by the use of pectolytic enzymes, i.e. the mean contents of these amines were lower in the wines with supplements of pectinases compared with the wines produced without enzymes. They also compared wines aged and not aged with yeast lees and they found that the mean content of methylamine and putrescine were higher in wines aged on yeast lees. This was probably because through the contact of wine with lees, the proteins are initially hydrolyzed to peptides of different molecular weight and these peptides are later degraded further to amino acids and amines as the consequence of yeast and bacteria lysis (Lonvaud-Funel, 2001). These results agree in part with those of Bauza et al. (1995), who also found a higher production of tyramine and putrescine in matured wines in contact with yeast lees, where lactic acid bacteria find more peptides and free amino acids to hydrolyze and decarboxylate. Intense and prolonged maceration produce wines with higher contents of histamine, tyramine, putrescine and cadaverine (Lonvaud-Funel and Joyeux, 1994). In this respect, pH is the most important factor determining not only the biological activity of bacteria in wine but also their variety. At higher pH is more complex the bacterial microflora, because pH acts as a selective factor of microorganisms in wine. At high pH, BA are always produced in high amounts (Lonvaud-Funel, 1991; Lonvaud-Funel and Joyeux, 1994).

Also during alcoholic fermentation, yeast can play indirectly an important role in the subsequent production of BA by LAB, altering the composition of amino acids that might also be released during autolysis (Villamiel-Guerra et al., 2008; Moreno-Arribas and Polo, 2009). The first gene of ornithine decarboxylase was identified, in LAB of oenological origin, isolated from wine lees (Marcobal et al., 2004). In 2011, the OIV adopted a guide, which established and accurately described the various actions to be implemented in vineyards and cellars to minimize the presence of BA in wines. Nitrogenous fertilization of the soil, the poor state of health of the grapes combined with mould, a high must pH and the development of certain yeasts during alcoholic fermentation can all favor a moderate content of BA; thereafter, certain bacteria can, during MLF, significantly increase the presence of BA in wines. Post-fermentative maceration can also favor the formation of BA. The mentioned actions in the document are particularly recommended when a wine has high pH and is aged with few prior oenological treatments (OIV code …, 2011).

3.3 Malolactic fermentation (MLF)

MLF is an important biological process in winemaking because it reduces wine acidity and, if carried out by proper strains of LAB, it improves the flavor and the microbial stability during the wine aging (Davis et al., 1985). MLF is therefore considered essential for most red and some white wines. *Oenococcus oeni*, due to its acid tolerance, is the most frequent bacterial species occurring in wine performing spontaneous MLF and thus it is also the preferred bacterium used as a starter culture in the induced MLF. However, *O. oeni* has been found capable of producing a wide range of BA (Lonvaud-Funel, 2001; Guerrini et al., 2002).

It is considered that the main increase in content of BA in wine is related to MLF. According to *in vitro* studies conducted by Moreno-Arribas et al. (2000), none of the four commercial malolactic starter cultures examined could produce histamine, tyramine or putrescine. Inoculation with *O. oeni* starter cultures that are unable to produce BA is a feasible option for the control of these compounds in wine (Martín-Álvarez et al., 2006). It seems that co-inoculation of *O. oeni* starter cultures during the alcoholic fermentation has the potential to curb BA production even more than conventional inoculation for MLF after the completion of alcoholic fermentation (Moreno-Arribas and Polo, 2009). Recent studies by Schneider et al. (2011) have shown that the wine inoculation of starter cultures after alcoholic fermentation results in lower histamine contents than in wines with spontaneous MLF. Regarding to Lopez et al. (1971) inoculation with a commercial bacterial starter culture resulted in lower BA content after MLF has already be finished, but this advantage was lost after seven months due to the development of indigenous LAB during this period. According to their studies, in order to

reduce BA formation during conservation, it is necessary to remove LAB or inhibit their activity suddenly after the completion of MLF.

3.4 Physiochemical composition of wine

Wine physiochemical factors such as pH, temperature, SO_2 and the variety of substrates and products of fermentation can influence the content and diversity of microorganisms in the wine but can also affect decarboxylase enzyme activity and gene expression.

The product of MLF, lactic acid, was found to inhibit histidine decarboxylase activity (Rollan et al., 1995; Lonvaud-Funel, 2001), while on the contrary, lactic acids does not appear to inhibit ornithine decarboxylase activity (Mangani et al., 2005). Citric acid, as well as succinic acid, D-sorbitol, and malic acid, may also inhibit histidine decarboxylase activity and tyramine decarboxylase activity to a small extent at contents usually present in wines after MLF (Rollan et al., 1995; Moreno-Arribas and Lonvaud-Funel, 1999; Smit et al., 2008; Naila et al., 2010). Other compounds found to inhibit tyramine decarboxylase activity to different extents include glycerol, β-mercaptoethanol, lactic acid and ethanol. However, Moreno-Arribas and Lonvaud-Funel (1999) concluded that even the highest contents of these compounds likely to be present in wine will not be sufficient to prevent the formation of tyramine.

Wine pH and ethanol content at values found in wine could inhibit decarboxylase enzyme activity (Leitão et al., 2000). Histidine decarboxylase activity and consequent histamine production is enhanced at pH 3.5 and by ethanol concentrations up to 10 %vol., where the conditions for histidine transport inside the cells are more favorable due to the fluidification of the cell membrane by ethanol (Lonvaud-Funel and Joyeux, 1994). A high ethanol concentration (12 %vol. or more), as is most often found in wine, reduces the histidine decarboxylase activity by altering the physiochemical properties of the membrane and slowing down histidine transport (Rollan et al., 1995).

According to some authors, the addition of SO_2 in grape must does not affect the formation of BA during alcoholic fermentation (Gárde-Cerdan et al., 2007). Studies carried out throughout the process of industrial wine production indicate that adding of SO_2 to red wines prevents the formation of BA during wine aging and maturation (Marcobal et al., 2006). Use of SO_2 is less effective due to the high pH values of many wines, and often the content of BA can rise in sulfited wines during aging. In fact several studies have shown that red wines with high histamine concentration (>10 mg l^{-1}) are characterized by pH values above 3.7 (Landete et al., 2005; Marcobal et al., 2006).

3.5 Conditions during aging and storage of wine

After MLF Landete et al. (2005) noticed a further increase of histamine content during the first six months of storage in bottles. Other studies showed an increase of histamine contents between four and eight months after MLF in Pinot noir and Chardonnay, while some studies showed an increase of histamine after eighteen months after MLF, while putrescine and tyramine contents seemed to increase immediately following MLF in red wines (Gerbaux and Monamy, 2000; Herbert et al., 2005). A reason for increased contents of BA can be aging wine in contact with yeast lees. Martín-Álvarez et al. (2006) left the wines in contact with the lees for two months after alcoholic fermentation, before aging in barrels. The average contents of methylamine and putrescine were higher in the wines aged on lees.

Other factors of wine aging could also play an important role in the accumulation of BA. These include wine filtration using diatoms that can adsorb amino acids and cationic proteins at their surface, affecting changes in BA content during aging.

It has also been shown that the type of oak used to make barrel (American, French, etc.) used for wine aging does not affect the accumulation of BA in the final product (Jiménez-Moreno et al., 2003). On the other hand, the type of container used for MLF seems to affect the final content of BA. Significantly higher contents of BA were detected in wines undergoing MLF in stainless steel tanks compared to those in which MLF was carried in oak barrels (Alcaide-Hidalgo et al., 2007).

3.6 Prevention of biogenic amine (BA) formation and decrease of their content in wine

The most practical way to control the problem of BA production is based on inhibiting the growth of indigenous decarboxylase-positive bacteria and other microorganisms responsible for this alteration. As mentioned above, SO_2 can prevent growth of these bacteria. There is also possibility to use together lysozyme with SO_2 to delay or inhibit the growth of LAB. Lysozyme is an enzyme that can cause lysis of the cell wall of Gram-positive bacteria, and pH value of grape must or wine can be high for maintaining the activity of lysozyme.

Clarification is the best oenological treatment to decrease the BA content of wine. Clarification can be carried out by physical methods (sedimentation, flotation, centrifugation and filtration) or by fining agents addition (gelatin, albumin, casein) or by pectolytic enzymes addition (Ribéreau-Gayon et al., 1998). Other authors showed that of these oenological coadjuvants, the most effective in dropping BA content is bentonite; a decrease in BA contents was namely directly related to the amount of bentonite used (Mannino et al., 2006). Kally and Body-Szalkai (1996) observed that in red wines, 80 g hl^{-1} of bentonite reduced histamine content by 60%. According to the research by Grossmann et al. (2007), the bentonite is more effective for removal of BA, when used in the must in comparison with the wine fining, where can be removed only minor amount of BA and especially aliphatic histamine, which is adsorbed on the surface of the bentonite.

4 CONCLUSION

The occurrence of BA in wines has been extensively studied in last few years, because these substances are potentially toxic to human health in high contents. In the available literature, a lot of different factors were shown to be involved in the production of BA in wines. Most of them are related to the winemaking conditions in the cellars and some of them are viticultural factors. During winemaking it is important to consider all factors beginning from viticultural practices, alcoholic and malolactic fermentation and physiochemical composition of wine, as well as aging and storage of wine. In the majority of studies MLF appears to be the stage causing the greatest increase of BA contents. Therefore, it can be concluded that the presence of LAB, which are capable of decarboxylation of amino acids, is the main reason of BA incidence in wine. It is very important to take care of cellar sanitation, because contamination with BA can be due to the poor sanitation status. The best way to decrease BA content is wine clarification, actually the use of good clarifiers (bentonite etc).

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