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Vitamins in wine: Which, what for, and how much?

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Abstract

Vitamins are essential compounds to yeasts, and notably in winemaking contexts. Vitamins are involved in numerous yeast metabolic pathways, including those of amino acids, fatty acids, and alcohols, which suggests their notable implication in fermentation courses, as well as in the development of aromatic compounds in wines. Although they are major components in the course of those microbial processes, their significance and impact have not been extensively studied in the context of winemaking and wine products, as most of the studies focusing on the subject in the past decades have relied on relatively insensitive and imprecise analytical methods. Therefore, this review provides an extensive overview of the current knowledge regarding the impacts of vitamins on grape must fermentations, wine-related yeast metabolisms, and requirements, as well as on the profile of wine sensory characteristics. We also highlight the methodologies and techniques developed over time to perform vitamin analysis in wines, and assess the importance of precisely defining the role played by vitamins in winemaking processes, to ensure finer control of the fermentation courses and product characteristics in a highly complex matrix.

1 | INTRODUCTION

Wine is a highly complex product, characterized by the broad diversity of the aroma profiles it displays, as well as in the numerous factors that intervene in the overall composition of the final product (Goode, 2005; Waterhouse et al., 2016). Yeasts are one of the most important of these factors, notably by contributing to fermenting processes, and through their requirement of, among other things, vitamins for the optimal management of several major metabolic and signaling pathways (Combs & McClung, 2017a, 2017k; Streit & Entcheva, 2003). Consequently, vitamins are primordial for certain yeast physiological functions, such as membrane integrity (Majerus et al., 1986). Thus, it has been found that vitamin deficiencies can lead to sluggish fermentations, impairing growth and fermentation rates (Ough et al., 1989).

This requirement aspect is a major criterion for defining growth factors such as vitamins; vitamins are indeed defined as organic compounds, distinct from fats, carbohydrates, and proteins, which are essential in minute amounts for normal physiological function, and which cannot be synthetized endogenously by the organism itself. Consequently, they have to be extracted from the

Nomenclature: CE, Capillary electrophoresis; CoA, Coenzyme A; DAPA, 7,8-Diamino-pelargonic acid; DTB, Dethiobiotin; ELISA, Enzyme-linked immunosorbent assay; FAD, Flavin adenine dinucleotide; FMN, Flavin mononucleotide; GC, Gas chromatography; GTP, Guanosine-5-triphosphate; HMP-P, 4-Amino2-methyl-5-pyrimidine phosphate; HMP-PP, 4-Amino2-methyl-5-pyrimidine diphosphate; HPLC, High performance liquid chromatography; KAPA, 7-Keto-8-amino-pelargonic acid; MIR, Mid-infrared; MS, Mass spectrometry; NAD, Nicotinamide adenine dinucleotide; NADP, Nicotinamide adenine dinucleotide phosphate; NIR, Near-infrared; PLP, Pyridoxal-5′-phosphate; RP, Reversed-phase; TMP, Thiamine monophosphate; TPP, Thiamine pyrophosphate; YAN, Yeast assimilable nitrogen.

growth environment (Combs & McClung, 2017a). Yeast metabolism, however, includes the de novo synthesis of several compounds commonly described as vitamins (Perli et al., 2020), but using this term to qualify said compounds as such for the wine yeasts considered depends on their capacity to synthetize them. In an effort to distinguish these specific compounds from other growth factors, the term vitamin will nonetheless be used henceforth.

Most of vitamins exist as groups of compounds that are all chemically related and share a common similar biological activity that allows them to meet a specific nutritional requirement (Combs & McClung, 2017a; Gregory, 2012) These different forms are frequently called vitamers. It should be noted, however, that not all the vitamers of a given vitamin can be qualified as metabolically active forms, as other forms correspond to dietary forms (Combs & McClung, 2017l); as such, special emphasis will be given to the metabolically active forms, which are especially significant in wine yeast metabolic processes. These multiple vitamins highlight the broad diversity of these bioactive compounds and, as such, render their analysis in wine samples complicated, because analytical methods require the development of techniques to account for all forms of a given vitamin (Gregory, 2012; Tahir & Xiaobo, 2019).

Interestingly, although vitamins prove to be of great interest in fermentation and winemaking, with regard to their significance in numerous yeast metabolic pathways, so far no review has assessed the different aspects of vitamins in oenological contexts. Most of the research on this topic has been conducted during ancient decades, but has left certain questions unanswered, such as the detailed characterization of the impact of vitamins on wine aromas. Furthermore, the absence of any rapid and sensitive method to perform analysis of vitamins in grape must and wine matrixes in the past decades did not allow the precise determination of yeast requirements, or the geographical characterization of grapes related to them.

This review will therefore focus on presenting an overview of vitamins in the oenological context, as well as provide a state of the art on the methods used for their analysis.

2 | VITAMINS CLASSIFICATION AND ROLES

Vitamins, as opposed to other nutrients, do neither serve structural functions nor lead to the release of significant energy through their catabolism, but rather hold highly specific metabolic functions (Combs & McClung, 2017a). Interestingly, vitamins solely display few close chemical and functional similarities, and therefore are only empirically categorized (Combs & McClung, 2017a). Thirteen compounds or group of compounds are currently recognized as vitamins (Table 1), and classified according to their physical properties, being either water or fat soluble. Water-soluble vitamins generally display polar or ionizable groups, whereas fat-soluble vitamins are more commonly characterized by aromatic and aliphatic groups (Combs & McClung, 2017l). Interestingly, although fat-soluble vitamins share a structure relying on five-carbon isoprenoid units, water-soluble vitamins do not generally present similarities in structures (Combs & McClung, 2017l).

It is also interesting to note that, among the water-soluble vitamins, a distinction is commonly made between ascorbic acid and others; as such, thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folic acid, and cobalamin are generally grouped under the "B-complex" or "B-group" denomination. B-group vitamins, contrarily to ascorbic acid, have been shown to display a catalytic function, and act as coenzymes in diverse metabolisms (Baigent & Carpenter, 2016; Combs & McClung, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g, 2017h, 2017i, 2017j, 2017l).

Only few vitamins appear to be directly biologically active; as such, a metabolic conversion to another species or a binding to a given protein often stands as necessary in order for the vitamin to become metabolically active (Combs & McClung, 2017l). Vitamin metabolic roles mostly concern coenzyme activities in diverse pathways, reduction–oxidation systems, antioxidant activities, as well as membrane integrity, cellular signaling, cellular protection, and yeast respiration (Combs & McClung, 2017a, 2017l; Perli et al., 2020).

Given the nature of the vitamins present in grape materials, the present review will henceforth discuss water-soluble vitamins, cobalamin being excepted, being seldom found in foods derived from plants (Combs & McClung, 2017j), as well as water-soluble vitamin-like factor *myo*-inositol, long considered a vitamin ("vitamin B7").

For further information regarding vitamins, the authors advise referring to thorough existing publications (Combs & McClung, 2017m; Perli et al., 2020; Zempleni et al., 2006).

3 | VITAMINS IN GRAPE MUSTS AND WINES

Water-soluble vitamins, including ascorbic acid and B-group thiamine, *myo*-inositol, pyridoxine, thiamine, pantothenic acid, folic acid, biotin, and riboflavin, are important compounds in grapes and wine products, although only present in minute amounts in these matrixes. Because all the experiments to determine the vitamin contents in grape musts and wines have been carried out over previous decades with analytical methods

TABLE 1 Vitamin classification (from Combs & McClung, 2017l)

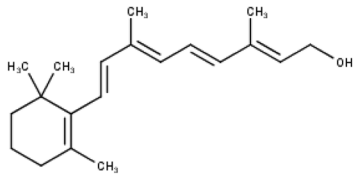
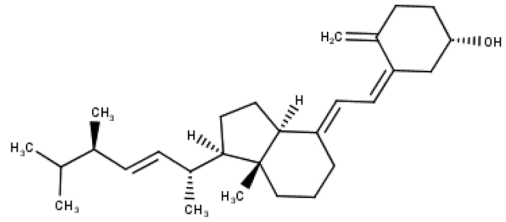
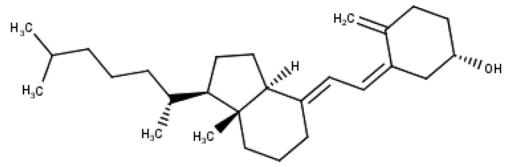
Group	Trivial designation	Solubility in organic solvents	Solubility in H_2O	Structure
Vitamin A	Retinol	+	–	
Vitamin D2	Ergocalciferol	+	–	
Vitamin D3	Cholecalciferol	+	–	

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TABLE 1 (Continued)

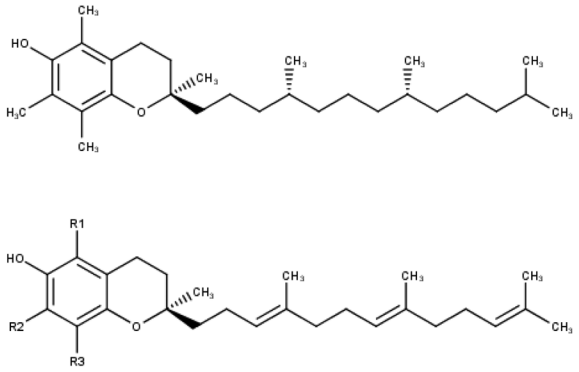
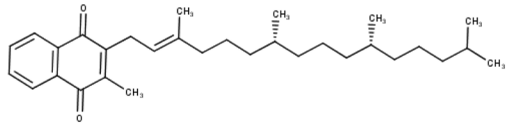
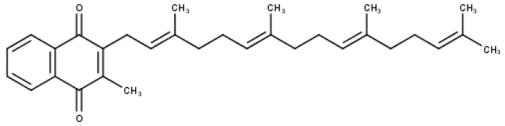
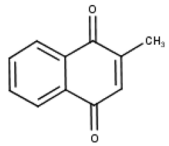
Vitamin E	Tocopherol Tocotrienol	+	–	
Vitamin K1	Phylloquinone	+	–	
Vitamin K2	Menaquinone	+	–	
Vitamin K3	Menadione	+	–	

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TABLE 1 (Continued)

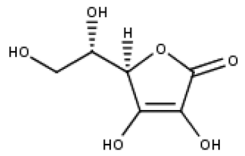
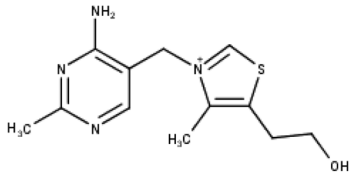
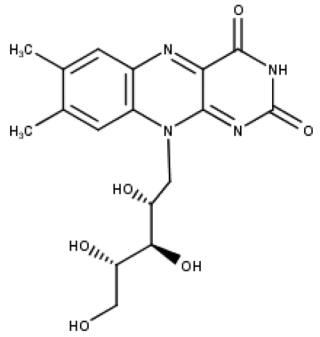
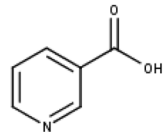
Vitamin C	Ascorbic acid	–	+	
Vitamin B1	Thiamine	–	+	
Vitamin B2	Riboflavin	–	+	
Vitamin B3	Niacin	–	+	

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TABLE 1 (Continued)

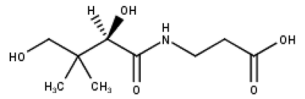
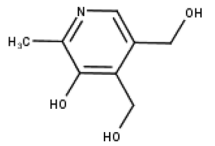
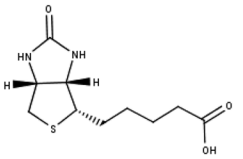
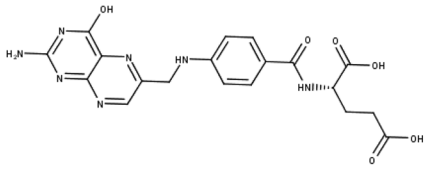
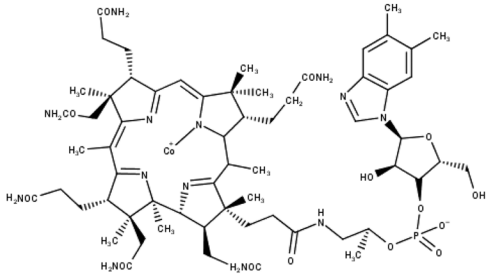
Vitamin B5	Pantothenic acid	–	+	
Vitamin B6	Pyridoxine	–	+	
Vitamin B8	Biotin	–	+	
itamin B9	Folic acid	–	+	
Vitamin B12	Cobalamin	–	+	

TABLE 2 Vitamer proportion of sun-dried raisins for thiamine, niacin, and pyridoxine (from Panagopoulou et al., 2019)

	Thiamine vitamers		Niacin vitamers		Pyridoxine vitamers	
	T	TPP	NM	NA	PM	PN
Proportion	71.9% ± 2.2%	31.0% ± 3.3%	56.2% ± 20.2%	44.0% ± 19.8%	43.1% ± 4.3%	57.3% ± 5.1%

Abbreviations: T, free thiamine; TPP, thiamine pyrophosphate; NM, nicotinamide; NA, nicotinic acid; PM, pyridoxamine; PN, pyridoxine.

of low sensitivity, no certainty exists regarding their proper ranges in such products.

To our knowledge, no study has been carried out to distinguish the vitamer proportions of each vitamin in grape musts and wines. However, a study performed on sun-dried raisins for a few vitamers (Panagopoulou et al., 2019) provided an initial estimation of their distribution tendency in grapes (Table 2).

3.1 | Vitamin contents in grape musts

3.1.1 | Ascorbic acid (C)

Vitamin C is the generic descriptor for compounds possessing, qualitatively, the biological activity of ascorbic acid, that is, 2,3-didehydro-l-threo-hexano-1,4-lactone, also occurring in its oxidized form, dehydroascorbic acid (Combs & McClung, 2017b). This water-soluble vitamin has a structure relying on a six-carbon lactone possessing a 2,3-enediol structure, and acts as a major antioxidant in metabolic systems (Combs & McClung, 2017b).

As such, ascorbic acid possesses the capacity of scavenging molecular oxygen before it undergoes oxidation reactions with phenolic compounds (Bradshaw et al., 2011). Interestingly, although being deprived from any vitamin properties, ascorbic acid isomer erythorbic acid possesses identic oxidation–reduction properties (Ewart et al., 1987), and can therefore similarly be used as a reducing agent in enology (Ribéreau-Gayon et al., 1977). Ascorbic acid functions as an oxidation–reduction system with unstable oxidized form dehydroascorbic acid (Makaga-Kabinda-Massard & Maujean, 1994), the reaction being catalyzed by iron and cooper.

The subsequently formed electrons then are susceptible of contributing to the reduction of certain wine constituents, such as the ferric iron involved in the iron casse wine issues (Ribéreau-Gayon et al., 2006). Ascorbic acid oxidation, in addition, leads to the formation of hydrogen peroxide H_2O_2, which can strongly impact wine properties (du Toit et al., 2006; Oliveira et al., 2011; Waterhouse & Laurie, 2006).

In addition, ascorbic acid also presents a protective effect against must oxidations catalyzed by tyrosinase and laccase, standing as a substrate to the latter (Dubernet et al., 1977), limiting their action by monopolizing oxygen through its fast reaction speed, rather than inhibiting the enzymes (Ribéreau-Gayon et al., 2006).

It is also interesting to note that the quinones produced through oxidation reactions can be reduced back to their associated phenols by the coupled oxidation of ascorbic acid (Cheynier & da Silva, 1991), therefore influencing wine composition and aroma profile.

Ascorbic acid content in grape musts has been shown to range between 30 and 572 mg/L (see Table 3), the high disparity in content measured resulting in particular from the dates of the experiments performed and the low sensitivity of the methods employed. It can therefore be assumed that ascorbic acid content does not actually reach such a high maximal value. Interestingly, this concentration decreases continuously during fermentation processes, and is reduced by at least half by the end of fermentation (Ournac, 1966), dropping to concentrations ranging between 1 and 30 mg/L (Genevois & Ribéreau-Gayon, 1947; Moreno & Peinado, 2012; Ournac, 1966), a decrease that has been attributed to enzymatic oxidation (Lodi, 1943).

It is also interesting to note that there does not seem to be any significant difference between white and red wines in terms of ascorbic acid content (Moreno & Peinado, 2012). Aging also significantly impacts vitamin C content in wines, because young wines present higher concentrations than older ones, this decrease being continuous over time (Ournac, 1966).

3.1.2 | Thiamine (B1)

Thiamine, also known as vitamin B1 or aneurin, is a water-soluble vitamin belonging to the B complex, whose trivial designation is 3-(4-amino-2-methylpyrimidin-5-pyrimidinyl)−5-(2-hydroxyethyl)−4-methylthiazolium (Combs & McClung, 2017c). Thiamine consists of a pyrimidine ring and a thiazole ring, both connected by a carbon link (Combs & McClung, 2017c). Although the most biologically active form of thiamine appears to be thiamine pyrophosphate (TPP), also known as cocarboxylase, the vitamin also exists intracellularly as thiamine monophosphate (TMP) and thiamine triphosphate (Perli et al., 2020).

Thiamine contents in grape musts have been reported to range between 80 µg/L and 1.2 mg/L (see Table 3), their average ranging between 0.1 and 1 mg/L. Interestingly, this

TABLE 3 Water-soluble vitamin contents of grape musts and juices (mg/L)

Reference	Hall et al. (1956)	Peynaud and Lafourcade (1958)	Castor (1953)	Juhász et al. (1987)	Matthews (1959) (bottled juices)	Radler (1957)	Burger et al. (1956) (frozen juices)
Assay	MA, thiochrome	MA	MA	MA	MA	MA	MA, thiochrome, photometry
T	0.29 to 0.75	0.16 to 0.45	0.12 to 0.47	0.08 to 0.30	Trace to 0.25	–	0.17 to 0.23
RF	0.12 to 0.20	0.003 to 0.060	0.06 to 0.26	0.01 to 1.13	Trace to 0.47	–	0.20 to 0.35
Na	1.55 to 2.49	–	–	–	–	–	1.40 to 2.60
NA[a]	–	–	0.79 to 3.75	–	1.41 to 2.13	1.80 to 8.80	–
NM[a]	–	0.86 to 2.56	–	–	–	–	–
PA	0.45 to 1.00	0.50 to 1.38	0.51 to 1.38	0.16 to 1.02	0.38 to 0.74	0.40 to 3.50	0.25 to 0.48
PN	0.60 to 1.06	0.16 to 0.53	0.48	0.33 to 0.88	Trace to 0.17	0.30 to 2.90	0.14 to 0.26
MI	–	380 to 710	388	–	340 to 482	–	–
B	–	0.002 to 0.004	0.002	–	0.006 to 0.016	0.001 to 0.060	–
FA	0.01 to 0.04	–	–	–	Trace to 0.003	–	0.02 to 0.05
AA	–	–	–	–	–	–	30 to 72
Reference	Perlman and Morgan (1945)	Ournac (1966)	Hagen et al. (2008)	Derradji-Benmeziane et al. (2014)	Dani et al. (2007)	Ough and Kunkee (1968)	
Assay	MA	nd	MA	Titration	Titration	MA	
T	0.70 to 1.20	–	–	–	–	–	
RF	0.20 to 1.45	–	–	–	–	–	
N[a]	–	–	–	–	–	–	
NA[a]	–	–	–	–	–	–	
NM[a]	–	–	–	–	–	–	
PA	0.40 to 10.50	–	0.21 to 1.26	–	–	–	
PN	0.70 to 1.45	–	–	–	–	–	
MI	–	–	–	–	–	–	
B	–	–	0.0001 to 0.0039	–	–	0.0006 to 0.0068	
FA	–	–	–	–	–	–	
AA	–	30 to 60	–	123 to 308	44 to 572	–	

Abbreviations: AA, ascorbic acid; B, biotin; FA, folic acid; I, inositol; MA, microbiological assay; NM, nicotinamide; NA, nicotinic acid; PA, pantothenic acid; P, pyridoxine; RF, riboflavin; T, thiamine. MA, microbial assay; nd, method employed non displayed.

[a]Due to the confusion often made among nicotinamide, nicotinic, and total niacin in early studies, it is not to be excluded that this numbers represent, in fact, other forms of the B3 vitamin.

vitamin is characterized by the capacity of being accumulated in high amounts by yeasts (Ough et al., 1989). Red wines appear to hold higher thiamine concentrations than white wines (Schanderl, 1950), seemingly indicating that exocarps and seeds are richer in this compound than pulps and juices are. Thiamine contents almost entirely disappear during alcoholic fermentation, as wine is estimated to possess only 3% to 5% of the initial concentration in fresh juices (Hall et al., 1956), and generally, thiamine content appears to be maintained during wine aging (Perlman & Morgan, 1945).

3.1.3 | Riboflavin (B2)

Riboflavin is a water-soluble vitamin from the B group, whose trivial designation is 7,8-dimethyl-10-(1′-d-ribityl)isoalloxazine. The compound was previously known as vitamin B2, vitamin G, or lactoflavin (Combs & McClung, 2017l), and exists in two metabolically active phosphorylated forms, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) (Combs & McClung, 2017l). The vitamin consists of a substituted isoalloxazine nucleus containing reducible nitrogen atoms, as well as a ribityl side chain (Combs & McClung, 2017d).

Riboflavin contents in grape musts have been shown to range between 3 μg/L and 1.45 mg/L (see Table 3), their average ranging between 1 and 100 μg/L, increasing to concentrations between 8 and 133 μg/L in white wines, and 0.47 to 1.9 μg/L in red wines (Ribéreau-Gayon, Peynaud, Sudraud, et al., 1975). This augmentation results notably from riboflavin biosynthesis performed by yeast *Saccharomyces cerevisiae* during alcoholic fermentation processes (Santos et al., 1995; Tamer et al., 1988). As such, it seems highly probable that riboflavin in musts and wines results from yeasts rather than extracted from the solid parts of the grapes harvested (Ournac, 1970).

The photosensitivity of riboflavin may often lead to rapid depletions in its levels in wine while aging (Moreno & Peinado, 2012); however, this diminution appears to occur faster in white wines than in red ones (Peynaud & Lafourcade, 1958), seemingly indicating the protective effect of dark colors on riboflavin, as well as the positive action of tannins that bind riboflavin and therefore limit its photoactivation (Jackson, 2008).

3.1.4 | Niacin (B3)

Niacin, also known as vitamin B3, is the generic descriptor for a B-group water-soluble vitamin and a generic descriptor for pyridine 3-carboxylic acid and derivatives, including both nicotinamide and nicotinic acid, that exhibit a nicotinamide biological activity (Combs & McClung, 2017l), which depends on the structural presence of a pyridine nucleus substituted with a β-carboxylic acid or associated amine, in which the nitrogen is capable of undergoing reversible redox reactions, adjacent to open pyridine carbon atoms (Combs & McClung, 2017e). Niacin exists under several forms in grape musts and wine media, and can be found in the free nicotinamide forms nicotinic acid, nicotinamide, ethyl nicotinate, nicotinuric acid, nicotinamide adenine dinucleotide (NAD), and nicotinamide adenine dinucleotide phosphate (NADP) (Lafourcade et al., 1956), the latter two being the metabolically active forms (Jackson, 2008).

Nicotinamide content in grape musts ranges between 0.86 and 2.56 mg/L (see Table 3), although the majority of contents reported are in the range of a few milligrams per liter. In addition, the products resulting from red grape varieties display higher contents than white ones (Castor, 1953). However, this concentration drops to values between 0.11 and 0.42 mg/L in wines (Castor, 1953; Lafourcade et al., 1956), this significant decrease being associated with the high consumptions exerted by yeasts, in spite of their capacity to synthetize the compound. However, some species, such as *Torulaspora delbrueckii*, lead to unchanged nicotinamide content in wines (Lafourcade et al., 1956).

Nicotinic acid concentrations reach the same average magnitudes as nicotinamide and have been reported to range between 0.79 and 8.80 mg/L (see Table 3). Nicotinic acid has been demonstrated to increase malic acid fermentation speeds when added to the fermenting medium (Peynaud, 1956).

3.1.5 | Pantothenic acid (B5)

Pantothenic acid, also named vitamin B5, is a water-soluble vitamin, whose trivial designation is dihydroxy-β,β-dimethylbutyryl-β- alanine, formerly named pantoyl-β-alanine. This compound has the particularity of existing in two metabolically active forms, that is, a coenzyme A (CoA) and an acyl-carrier protein, that play key roles in metabolism, functioning as a coenzyme in fatty acid metabolism (Combs & McClung, 2017h).

Grapes were reported to contain an average of 8.5 and 6.8 mg/L pantothenic acid in red and white cultivars, respectively, its high range of variations in content suggesting that limitations may occur during the fermentation processes, where the must was characterized by low concentrations (Hagen et al., 2008). It appears that the compound is extracted in high proportions from the grapes to the musts, because 66% to 93% of the initial content can be found in the musts (Hall et al., 1956), leading to must concentrations ranging between 0.16 μg/L and 10.50 mg/L

(see Table 3), although most of the studies presented ranges averaging at contents of 0.1 to 1 mg/L.

Additional losses are to be observed during aging, ranging from 12% to 61% in a 5 years period (Castor, 1953).

3.1.6 | Pyridoxine (B6)

Pyridoxine, also called vitamin B6, is one of the eight water-soluble vitamins in the B complex, characterized by a tetra-substituted pyrimidine ring, linked to a methyl, an hydroxyl, and two methyl-hydroxyl groups (Perli et al., 2020). The vitamin exists in two active forms, pyridoxamine-5′-phosphate and pyridoxal-5′-phosphate (PLP), that can be converted from one form to the other (Combs & McClung, 2017l).

Amounts of pyridoxine in grapes reach an average of 1.25 mg/L with red cultivars, but differ and drop to 0.88 mg/L with white cultivars (Hall et al., 1956). A total of 50% to 90% of pyridoxine contained by grapes are extracted in the musts, leading to concentrations that have been reported to range between 0.14 and 2.9 mg/L (see Table 3), their average ranging between 0.1 and 1 mg/L, before further decreasing when reaching the final wine product (40% in white wines and 60% in red wines, respectively) (Hall et al., 1956), therefore showing a significant loss during fermentation.

3.1.7 | *myo*-Inositol

myo-Inositol is the major form of inositol observed, and is a water-soluble vitamin, structured as a hydroxylated cyclic six-carbon compound, whose trivial designation is cis-1,2,3,5-trans-4,6-cyclohexanehexol (Combs & McClung, 2017k). It is also the only stereoisomeric form of cyclohexitol to present a biological activity (Combs & McClung, 2017k), whereas two minor (scyllo- and chiro-) forms are also found in wine products (Waterhouse et al., 2016).

Inositol contents were reported to range between 340 and 710 mg/L in grape musts (see Table 3), sufficient to integrally cover yeast requirements (Ournac, 1970). No significant diminution in inositol contents is observed in wines; however, a difference in concentrations has been reported between white and red wines, reaching 220 to 730 mg/L and 290 to 334 mg/L, respectively (Ribéreau-Gayon, Peynaud, Ribéreau-Gayon, et al., 1975). Inositol, which is a stable compound, is, however, at risk of disappearing through microbial fermentation during or following malolactic fermentation (Ournac, 1970).

3.1.8 | Biotin (B8)

Biotin, also known as vitamin B8, is a water-soluble vitamin, whose trivial designation is *cis*-hexahydro-2-oxo-1H-thieno[3,4-d]imidazole- 4-pentanoic acid, and formerly known as vitamin H or coenzyme R. The structure of biotin is formed by an imidazole, which is fused to a sulfur tetrahydrothiophene ring, substituted with a valeric acid chain (Perli et al., 2020).

Grapes have been reported to contain low amounts of biotin when compared to other fruits (Radler, 1957), its concentrations, however, varying between vine cultivars (Ough & Kunkee, 1968), because, in addition, red grapes have been shown to contain more biotin than white grapes (Ough & Kunkee, 1968). In red grape juices, biotin contents indeed reach an average of 2.85 μg/L, whereas they drop to 1.47 μg/L in white grape juices (Ough & Kunkee, 1968). This significant difference, however, appears to be typical for all B-group vitamins (Hall et al., 1956). More generally, biotin content in grape musts has been reported to range between 0.1 and 60.0 μg/L in previous studies (see Table 3), therefore asserting the low concentrations displayed by this vitamin in such products. In addition, it has been demonstrated that biotin content drops by 95% during alcoholic fermentation (Castor, 1953), leading to lowered concentrations in wines than in grape musts.

3.1.9 | Folic acid (B9)

Folic acid, also called pteroylmonoglutamic acid or vitamin B9, is the generic descriptor for all compounds sharing its biological activity, a group of heterocyclic compounds based on the *N*-[(6-pteridinyl)methyl]-p-aminobenzoic acid skeleton conjugated with glutamic acid residues (Combs & McClung, 2017l). Pteroylglutamic acid is considered as the representative form of the folates group, whereas its metabolically active forms are pteroylpolyglutamates (Combs & McClung, 2017l). The group includes a large number of pteridine derivatives, their pteridine nucleus being differently hydrogenated, capable of binding single-carbon units to nitrogen in positions 5 and 10, and characterized by glutamyl residues (Combs & McClung, 2017i).

Folic acid content in grape musts ranges between 3 and 50 $\mu g/L^{-1}$ (see Table 3), although most of the contents reported are of a magnitude of several micrograms per liter, and those concentrations decrease slightly to reach 0.4 to 4.5 μg/L in wines (Moreno & Peinado, 2012). In addition, no diminution in these contents has been observed during wine aging (Ournac, 1970), even though folic acids present a light lability.

3.2 | Impact of winemaking practices on vitamin contents in wine products

In addition to the significant influence of the original grape material on the must and wine vitamin contents, it appears that winemaking practices are able to modulate and strongly impact the concentrations that are to be found in such products.

3.2.1 | Addition of sulfites

Sulfiting processes lead to a nearly complete loss of thiamine in wines (Peynaud & Lafourcade, 1958). Indeed, bisulfite has been shown to trigger the cleavage of thiamine, which disappears to form (6-amino-2-methylpyrimid-5-yl)methanesulfonic acid and 5-,B-hydroxyethyl-4-methylthiazole (Leichter & Joslyn, 1969). Diminutions in riboflavin content following sulfite additions have been reported (Hall et al., 1956; Perlman & Morgan, 1945), although no agreement exists on the matter, because contradictory conclusions have also been drawn (Peynaud & Lafourcade, 1958). Sulfite additions have also been shown to protect pantothenic acid (Perlman & Morgan, 1945) and *myo*-inositol (Peynaud & Lafourcade, 1955) from bacterial degradations.

3.2.2 | Addition of clarifying agents

Additions of potassium ferrocyanide and bentonite have been demonstrated to have significant effects on several B-groups vitamins, including thiamine, riboflavin, pantothenic acid, pyridoxine, folic acid, and biotin, leading to decreases that can range between 9% and 67% of losses (Champeau et al., 1963).

Likewise, kaolin additions notably impact vitamin concentrations in wines, leading significant niacin, biotin, pyridoxine, and riboflavin contents to drop from 43% to 53% in treated wines (Champeau et al., 1963).

Clarifications using gelatin and tannins, however, have been proved to slightly impact most vitamin contents, leading to decreases ranging between 4% and 18%. However, it significantly affects biotin concentrations in wine, because 61% decreases have been recorded when compared to untreated wines (Champeau et al., 1963).

3.2.3 | Vatting length and lees

Vitamin contents in wine also appear to be related to the time of racking, because a long contact period between wines and lees after the completion of fermentation allows the exsorption of vitamin resources by yeasts into the liquid medium (Ournac & Flanzy, 1967), as well as the transfer of vitamin contents from the solid part of the harvest toward the wines (Lafourcade et al., 1956). As such, longer vatting periods have been shown to lead to higher thiamine, riboflavin, and niacin contents in wines (Lafourcade et al., 1956; Moreno & Peinado, 2012; Ournac & Flanzy, 1967).

3.2.4 | Vitamin enrichment

Thiamine and ascorbic acid additions to grape musts can be operated during winemaking course. As such, enrichment can contribute avoiding depletions in these growth factors to prevent nutritional deficiencies and their resulting undesirable impacts on wines, as well as to reinforce antioxidant properties of the musts.

Thiamine enrichment

Thiamine hydrochloride can therefore be used as a processing aid, and added to musts in order to accelerate alcoholic fermentation and limit the formation of sulfur dioxide-binding compounds during alcoholic fermentation, which can allow reductions in added SO_2 doses to grape musts (Labuschagne & Divol, 2021; Organisation Internationale de la Vigne et du Vin, 2020; Ribéreau-Gayon et al., 2006). Current regulations allow for maximal legal doses of 60 mg/hl of thiamine hydrochloride added to the must (Commission Européenne, 2019; Organisation Internationale de la Vigne et du Vin, 2020). Similarly, thiamine hydrochloride can be added to base wines destined for secondary fermentation in the course of sparkling wines production, in order to ensure proper multiplication of yeasts in bottles or closed tanks during this phase. Similarly to primary fermentation regulations, a maximal legal dose of 60 mg/hl of thiamine hydrochloride added is allowed by current governances (Commission Européenne, 2019; Organisation Internationale de la Vigne et du Vin, 2020).

Ascorbic acid enrichment

Ascorbic acid can similarly be used as an additive, either in its ascorbic acid form or as erythorbic acid, to act as an antioxidant in grape products. The addition can be operated at different winemaking stages, either before the grape crushing to protect the aromatic compounds of the berry against oxidation or immediately after such crushing to gain a similar protective effect (Organisation Internationale de la Vigne et du Vin, 2020). Finally, ascorbic acid additions to wine can be performed during bottling to ensure protection against oxidation and its resulting alterations of color and flavor. Current regulations allow for maximal doses in grape musts, either through additions at

the grape or must stages, of 250 mg/L ascorbic acid; similarly, a maximal addition of 250 mg/L in wines is allowed, the final ascorbic acid dose being authorized to reach a maximal total of 350 mg/L should additions have also been made on grape or musts (Commission Européenne, 2019; Organisation Internationale de la Vigne et du Vin, 2020). However, it appears preferable to proceed to additions at concentrations between 50 and 100 mg/L, because higher additions are susceptible of affecting wine taste (Ribéreau-Gayon et al., 2006). It is advised to use both sulfur dioxide and ascorbic acid to avoid the formation of undesirable molecules, such as hydrogen peroxide, following ascorbic acid oxidation (Ribéreau-Gayon et al., 2006). Both sulfur dioxide and ascorbic acid have different antioxidant properties, because the first is characterized by a stable and delayed effect that cannot prevent iron casse, but persists even in case of subsequent oxygenations, whereas the latter has an immediate action against oxidation that is able to avoid iron casse, but cannot persist in case of prolonged contact with oxygen (Ribéreau-Gayon et al., 2006).

4 | WINE-RELATED YEASTS METABOLISM AND REQUIREMENTS

Vitamin concentrations in wines are not usually limiting in grape musts, because additions of a mixture of biotin, thiamine, *myo*-inositol, pantothenic acid, nicotinic acid, and pyridoxine in several musts only led to limited effects on fermentations (Sablayrolles & Salmon, 2001). However, growth responses were reported for 38 kinds of yeasts cultured in defined medium supplemented with various contents of vitamins; thiamine requirements appeared for 15 species, 14 for pantothenic acid, six for nicotinic acid, 36 for biotin, four for inositol, six for pyridoxine, and none for riboflavin (Burkholder, 1943). Therefore, those five vitamins have been described as essential vitamins required by yeasts (Burkholder, 1943).

In the subsequent descriptions of vitamin significance in yeast metabolisms, *Saccharomyces cerevisiae* will be described in particular, and therefore considered as a model species for other wine-related yeasts.

4.1 | Vitamin biosynthesis and uptake by wine-related yeasts

4.1.1 | Vitamin de novo biosynthesis mechanisms

Most wild-type strains of *S. cerevisiae* are phototrophic for all B-group vitamins, biotin being excepted, as its biosynthesis appears to be a variable trait between strains (Hall & Dietrich, 2007). Most strains of *S. cerevisiae* are not capable of synthetizing biotin de novo, although possessing the ability of performing the last three steps of biotin biosynthesis and generating biotin from its precursors 7-keto-8-amino-pelargonic acid (KAPA), 7,8-diamino-pelargonic acid (DAPA), or dethiobiotin (DTB) (Ohsugi & Imanishi, 1985).

B-group vitamin de novo biosynthesis pathways have be shown to be highly interconnected in the model yeast *S. cerevisiae* (Figure 1); as such, the pyrimidine substrate that ultimately leads to the formation of thiamine is synthetized in yeast cells from histidine and PLP (Zeidler et al., 2003), a phosphorylated pyridoxine vitamer, whereas the thiamine thiazole moiety synthesis has been shown to notably proceed in relationship to a reaction that consumes NAD^+ as a substrate and releases nicotinamide as a by-product (Chatterjee et al., 2007), therefore asserting the existing linkage between thiamine and niacin.

Contrarily to other biological kingdoms, yeasts and other fungi are not able of directly synthetizing ascorbic acid from aldoses, performing a de novo biosynthesis pathway leading to the formation of its five-carbon analogue, *erythro*-ascorbic acid, highly resembling the biosynthesis pathway for the formation of ascorbic acid that can be found in plants (Hancock et al., 2000). *erythro*-Ascorbic acid is synthetized from arabinose, initially oxidized by a NAD-specific arabinose dehydrogenase into the corresponding aldonolactone, that spontaneously rearranges into a more stable isomer, before being finally oxidized by an FAD-containing enzyme. The final product then spontaneously isomerizes to *erythro*-ascorbic acid (Loewus, 1999).

Although the pathway leading to the synthesis of the valeric acid side chain of biotin has still not been entirely detailed (Hall & Dietrich, 2007), it has been long established that reactions involved in the formation of biotin ring structures from intermediates KAPA and DAPA are highly conserved among both yeasts and bacteria. This pathway corresponds, successively, to an initial conversion of KAPA to DAPA by an DAPA aminotransferase, DAPA being further converted to DTB through the activity of a dethiobiotin synthetase (Phalip et al., 1999), before the final conversion of DTB to biotin by a biotin synthase (Berkovitch et al., 2004). It is interesting to note that the first reaction step in the formation of biotin from KAPA connects biotin metabolism to pyridoxine metabolism, because the DAPA aminotransferase performing the reaction notably requires PLP as cofactor (Phalip et al., 1999).

The de novo pathway for biosynthesis of folates by yeasts is well-conserved throughout evolution, and is realized through the synthesis of folates pteridine ring (2-amino-4-hydroxy-6-hydroxymethyldihydropterin diphosphate) from guanosine-5-triphosphate (GTP),

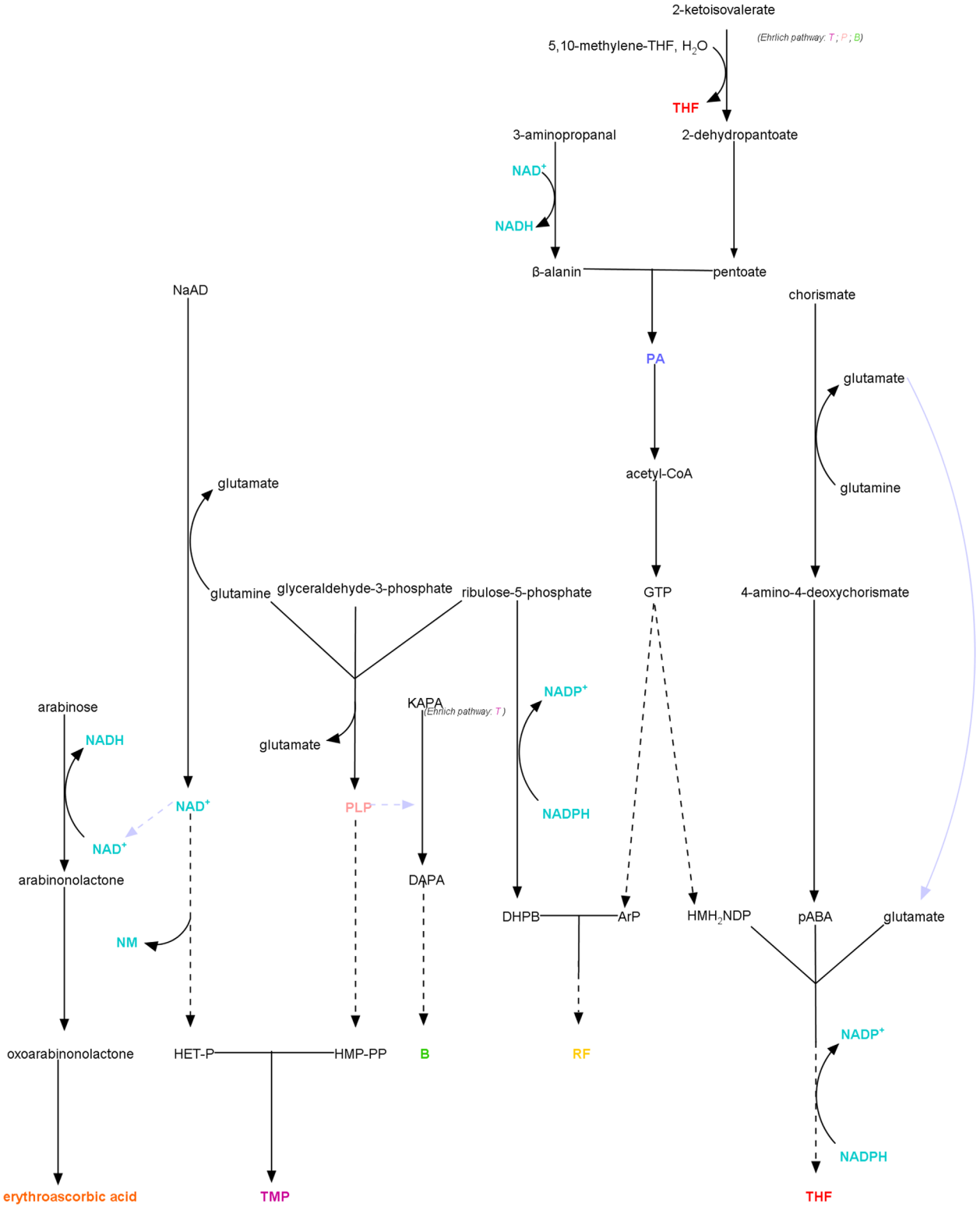


FIGURE 1 Water-soluble vitamin biosynthesis pathways interconnections in *S. cerevisiae*

ArP, 5-amino-6-ribitylamino-2,4(1H,3H) pyrimidinedione; B, biotin; DAPA, 7,8-diamino-pelargonic acid; DHPB, 3,4-dihydroxy-2-butanone 4-phosphate; eAA, erythroascorbic acid; GTP, guanosine triphosphate; HET-P, 5-(2-hydroxyethyl)−4-methyl-thiazole phosphate; HMH_2NDP, 6-hydroxymethyl-7,8-dihydroneopterin diphosphate; HMP-PP, 4-amino-5-hydroxymethyl-2-methylpyrimidine diphosphate; KAPA, 7-keto-8-amino-pelargonic acid; NaAD, nicotinate adenine dinucleotide; NAD(H), nicotinamide adenine dinucleotide; NADP(H), nicotinamide adenine dinucleotide phosphate; PA, pantothenic acid; pABA, *para*-aminobenzoic acid; PLP, pyridoxal phosphate; RF, riboflavin; THF, tetrahydrofolate; TMP, thiamine monophosphate.

common precursor to riboflavin, and its further condensation with para-aminobenzoic acid by dihydropteroate synthase (Rossi et al., 2016). The resulting compound, 7,8-dehydropteroate, undergoes, successively, the addition of a glutamate moiety, and a subsequent reduction to form the first biological form of folate, tetrahydrofolate (Rossi et al., 2016).

myo-Inositol is formed from glucose-6-phosphate through two enzyme-catalyzed reactions: an initial conversion of glucose-6-phosphate to myo-inositol-1-phosphate by the associated synthase (Donahue & Henry, 1981), before its subsequent dephosphorylation by the heterodimeric enzyme inositol 3-phosphate monophosphatase (Murray & Greenberg, 2000).

Niacin, including its essential redox cofactor NAD^+ form (Voet et al., 2006), is formed from tryptophan in a nine reactions de novo biosynthesis pathway, for which several enzymes are characterized by a strict molecular oxygen requirement, therefore explaining the necessity of ensuring nicotinic acid sufficient presence for *S. cerevisiae* in anaerobic conditions (Panozzo et al., 2002), and as a consequence, during grape carbonic macerations, notably.

Pantothenic acid is synthetized through the adenosine triphosphate-dependent condensation of pantoate with β-alanine, catalyzed by pantothenate synthetase (Leonardi & Jackowski, 2007). Interestingly, pantoate is formed from 2-keto-isovalerate (Leonardi & Jackowski, 2007; Lussier et al., 1997), a compound that, as an α-ketoacid, is linked to the Ehrlich metabolic pathway for the degradation of amino acids, in which pyridoxine, biotin, and thiamine all have crucial roles (Müller, 2014, 2018), further highlighting the intricate connections between all B-group vitamins' respective metabolisms.

De novo biosynthesis of pyridoxine's active form PLP by *S. cerevisiae* involves a reaction catalyzed by an heterodimeric enzyme PLP synthase (Raschle et al., 2005), in which glutamine is hydrolyzed to form ammonia, further channeled to the enzyme synthase subunit active site to be condensed with ribulose-5-phosphate and glyceraldehyde-3-phosphate in order to yield PLP (Hanes et al., 2008).

Riboflavin is synthetized de novo from GTP and ribulose-5-phosphate through a succession of enzymatic reactions, both compounds leading to the formation of, respectively, 5-amino-6-ribityl-aminouracil and 3,4-dihydroxy-2-butanone-4-phosphate, fused to form 6,7-dimethyl-8-ribityl lumazine through the activity of enzyme 6,7-dimethyl-8-ribityl lumazine synthase, further converted to riboflavin by riboflavin synthase (Gudipati et al., 2014). Interestingly, GTP results from acetyl-CoA conversions (Liu et al., 2020), itself being synthetized from pantothenic acid (Combs & McClung, 2017h), and its metabolism being impacted by biotin (Hoja et al., 2004; Morris et al., 1987), further connecting riboflavin metabolism to those of other B-group vitamins.

Saccharomyces cerevisiae biosynthesis of thiamine precursor 4-amino2-methyl-5-pyrimidine diphosphate (HMP-PP) is operated by the initial formation of 4-amino-2-methyl-5-pyrimidine phosphate (HMP-P) from PLP and histidine (Coquille et al., 2012), then by its subsequent phosphorylation to HMP-PP by HMP-P kinase (Kawasaki et al., 2005).

4.1.2 | Vitamin uptake from extracellular environments

In addition to de novo biosynthesis pathways, metabolic processes for the uptake of numerous vitamers from the cell extracellular environment exist (Table 4) (Paalme et al., 2014). De novo biosynthesis of vitamins by yeasts is a complex and demanding process, and such uptakes allow the cell to spare intracellular resources to permit other metabolic pathways, and are often preferentially adopted by the yeast (Ericsson et al., 2008; Paalme et al., 2014).

As such, control systems have evolved in yeasts for the biosynthesis and uptake of vitamins, such as the highly controlled gene system existing for thiamine: the expressions of the genes that encode the enzymes involved in the metabolism of thiamine in *S. cerevisiae* (THI genes) are severely repressed by exogenous thiamine and concomitantly activated by its absence, whereas TPP acts as corepressor in the processes (Nishimura et al., 1991, 1997; Nosaka et al., 2005).

4.1.3 | Bioconversion of vitamins towards their active forms upon biosynthesis or uptake

Upon biosynthesis or uptake, several vitamins require further conversions in order to attain their metabolically active forms (Table 5) and therefore, subsequently intervene in biochemical pathways.

As such, both biotin and niacin undergo bioconversions involved in their respective de novo biosynthesis pathways in order to attain their metabolically active forms. Indeed, should biotin be taken up as KAPA or DAPA through the Bio5 transporter, the compound would go through the final reaction steps of the biosynthesis pathway to form biotin (Phalip et al., 1999). Similarly, nicotinic acid obtained from the extracellular environment is converted to nicotinic acid mononucleotide, to subsequently enter the niacin de novo biosynthetic pathway and be converted toward active forms NAD and NADP (Perli et al., 2020). Nicotinamide riboside resulting from uptake through the Nrt1 transporter is then converted to both active forms as well, either

TABLE 4 Transporters for extracellular vitamin uptake in *Saccharomyces cerevisiae*

Vitamin	Transporter	Substrate	Km	Reference
Biotin	Vht1 Bio5[a]	Biotin KAPA[a] and DAPA[a]	0.3 μM Unknown	Phalip et al., 1999; Rogers & Lichstein, 1969a, 1969b; Stolz et al., 1999
Folic acid	unknown	unknown	Unknown	Bayly et al., 2001; Güldener et al., 2004; Ouameur, 2011
Inositol	Itr1p Itr2p	myo-Inositol	Unknown 0.46 mM	Lai & McGraw, 1994; Nikawa et al., 1991
Niacin	Tna1p Nrt1	Nicotinic acid Nicotinamide riboside	1.7 μM 22 M	Belenky et al., 2008; Belenky et al., 2011; Llorente & Dujon, 2000
Pantothenic acid	Fen2p	Pantothenic acid	3.5 μM	Stolz & Sauer, 1999
Pyridoxine	Tpn1p	Pyridoxine Pyridoxal Pyridoxamine	0.55 μM	Stolz & Vielreicher, 2003
Riboflavin	Mch5p	Riboflavin	17 μM	Reihl & Stolz, 2005; Spitzner et al., 2008
Thiamine	Thi7p (Thi10) Thi71p Thi72p	Thiamine	0.18 μM Unknown Unknown	Enjo et al., 1997; Mojzita & Hohmann, 2006; Singleton, 1997

[a]Bio5 takes KAPA and DAPA up into *S. cerevisiae*, although not directly providing biotin. Both compounds are precursors in the biotin biosynthesis pathway (Phalip et al., 1999), contributing to the accumulation of the vitamin in the cell.

TABLE 5 Relevant forms of wine-related vitamins and their associated metabolic functions (from Combs & McClung, 2017a, 2017h)

Vitamin group	Vitamers	Active forms	Metabolic functions
Vitamin C	Ascorbic acid Dehydroascorbic acid	Ascorbic acid Dehydroascorbic acid	Reductant in hydroxylations
Vitamin B1	Thiamine	TPP	Coenzyme for decarboxylations of 2-keto acids and transketolations
Vitamin B2	Riboflavin	FMN FAD	Coenzyme in redox reactions of fatty acids and TCA cycle.
Vitamin B3	Nicotinic acid Nicotinamide	NAD NADP	Coenzyme for several dehydrogenases
Vitamin B5	Pantothenic acid	CoA Acyl carrier protein	Coenzyme in fatty acid metabolism
Vitamin B6	Pyridoxol Pyridoxal Pyridoxamine	PLP Pyridoxamine-5′-phosphate	Coenzyme in amino acid metabolism
Inositol	*myo*-Inositol	*myo*-Inositol	Affects membrane structure and function, second messenger of Ca^{2+} signaling
Vitamin B8	Biotin	Biotin	Coenzyme for carboxylations
Vitamin B9	Folic acid Polyglutamyl folacins	Pteroylpolyglutamates	Coenzyme in single-carbon metabolism

by prior conversion toward nicotinic acid or by being phosphorylated to precursor nicotinamide nucleotide (Perli et al., 2020).

Similarly, B-group vitamins pyridoxine and thiamine are converted toward their respective active forms PLP and TPP through the action of kinases that ensure their adequate phosphorylation upon uptake (Di Salvo et al., 2011; Müller et al., 2009). If pyridoxine be taken up from the environments in forms pyridoxine or pyridoxamine, its appropriate conversion toward active form PLP requires additional oxidation following the preceding phosphorylation (Loubbardi et al., 1995). Interestingly, although bacteria are able to directly perform TPP synthesis from TMP resulting from the biosynthesis pathway, yeasts require TMP dephosphorylation toward thiamine before being able to perform the second conversion step toward TPP (Müller et al., 2009).

In an equivalent way, the biologically active coenzyme forms of riboflavin, FMN and FAD, are synthetized from the riboflavin taken up from the yeast extracellular environment by a riboflavin kinase and an FAD synthetase, respectively (Santos et al., 2000; Wu et al., 1995).

The active form, CoA, of pantothenic acid is obtained through several successive reactions, notably involving kinases and ligases (Leonardi & Jackowski, 2007); the vitamin's second metabolically active form, the acyl-carrier protein, however, can then be obtained by the action of a transferase on the previously formed CoA (Leonardi & Jackowski, 2007).

Finally, the two metabolically active forms of vitamin C, ascorbic acid and dehydroascorbic acid (Combs & McClung, 2017b), act as an oxidation–reduction system. Although the reaction involved is theoretically reversible, dehydroascorbic acid generally disappears, being instable in wine substrates (Makaga-Kabinda-Massard & Maujean, 1994).

4.2 | Roles of wine-related vitamins in yeast metabolism

Vitamins are involved in several pathways of yeast metabolism, and intervene in numerous physiological functions (Table 5), therefore highlighting their significance in yeast biological reactions, and as such, in fermentation and other notable winemaking processes.

As an antioxidant, ascorbic acid, through its different forms, composes a reversible redox system, and acts as an effective quencher of free radicals such as singlet oxygen (Combs & McClung, 2017b). In addition, ascorbic acid acts as cosubstrate for numerous enzymes, including mono- and dioxygenases (Combs & McClung, 2017b), and in particular, Fe- and 2-oxoglutarate-dependent dioxygenases, involved in a wide range of metabolic functions (Kuiper & Vissers, 2014).

Biotin plays a major role as a coenzyme in carboxylases intervening in fatty acid synthesis, sugar, and amino acid metabolisms (Streit & Entcheva, 2003). *Saccharomyces cerevisiae* presents several biotin-dependent enzymatic activities, including cytosolic, mitochondrial acetyl-CoA, and pyruvate carboxylases (Hoja et al., 2004; Morris et al., 1987; Wakil et al., 1958). As such, six carboxykinase reactions have been identified as biotin-dependent processes, including the binding of bicarbonate to acetyl-CoA through the activity of the acetyl-CoA carboxylase. This reaction, leading to the formation of malonyl-CoA, is the first committed step in fatty acid biosynthesis, therefore asserting the essential role played by biotin in those metabolic pathways. Among the other biotin-dependent carboxylases, urea carboxylase is a necessary enzyme for the utilization of nitrogen from arginine (Cooper, 1982), which is a major amino acid in grape musts (Spayd & Andersen-Bagge, 1996) and acts as a storage form for nitrogen (Whitney et al., 1973).

Biotin also plays a significant role in the Ehrlich degradation pathway for amino acids, acting as a coenzyme in the decarboxylation step (Müller, 2018), further asserting the intricate relationship between biotin and amino acid metabolisms in yeast. As it is involved in the Ehrlich pathway, biotin also contributes toward influencing the production of higher alcohols by wine-related yeasts.

In addition, yeast assimilable nitrogen (YAN) and biotin have been proved to be in interaction, as fermentation times by yeasts show their interdependence, and as such, are reduced by raising biotin contents in the presence of high YAN (Bohlscheid et al., 2007). At high YAN concentrations, yeasts are more metabolically active (Backhus et al., 2001; Bely et al., 1994; Cantarelli, 1957; Henschke & Jiranek, 1993; O'Connor-Cox et al., 1991), and would therefore express higher needs for pyruvate carboxylase, urea carboxylase, and acetyl-CoA carboxylase, consequently increasing the demand for biotin to ensure their production (Bohlscheid et al., 2007).

The principal function of folate coenzymes is to accept or donate one-carbon unit in key metabolic pathways (Bailey & Gregory, 1999) that are active in single-carbon metabolism (Combs & McClung, 2017i), and which intervene in transaminations and in ergosterol synthesis in yeast metabolism (Jackson, 2008). Folates are required for the synthesis of both methionine and purines, as well as for interconversion between serine and glycine, and are therefore crucial in yeast cellular replication and growth (Hjortmo et al., 2008). Involved in the conversion between homocysteine and methionine, folates also allow sulfur assimilation in yeasts (Boulton et al., 1999).

Inositol appears to play a significant role in contributing to the membrane integrity of yeasts (Majerus et al., 1986). This compound serves as an essential precursor in yeasts, intervening in the synthesis of phosphatidylinositol, which acts as a precursor to signaling molecules (Carman & Han, 2011; Henry et al., 2012), and plays a role in the synthesis of lipids deriving from phosphatidic acid (Henry et al., 2012).

NAD and NADP are the active forms of niacin, and are metabolically involved in dehydrogenation reactions (Jackson, 2008). They play a central role in the metabolism of ethanol, acting as a coenzyme in the conversion of ethanol to acetaldehyde, that can be further converted to acetate (Kirkland & Meyer-Ficca, 2018). Accordingly, acetate accumulation has been proved to be stimulated by nicotinic acid without affecting the yeast growth rate or biomass yield (Monk & Cowley, 1984).

In addition, NAD^+ and $NADP^+$ are essential redox cofactors for numerous oxidoreductases (Voet et al., 2006), and NAD^+ acts as a substrate for several enzymes, including cyclic ADP-ribose synthases and sirtuin protein deacetylases (Culver et al., 1997; Wierman & Smith, 2014), which are significant in the maintenance and regulation of chromatin structure, calcium signaling, life span, and DNA repair (Bürkle, 2005; Chini, 2009; Kato & Lin, 2014; Lin & Guarente, 2003; Rusche et al., 2003). NAD^+ and $NADP^+$ are both significant compounds for many oxidation–reduction reactions in yeasts (Kawai et al., 2001).

Pantothenic acid exists in two different metabolically active forms, CoA and the acyl-carrier protein, both acting as key compounds in metabolism (Combs & McClung, 2017h). CoA consists of a β-mercaptoethylamine group and a 3′-phosphoadenosine moiety bonded to pantothenic acid residues and functions as a carrier of acetyl and other acyl groups (Voet et al., 2006). CoA is the source of the prosthetic group that can be found in numerous proteins functioning as acyl, aminoacyl, and peptidyl group carriers (Leonardi & Jackowski, 2007), and is the precursor of several major compounds, such as methionine, whose biosynthesis derives from succinyl-CoA (Primerano & Burns, 1982). Interestingly, methionine itself plays a key role in the regulation of sulfide production from inorganic sulfur compounds by yeasts (Wainwright, 1970). As a precursor for CoA, pantothenate also appears to be highly significant in fatty acid metabolism, because the growing fatty acid chain is elongated by the addition of units derived from acetyl CoA, and intermediates in fatty acid synthesis are linked to groups belonging to an acyl carrier protein (Berg et al., 2002). Among the other metabolic processes in which CoA intervenes, mention can be made in particular of the oxidation of ketoacids (Mooney et al., 2002), the tricarboxylic acid cycle (Van Winkle, 1985), which is highly significant in carbohydrate and amino acid metabolisms, and choline metabolism (Jope & Jenden, 1980), proven to induce notable changes in yeasts (Ali & Karuppayil, 2018).

Pyridoxine is biologically active through, notably, its PLP form, which acts as a versatile coenzyme or substrate for more than 50 *S. cerevisiae* enzymes involved in amino-acid, glucose, lipid, and thiamine metabolisms (Perli et al., 2020). The versatility of PLP-dependent reactions relies on the compound capacity of covalently binding the substrate, and subsequently acting as an electrophilic catalyst to stabilize an iminium salt structure-containing carbanionic reaction intermediates (Müller, 2018). As such, PLP notably serves as a coenzyme for transamination, racemization, and decarboxylation reactions (Koser, 1968) through the formation of a Schiff base (John, 1995), and intervenes as a cofactor in carbohydrate and sulfur metabolism (Koser, 1968). PLP has also been thoroughly described for its interventions in amino acid metabolism (Grogan, 1988; Käck et al., 1999; Mihara et al., 1997; Palm et al., 1990), and especially for its significance in the Ehrlich pathway for the degradation of amino acids (Hazelwood et al., 2008). As such, its impact on methionine and cysteine metabolisms has been reported, thus relating pyridoxine to sulfur-containing compounds metabolisms in yeasts (Müller, 2018). In addition, PLP, as an effective singlet oxygen quencher, plays an important role against photosensitization in fungi (Bilski et al., 2000), and it has been demonstrated that pyridoxine, as well as thiamine, is a major component of yeast respiration through the activities of heme-containing enzymes (Nakamura et al., 1980).

Riboflavin functions as an enzyme cofactor, as well as a cofactor in metabolic oxidation–reduction reactions (Combs & McClung, 2017a), playing an essential role in the intermediary metabolism of carbohydrates, amino acids, and lipids and in the activation of pyridoxine and folic acid in their functional forms. It also intervenes in cellular antioxidant protection by maintaining the glutathione redox cycle and providing reducing equivalents (Combs & McClung, 2017d). These functions are handled by the vitamin through flavoproteins, coenzymes that serve as switching sites between electron donors and acceptors, and therefore acting as highly versatile redox cofactors (Combs & McClung, 2017d). FAD acts as a cofactor for 84% of the flavoenzymes, including oxidases and dehydrogenases, whereas FMN is a cofactor for 16% of them (Combs & McClung, 2017d). As such, FAD is a cofactor for pyruvate dehydrogenase (Voet et al., 2006), therefore asserting its significance in glycolysis and in the TCA cycle.

The most biologically active form of thiamine appears to be TPP, also known as cocarboxylase, involved in the conversion of pyruvic acid to carbon dioxide and acetaldehyde (Trevelyan & Harrison, 1954). Thiamine, in the form of TPP, is involved as a cofactor in numerous

TABLE 6 Wine-related yeasts requirements for vitamins: Concentrations of vitamins in grape musts and vitamin requirements for *Saccharomyces cerevisiae*

		Vitamin requirements (mg/L)			Nature of the requirement	
Vitamin	**Contents: orders of magnitude in grape musts (mg/L) (see Table 2)**	**Growth (Shinohara et al., 1996)**	**Fermentation (Shinohara et al., 1996)**	**Jones et al. (1981)**	**Shinohara et al. (1996)**	**Barnett et al. (1990)**
Ascorbic acid	10 to 1000	nd.	nd.	nd.	nd.	nd.
Biotin	0.001 to 0.1	0.002	0.020	0.005 to 0.05	Δ	○
Folic acid	0.001 to 0.1	0.002	0.0015	0.5 to 5	○	nd.
Inositol	100 to 1000	2	≥10	–	–	–
Niacin	0.1 to 1	0.4	0.4	0.1 to 1	–	○
Pantothenic acid	0.1 to 1	0.4	2	0.2 to 2	–	○
Pyridoxine	0.1 to 1	0.4	0.4	0.1 to 1	–	○
Riboflavin	0.1 to 1	0.2	0.2	0.2 to 0.25	–	nd.
Thiamine	0.1 to 1	0.4	0.4	0.1 to 1	–	Δ

Note: ○ = essential; Δ = variable; – = no requirement.

enzymes, including pyruvate decarboxylase, pentose phosphate pathway transketolase, TCA cycle dehydrogenase, and 2-oxo-glutarate dehydrogenase (Ericsson et al., 2008). These TPP-dependent enzymes play major roles in carbohydrate metabolism (Hohmann & Meacock, 1998), with TPP appearing to be especially significant in pyruvate metabolism, because it cannot be further degraded without the vitamin (Ericsson et al., 2008; Hohmann & Meacock, 1998). Therefore, the biosynthesis processes for isoleucine and valine, both resulting from pyruvate, are also dependent on TPP (Hohmann & Meacock, 1998). TPP metabolic significance has also been demonstrated in the pentose phosphate pathway, producing precursors for biosynthetic processes, and in the catabolism of branched chain amino acids (Hohmann & Meacock, 1998). TPP is, in addition, essential in the Ehrlich pathway for the degradation of amino acids, and therefore significantly impacts amino acid, alcohol, and aldehyde metabolisms in yeasts (Müller, 2014).

4.3 | Wine-related yeast requirement for vitamins

4.3.1 | Nature and extent of vitamin requirements in wine yeasts

Similar to vitamin de novo biosynthesis capacities, *S. cerevisiae* requirements for water-soluble vitamins appear to be controversial and strain dependent (Barnett et al., 1990; Burkholder, 1943; Shinohara et al., 1996). However, general conclusions regarding the existence of requirements for biotin, folic acid, niacin, pantothenic acid, pyridoxine, and thiamine can be drawn from previous studies (Table 7). Interestingly, these requirements seem to be covered by the global contents naturally displayed by grape musts (Tables 6 and 7), leading to the assumption that, should punctual deficiencies be avoided, grape musts are optimal for *S. cerevisiae* growth and alcoholic fermentation regarding vitamins.

Vitamin contents have been considered as a means of regulating contaminations by undesirable yeasts, such as *Brettanomyces bruxellensis* (Uscanga et al., 2000; Von Cosmos & Edwards, 2016). However, the great diversity and many contradictions of the conclusions on yeast vitamin requirements, associated with both the strain and the stage of vinification considered, render such strategies very difficult (Von Cosmos & Edwards, 2016). *myo*-Inositol could be considered as a means of preventing the development of undesirable yeasts such as *Brettanomyces anomalus* and *Hanseniaspora uvarum*, because both species have been described as having a strict requirement for it, whereas *Saccharomyces cerevisiae* would not be affected by its absence (Table 7); however, the high inositol contents present in musts can be assumed to naturally cover *B. anomalus* and *H. uvarum*, excluding the vitamin as a means of regulation. The variable requirement of *S. cerevisiae* regarding thiamine (Table 7) could, however, allow for the establishment of strategies to limit infections in wine: selecting a thiamine-independent *S. cerevisiae* strain would allow winemaking with thiamine-deficient musts, impairing the development of unwanted yeasts that exhibit either a strict or variable requirement toward thiamine, such as *B. anomalus*, *B. bruxellensis*, *H. uvarum*, or *Pichia anomala*. However, such strategies should be closely controlled, in order to avoid any

TABLE 7 Wine-related yeasts requirements for vitamins: Vitamin requirements of the principal grape and wine yeasts according to their growth response (Barnett et al., 1990) (ascorbic acid, folic acid, riboflavin: Data not found)

Yeast species	Biotin	*myo*-Inositol	Niacin	Pantothenic acid	Pyridoxine	Thiamine
Brettanomyces anomalus	○	○	Δ	Δ	–	○
Brettanomyces bruxellensis	Δ	–	–	–	–	Δ
Candida famata	○	–	–	–	–	○
Candida vini	○	Δ	–	–	–	○
Hanseniaspora uvarum	Δ	○	○	○	○	Δ
Lachancea thermolerans	○	–	–	–	–	–
Metschnikowia pulcherrima	–	–	–	–	–	–
Pichia anomala	–	–	–	–	–	○
Pichia fermentans	Δ	–	–	–	–	Δ
Pichia membranifaciens	Δ	Δ	–	Δ	Δ	Δ
Saccharomyces cerevisiae	○	–	○	○	○	Δ
Saccharomycodes ludwigii	Δ	○	Δ	Δ	Δ	Δ
Schizosaccharomyces pombe	Δ	○	○	Δ	Δ	Δ
Starmerella bacillaris	Δ	–	–	–	–	–
Zygosaccharomyces bailii	○	–	–	–	–	–

Note: ○ = essential; Δ = variable; – = no requirement.

detrimental effects on wine fermentations due to vitamin deficiencies.

4.3.2 | Impact of vitamin deficiencies on wine fermentations

Ascorbic acid was not found to be an essential vitamin for wine yeasts (Ough et al., 1989), and therefore, its deficiency is not assumed to have any significant effect on fermentation rates.

Absences of biotin in the extracellular environment of yeasts cultivated in synthetic medium seem to trigger decreases in fermentation rates and growth, therefore suggesting the essential character of this vitamin for yeasts (Ough et al., 1989). Biotin-requiring *S. cerevisiae* strains grown in suboptimal concentrations regarding biotin contents have been demonstrated to display alterations in their fine cell structure, including, notably, polymerization damage of cytoplasmic and vacuolar membranes, as well as splits along their lipid layer and greater numbers of large storage granules (Dixon & Rose, 1964). These effects are associated with the strict requirement for biotin to process fatty acid biosynthesis, as this compound plays major roles in maintaining membrane integrity in yeast cells (Watson, 2015). As such, this function might justify the biotin requirement by wine yeasts, contributing to their capacity to survive osmotic and ethanol stresses during fermentations. However, it appears that the low amounts of biotin present in musts are sufficient to support yeast growth, because additions to the medium do not have any impact on fermentation rates (Ough & Kunkee, 1967). It should also be noted that biotin is the only essential vitamin to the genus *Saccharomyces*, although growth is highly stimulated in the presence of other vitamins (Castor & Archer, 1956). Interestingly, biotin depletions in the medium lead yeasts to synthesize higher contents of niacin, as well as thiamine and riboflavin, whereas these contents decrease when yeasts are deficient in pantothenic acid (Ournac, 1970).

Inositol requirements and effects appear to be highly related to the presence of other vitamins in the growth media, because its effects are practically nonexistent when the compound is added by itself, but becomes a limiting factor for growth when other growth factors are supplied (Williams, 1941). However, it appears that the elimination of inositol from the growth medium tends to result in decreased fermentation rates and cell viabilities in *S. cerevisiae* strains (Ough et al., 1989), although no specific study on wine fermentations has been performed so far. A positive effect of inositol on yeasts has been observed in conditions of low temperatures, in relation to yeast membrane rigidification in response to the cold (Patton-Vogt & Henry, 1998): in limited inositol conditions, no reshaping of the membrane lipid composition appears to occur (López-Malo et al., 2015), therefore potentially affecting cell survival. In addition, low levels of inositol have been found to result in elevated formations of succinic acid (Boulton et al., 1999).

Absences of exogenous pantothenic acid were proved to result in a decrease of fermentation rates and cell viabilities of *S. cerevisiae* strains (Ough et al., 1989), and pantothenic

acid-deficient cells appear to be associated with lower oxygen uptakes (Hosono et al., 1972). In addition, deficiencies in pantothenic acid result in a significant accumulation of hydrogen sulfide (Hosono et al., 1972), a compound that tends to form reductive off-flavors in wine. Concentrations in higher alcohols and lipid metabolism in *S. cerevisiae* also appear to be affected by pantothenic acid deprivations (Wang et al., 2003), because the compound is a precursor in the synthesis of acetyl-CoA, itself intervening in higher alcohols and fatty acids biosynthesis (Combs & McClung, 2017h). The decrease in fatty acid synthesis resulting from a deficiency in pantothenic acid could lead to a risk of damaging yeast cell membranes, mostly formed by phospholipids (Watson, 2015), and therefore, jeopardizing cell survival. In addition, it has been shown that pantothenic acid triggers yeast cell death when present in growth-restricting amounts in a nitrogen-rich medium (Duc et al., 2017); therefore, the amounts of assimilable nitrogen present in the cultivation medium could lead to a modulation of losses in cell viability when in conditions of pantothenic acid deprivation.

It has been demonstrated that additions of pyridoxine in cultivation media increased fermentation rates and yeast growth in *S. cerevisiae* strains, regardless of the nitrogen content in the medium, thereby proving the effect played by pyridoxine on growth and fermentation kinetics (Xing, 2007). In addition, it has been reported that pyridoxine may impact hydrogen sulfide (H_2S) production, because the depletion of pyridoxine tends to lead to low H_2S levels (Xing, 2007). However, it should be noted that B vitamins thiamine and pyridoxine both serve as coenzymes in yeast metabolism during fermentation (Trevelyan & Harrison, 1954), and can assist each other during their respective syntheses (Chiao & Peterson, 1956), therefore ensuring normal yeast growth if the cultivation medium is deficient in one of either vitamin. In addition, thiamine and pyridoxine appear to interact, the result of which has an effect on yeast metabolism, such as yeast growth inhibition in pyridoxine-free media when supplied with additional thiamine, solved by the addition of pyridoxine (Chiao & Peterson, 1956).

Riboflavin is not considered a growth factor for *Saccharomyces* yeasts, because many species of the genus synthetize most of the quantities observed in the medium (Ournac, 1970). However, the vitamin has been demonstrated to catalyze the degradation of sulfur-containing amino acids upon activation by light (Jackson, 2008), significantly affecting their availability for wine yeasts.

Thiamine has been proved to be essential to fermenting yeasts, because a lack of exogenous thiamine in the cultivation medium tends to lead to sluggish or stuck fermentations, and this phenomenon is heightened in the presence of high assimilable nitrogen concentrations (Bataillon et al., 1996). Under thiamine-depleted conditions, it has been shown that thiamine synthesis-related proteins Thi4 and Thi5 are among the most abundant proteins in *S. cerevisiae* (Muller et al., 1999), acting as suicide enzymes in order to maintain thiamine levels, and therefore highlighting the metabolic focus given to thiamine synthesis in such limiting conditions. Thiamine serves as an activator for fermentation, improving cell growth and fermentation rates (Bataillon et al., 1996; Laser, 1941; Trevelyan & Harrison, 1954). Thiamine addition indeed has been proved to decrease pyruvate accumulation (Trevelyan & Harrison, 1954), therefore translating an increase in the conversion of pyruvate toward ethanol, which implies an increase in the fermentation rate. In addition, low levels of thiamine have been proved to affect yeast metabolism rates at low temperatures, and during lag phases, in particular, because the low metabolic rates due to low temperatures result in reduced uptakes, and therefore, in longer lag phases (Ferreira et al., 2017). Thiamine appears to affect the synthesis of other compounds during fermentation processes. For instance, it has been proved to reduce the concentrations in carbonyl compounds, because TPP, standing as an Mg^{3+} ternary complex in enzymes, is able to react as an ylid attacking carbonyl functions (Zempleni et al., 2006), therefore contributing in the decarboxylation of ketonic acids, such as pyruvic acid and α-ketoglutaric acid (Lafon-Lafourcade, 1983). Such carbonyl compounds bind to sulfur dioxide (SO_2) (Tuite & Oliver, 1991), thereby rendering SO_2 more available in the media, leading to the enhanced control of spoilage organisms (Jackson, 2008). In addition, thiamine serves as a coenzyme in sulfite and sulphate reductions, affecting H_2S formation (Eschenbruch, 1974; Wainwright, 1971). The concentrations and relative proportions of higher alcohols produced during fermentation also appear to be reduced by the vitamin (Jackson, 2008). Finally, thiamine was proved to increase the resistance of *S. cerevisiae* against oxidative, osmotic, and thermal stress through the maintenance of redox balance in yeast cells, partly independently of the functions of TPP-dependent enzymes (Wolak et al., 2014).

5 | IMPACT OF VITAMINS ON WINE SENSORY PROPERTIES

5.1 | Aromas

Vitamins intervene in several metabolisms, including those of significant aroma precursors or aromatic compounds, and therefore have indirect effects on the development of wine aroma profiles, contributing to the synthesis of several flavor-significant molecule families.

5.1.1 | Thiamine

Thiamine, as a major cofactor in several metabolisms, intervenes in the synthesis and evolution of several predominant aromatic compounds. As such, it has been demonstrated that the wine yeast production of acetic acid, a highly significant compound regarding the wine aroma profile, is stimulated dosage dependently by additions of the vitamin (Eglinton & Henschke, 1993; Hannemann, 1985). Because this compound is the major component contributing to volatile acidity (Fowles, 1992), and at high concentrations, liable to significantly impair wine by conferring it a vinegar-like character (Swiegers et al., 2005), it is of the utmost importance to control its content in wine in order to maintain a balance between the freshness provided by acidity, and the negative impact that excessive concentrations may have on flavors.

Such an effect by thiamine on acetic acid production also implies a redirection of pyruvate carbon away from succinic acid metabolic pathways, and therefore suggests an impact by vitamins on the TCA cycle and the aromatically significant compounds involved in it. Five vitamin-derived cofactors are involved in the TCA cycle, required for the reactions related to the entrance of pyruvic acid and glutamate into the cycle (Coulter et al., 2004), some notably resulting from thiamine (Lehninger et al., 2005), proving the effect of this vitamin on the biosynthesis of TCA cycle compounds, including succinic acid. Accordingly, additions of thiamine in synthetic media have been demonstrated to increase contents of succinic acid (Ribéreau-Gayon et al., 1956). Succinic acid, which contributes to wine titratable acidity, has been reported as the main nonvolatile carboxylic acid produced by yeasts during wine fermentations (Radler, 1993) and has been described as having an unusual taste, characterized by both salty and bitter descriptors (Whiting, 1976). It has also been established that succinic acid contributes to the vinosity character of wine, and to the characteristic taste of all fermented beverages (Peynaud, 1984). It can be assumed, in addition, that, by having an effect on succinic acid contents in wine, thiamine is susceptible to have a similar effect on concentrations of succinate-derived aromatic compounds, such as diethyl succinate, which occurs naturally in grapes, bringing fruity melon notes to wine (Lasik-Kurdys et al., 2018).

As with the effect of thiamine on succinate contents through its impact on the TCA cycle, it is highly possible that the vitamin has a comparable influence on citrate concentrations in wine, most probably also heightening them when thiamine contents increase. Citrate has been shown to have several effects on wine aromas; its degradation by wine acid lactic bacteria does indeed lead to increases in wine volatile acidity, although the concentrations concerned do not impair wine quality (Belda et al., 2017). Citrate fermentation, in addition, leads to the production of diacetyl, which is responsible for buttery aromas in wine (Belda et al., 2017).

One of the primary roles of thiamine in metabolism appears in its involvement in the Ehrlich pathway for the degradation of amino acids, in which TPP acts as an essential cofactor to ensure the decarboxylation reaction (Müller, 2014), from an α-ketoacid toward a fusel aldehyde, that can be further reduced to the associated higher alcohol (Hazelwood et al., 2008). Higher alcohols, also called fusel alcohols, are significant components of the flavor and aroma of alcoholic fermented beverages (Suomalainen, 1971; Suomalainen & Lehtonen, 1979), and have both positive and negative impacts on wine taste (Swiegers et al., 2005). Moderate concentrations of such compounds have been established as contributing to wine complexity and excessive contents are regarded as a negative quality factor (Rapp & Mandery, 1986), possibly resulting in strong and pungent flavors, whereas optimal levels would rather lead to fruity characters (Lambrechts & Pretorius, 2000; Nykanen et al., 1977; Swiegers & Pretorius, 2005). Among those higher alcohols, isobutanol, isoleucine 2-methylbutanol, and leucine isoamyl alcohol, in particular, have been proved to have a negative impact on wine taste (Müller, 2014, 2018). It should also be noted that further esterification of higher alcohols with carboxylic acid leads to more pleasant aromas, such as isoamyl acetate, characterized by banana flavors (Müller, 2014, 2018).

In addition, it is interesting to note that TPP deficiencies have been proved to lead to the development of off-flavors in wine, because the build-up of phosphoenolpyruvate and ketocarboxylic acids resulting from the impossibility to conduct the TPP-dependent decarboxylation leads to evasive reactions and to their subsequent off-flavor by-products (Müller, 2014).

Also resulting from amino acid degradation, 2-aminoacetophenone is the compound responsible for the atypical age tone wine defect, associated with moth powder or naphthalene descriptors, resulting from tryptophan metabolism, in which thiamine is therefore essential (Müller, 2014).

Interestingly, thiamine-dependent carboligases also significantly intervene in the biosynthesis of aroma precursors during lactic acid fermentations, leading to the formation of compounds such as diacetyl or acetoin, the latter being responsible for the further synthesis of a 3-hydroxy-4-phenylbutan-2-one compound through its condensation. Interestingly, this molecule appears to be characteristic of Riesling wines, and is associated with strong floral smells (Müller, 2014).

5.1.2 | Riboflavin

Riboflavin contributes to the occasional genesis of sulfide off-flavors in bottled wines. The vitamin indeed catalyzes the degradation of sulfur-containing amino acids when photoactivated, and therefore leads to the formation of free radicals that are susceptible to combining to form methanethiol and dimethyl disulfide, as well as hydrogen sulfide (Jackson, 2008), respectively, described as cooked cabbage and reduced tastes, corn and molasses, and finally, rotten egg (Fracassetti & Vigentini, 2018).

These compounds lead to the development of the light-struck (*goût de lumière*) fault in champagne, induced by radiation corresponding to the peaks of the absorption spectrum in riboflavin (440 and 370 nm); therefore, wines with high riboflavin contents are at a higher risk of developing the *goût de lumière* aftertaste (Jackson, 2008).

5.1.3 | Niacin, pantothenic acid, and biotin

Interestingly, the effects of thiamine on acetic acid, succinic acid, and citric acid contents in wines are very similar to those induced by niacin, pantothenic acid, and biotin. Niacin indeed leads to dosage-dependent stimulations of acetic acid production when added to the yeast growth medium (Monk & Cowley, 1984) during fermentation, and is involved in succinic acid metabolism.

Similarly, additions of pantothenic acid and biotin to yeast growth media have been proved to lead to increased contents of succinic acid (Ribéreau-Gayon et al., 1956), in accordance with the metabolic requirement for pantothenic acid-derived and biotin-derived cofactors in order to process the TCA cycle (Coulter et al., 2004; Lehninger et al., 2005; Schwartz & Radler, 1988).

As such, it can be assumed that both vitamins are susceptible to possessing an impact similar to that of thiamine on wine regarding acetic acid, succinic acid, and citric acid concentrations, most likely contributing to heightening them when added to grape musts, and therefore, acting as significant agents regarding wine acidity.

It is also interesting to note that biotin, acting as a cofactor in the decarboxylation step of the Ehrlich pathway alongside thiamine (Müller, 2014), is also a significant compound regarding the formation of the subsequent aromatic molecules.

5.1.4 | Pyridoxine

The Ehrlich pathway for the degradation of amino acids requires, in addition to TPP to process its decarboxylation reaction, the presence of pyridoxine in order to occur, therefore asserting the major role played by the vitamin in the development of aromatic compounds. The Ehrlich pathway transamination reaction, converting an amino acid to the corresponding α-ketoacid, requires PLP as a cofactor (Müller, 2018), establishing the significance of pyridoxine in the development of unpleasant aromatic compounds α-ketoacids and fusel alcohols. As such, pyridoxine is also involved in the genesis of the atypical age tone wine defect, resulting from the formation of 2-aminoacetophenone (Müller, 2018).

Interestingly, cysteine and methionine metabolisms, which are the major contributors to the development of volatile sulfur compounds, are almost exclusively related to PLP-dependent enzymes (Müller, 2018), therefore showing the predominant impact of the vitamin on the development of these off-flavor-causing molecules. Among the other sulfur-containing compounds synthetized through the Ehrlich degradation of cysteine and methionine, it is interesting to cite methanethiol and dimethyl sulfide, as well as ethanethiol (Müller, 2018), the latter being commonly described in olfactory terms as onion, rubber, and putrefaction (Fracassetti & Vigentini, 2018).

More globally, the formation of aromatic thiols is highly influenced by pyridoxine, through the β-lyase activity of PLP-dependent enzymes (Müller, 2018). Such compounds have been proved to contribute in a concentration-correlated way to the positive aroma of certain varieties, such as Sauvignon blanc, and are mostly characterized by pleasant tropical fruit descriptors. However, any excess of these molecules leads to negative impacts on wine taste, which is then often described as having "cat urine" aromas (Müller, 2018). It is also interesting to note that the Ehrlich degradation of methionine leads to the synthesis of S-adenosyl methionine, which directly contributes to the vegetative aroma profile of wines, and is a notable component, in addition to the contribution of thiol, of the character of the Sauvignon blanc variety (Müller, 2018).

5.1.5 | Ascorbic acid

In the presence of oxygen, the oxidation of ascorbic acid leads to the formation of hydrogen peroxide, a compound characterized by strong oxidant properties and susceptibility to highly altering wine composition (Elias & Waterhouse, 2010; Laurie & Waterhouse, 2006; Ribéreau-Gayon et al., 2006). Among such effects, in particular, its interaction with SO_2 has been reported, as free SO_2 is preferentially oxidized by hydrogen peroxide to form sulfuric acid (Ribéreau-Gayon et al., 2006). In addition to reducing the amounts of hydrogen peroxide present in wines, SO_2 is a compound that contributes diversely to the development

of aromas in wine by combining with different substances (Giacosa et al., 2019).

Ascorbic acid additions to wine during bottling were shown to have little impact on wine aroma and flavor during the first 6 months of aging, whereas for storage durations longer than 3 years, such additions led to wines presenting either no difference in aroma or with less oxidized and more fresh fruity aromas (Skouroumounis et al., 2005). In addition, concentrations of damascenone, a compound that has been associated with descriptors such as "fruity-flowery," "woody," "honey-like," "apple," and "baked apple" (Aznar et al., 2001; Ferreira et al., 2002; Kotseridis & Baumes, 2000; Kotseridis et al., 1998; Kováts, 1987), appear to be similar, or slightly lower in wines to which acid ascorbic was added (Skouroumounis et al., 2005). Therefore, ascorbic acid could contribute toward modulating such fruity aromas during white wine aging.

5.2 | Color

The antioxidant role exerted by ascorbic acid on the browning of wines has been extensively studied, and although it was initially concluded that ascorbic acid additions to wines could promote white browning (Bradshaw et al., 2001), it has since been established that ascorbic acid-induced browning is not necessarily accompanied by oxidized aromas and flavors (Peng et al., 1998). Such changes in white wine color as a consequence of oxidation have been theorized as resulting from reactions between the phenolic compounds in wine and oxygen. As such, yellow xanthylium salts formed from catechin are assumed to contribute to the color of aged white wines (Es-Safi et al., 2003). In addition, it has been demonstrated that Chardonnay wines with ascorbic acid additions are generally perceived as less brown than the corresponding ones without such additions (Skouroumounis et al., 2005), whereas Riesling wines do not present any significant difference related to ascorbic acid additions, although they are generally recognized as higher in yellow hue (Skouroumounis et al., 2005). More generally, it is assumed that ascorbic acid might reduce the perceived brownness of wine both by concomitantly increasing yellowness (Skouroumounis et al., 2005) and diminishing phenolic pinking (Simpson et al., 1983). In addition, ascorbic acid possesses the ability to complex iron to maintain it in its divalent state (Combs & McClung, 2017b), which contributes to preventing ferric casse in wines (Fowles, 1992). Indeed, the oxidation–reduction system formed by ascorbic acid and dehydroascorbic acid leads to the formation of two electrons during ascorbic acid oxidation to dehydroascorbic acid. The two electrons formed during the course of the reaction are able to subsequently reduce certain wine constituents, including ferric iron.

Such an oxidation to the ferric state can result in the formation of a blue casse in red wines through the formation of insoluble particles when ferric ions combine with the anthocyanins and tannins that can be found in wines (Jackson, 2008). Because it allows the formation of electrons that can successfully reduce ferric iron to its ferrous state, ascorbic acid therefore acts as an efficient agent for preventing the ferric casse wine default.

The potential effect that nicotinate and nicotinamide have on wine color could also be considered; both compounds can, through a succession of metabolism reactions, lead to the formation of a blue pigment, which appears in the form of diazodiphenoquinone in acidic media (Kanehisa & Goto, 2000; National Center for Biotechnology Information, 2020). Although the presence of such a compound in grape musts and wine samples has not been investigated, it cannot be excluded that it may be found in these products, and that it may make a tenuous contribution to wine color. Because diazodiphenoquinone is related to niacin compounds through metabolism, it can be conjectured that high concentrations of nicotinic acid or nicotinamide may contribute to modulating wine color through the formation of such a blue pigment.

Riboflavin is a yellow pigment that is relatively stable in white wines that are stored in dark conditions and at elevated temperatures, but undergoes rapid degradation when exposed to light (Dias et al., 2012; Perlman & Morgan, 1945). It can therefore be assumed that, as a pigment, this vitamin can contribute to white wine color and to its degree of yellowness. In addition, riboflavin has been found to possibly act as a protective agent, preventing or minimizing the development of catechin-type phenolic-derived pigments that are formed when white wine is exposed to short wavelength radiation, and only allows pigmentation when entirely broken down in wine (Dias et al., 2010). Pigmentation observed subsequent to riboflavin degradation has been theorized to be a degradation product of the vitamin rather than a phenolic-based pigment (Dias et al., 2010). Thus, riboflavin has been shown to undergo several reactions when exposed to light, resulting in photoproducts that contribute to pigmentation development in wine (Dias et al., 2012).

It is interesting to note that combined light and riboflavin treatment applied to *Vitis coignetiea* anthocyanins led to the production of singlet oxygen that significantly increased their degradation (Kim et al., 2010). Although the species on which the study was performed was different from the *Vitis* sp. varieties that are most commonly employed for wine production in occidental countries (e.g. *Vitis vinifera*), the wild *V. coignetiea* fruit is

similar to grape, and it could be envisioned that such a comparable effect exists in *V. vinifera* products, and therefore affects wine color.

6 | VITAMIN ANALYSIS IN GRAPE MUSTS AND WINES

Because vitamins are highly significant compounds regarding yeast metabolisms and their subsequent impact on winemaking, methods for analyzing them in grape musts and wines have been developed over the years depending on the technologies existing at each time. Such techniques have evolved over time to provide more sensitive and robust analyses, formulated for a wide range of food matrixes to implement diverse modes of quantification. However, reflecting the lack of studies focusing on vitamins in grape must and wine media in recent years, only a few solutions exist to perform vitamin analysis in such matrixes, highlighting the limited number of strategies capable of evaluating the significance of vitamins in oenology and winemaking.

6.1 | Vitamin extraction from grape must and wine matrixes

Assessment of total vitamin contents requires an extraction procedure capable of releasing the bound forms of the vitamin for forward analysis and quantification (Ball, 1994a). Therefore, the method must be efficient enough to break the bonds between the vitamin and other compounds, such as proteins, carbohydrates, or esters, without thermally or chemically impairing the molecule in the process (Ball, 1994a). Such an extraction is often performed through procedures involving acid or enzymatic hydrolysis steps, should the vitamin be unstable under acidic conditions. Extraction methods are usually specific for each vitamin and designed to ensure its stabilization; however, some procedures are applicable to carry out the simultaneous extraction of several vitamins (Chang & Zhang, 2017). Acid hydrolysis in an autoclave leads to protein denaturation and starch hydrolysis toward soluble sugars, as well as dephosphorylation of the bound forms of specific vitamins, such as pyridoxine, to their free vitamer forms (Ball, 1994a). Alternate hydrolysis steps relying on enzymatic digestions can be performed to release vitamins from their phosphorylated forms, and to release bound forms of acidic or alkaline sensible vitamins (Ball, 1994a). Takadiastase or other diastatic enzyme preparations have been suggested as means to conduct the enzymatic hydrolysis step, because they contain phosphatase activity and α-amylase (Ball, 1994a). Overnight incubations are often recommended for complete hydrolysis by takadiastase (Lumley, 1993).

As such, procedures recommended for vitamin extraction rely on the use of both hot acid digestion and enzymatic hydrolysis for thiamine, riboflavin, pyridoxine, and biotin (Ball, 1994a; Chang & Zhang, 2017)—hot acidic treatment appears to suffice to perform niacin extraction (Ball, 1994a), whereas pantothenic acid and folic acid can be thoroughly extracted using enzymatic digestions (Ball, 1994a). Ascorbic acid, however, appears to require acids such as metaphosphoric acid, oxalic acid, or acetic acid (Ball, 1994a; Chang & Zhang, 2017) in order to stabilize and avoid its oxidation toward dehydroascorbic acid by inactivating enzyme ascorbic acid oxidase.

6.2 | Assays for the determination of vitamins in grape musts and wines

Numerous techniques can be used to analyze the water-soluble vitamin contents in grape musts and wine products, ranging from microbiological to chemical assays, leading to either only the asynchronous determination of different vitamins or simultaneous determinations (Table 8).

6.2.1 | Biological and chemical determination

Microbial assays

Microbiological assays for the determination of vitamins rely on the specific growth requirements of selected microorganisms, which are usually lactic acid bacteria, as their growth presents the advantage of being easily monitored using turbidimetry, optical density assays, or lactic acid titration (Lumley, 1993). Microbial assays rely on the addition of a dilution series of the sample extract to a basal medium designed to fulfill all the test organism growth requirements, except the vitamin of interest. After inoculation with the test organism and incubation, growth will occur in proportion to the vitamin content of the sample extract, allowing precise quantification by using vitamin standards (Lumley, 1993). When growth has reached its maximum, set by the limitations in the vitamin of interest, the growth response is measured photometrically or by monitoring the metabolic products, using an appropriate assay method (Ball, 1994b), for example, turbidity or acidity.

Acid titrations

Water-soluble vitamins such as pantothenic acid or ascorbic acid present chemical properties that allow for redox

TABLE 8 Assays for the determination of water-soluble vitamins in must and wine samples

Assay	Type	Analysis	LOD	Notes	References
MA	Biological	Asynchronous	–	Poor precision and accuracy	Johnson, 1946; Zhang et al., 2018
Acid titration	Chemical	Asynchronous	2.0 mg/L	Requires an acid group in the vitamin	AOAC, 1968; da Silva et al., 2017
Spectrophotometry	Physical	Asynchronous	0.5 mg/L	Possible interferences with color	da Silva et al., 2017
HPLC–UV	Chromatography	Simultaneous	0.06 to 5.85 μg/L	–	Panagopoulou et al., 2019; Sasaki et al., 2020
HPLC–fluorescence	Chromatography	Simultaneous	0.6 to 61 μg/L	Direct analysis only for B1, B2, and B6	Gliszczyńska-Świgło & Rybicka, 2015; Hucker et al., 2011
UPLC–TQMS	Chromatography	Simultaneous	0.005 to 0.03 μg/L	Matrix effects	Lu et al., 2008; Zhang et al., 2018
GC–EI–MS	Chromatography	Simultaneous	2.00 to 500 μg/L	Biotin not compatible	Deutsch & Kolhouse, 1993; Nùñez-Vergara et al., 2001
GC-FID–MS	Chromatography	Simultaneous	2 μg/L to 5 mg/L	Biotin not compatible	Lin et al., 2000; Tanaka et al., 1989
HPTLC	Chromatography	Simultaneous	4.081 to 21.049 mg/spot	–	Urgessa, 2008
CE–MS–MS	Electrophoresis	Simultaneous	0.01 to 0.19 mg/L	Requires adaptations regarding acidity and ethanol contents	Coelho et al., 2016; do Lago & Cieslarová, 2018
CZE	Electrophoresis	Simultaneous	0 to 5 μg/L	Requires the use of LID detectors for sufficient sensitivity.	Cataldi, Nardiello, De Benedetto, et al., 2002; Cataldi, Nardiello, Scrano, et al., 2002
MEKC	Electrophoresis	Simultaneous	0.1 to 1.20 mg/L	–	Gadzala-Kopciuch et al., 2003
MEEKC	Electrophoresis	Simultaneous	0.2 to 12 μg/mL	–	Aurora-Prado et al., 2010; Yin et al., 2008
Biosensors	Diverse	Diverse	–	Extremely variable detection capacities due to high variability in biosensors	Caelen et al., 2004; Lowe, 1984
Immunoassays	Biological	Asynchronous	0.02 to 7.84 μg/L	Not extraction required	Ravi & Venkatesh, 2017; Zeng et al., 2018; Zhang et al., 2018

Abbreviations: HPTLC, high-performance-thin layer chromatography; CZE, capillary zone electrophoresis; UPLC–TQMS: ultraperformance liquid chromatography coupled with tandem quadrupole mass spectrometry; GC–EI–MS, GC coupled with electron ionization mass spectrometry; GC–FID–MS, GC coupled with flame ionization detection mass spectrometry; MEEKC, microemulsion electrokinetic chromatography; MEKC, micellar electrokinetic chromatography.

titration in the medium, thereby permitting the quantitation of the compound. Methods have been developed for both vitamins (Argade & Pande, 2016; Karabagias et al., 2020; Ma et al., 2020; Zook et al., 1956). However, such methods lead only to the determination of individual vitamins and do not render any simultaneous determination of all the vitamins present possible.

6.2.2 | Chromatography-based methods

High-performance liquid chromatography

Because water-soluble vitamins are nonvolatile and hydrophilic, the most extensively used methods for their determination are reversed-phase (RP) high-performance liquid chromatography (HPLC) procedures, relying on a C18 column and aqueous-organic phases in acidic media, to obtain the simultaneous determination of all the vitamins in one injection, with the exception of cobalamin (Amidzic et al., 2005). However, ion-exchange HPLC also appears to be used occasionally to perform vitamin analysis (Nollet, 2000). HPLC presents the advantage of separating the vitamins from interfering compounds that are inherent in complex food matrixes, such as wine, while also providing increased speed of analysis, precision, and allowing for the simultaneous quantitation of several vitamins (Nollet, 2000). However, detection sensitivity often appears to be an issue regarding vitamin analysis in

food matrixes, because their contents may occur in trace quantities. Therefore, ultraviolet absorbance appears to be a commonly employed detection method, whereas fluorescence and electrochemical detection are specifically used when physicochemical properties permit, and when increased sensitivity and selectivity are desired (Nollet, 2000).

The simultaneous separation and determination of water-soluble vitamins in wine matrixes is achieved through methods that have been developed to assess two to four vitamins together, with some procedures requiring successive chromatographic runs on the same column to perform the separation, although this can be avoided by connecting several detectors in series (Rizzolo & Polesello, 1992). Ion-paired RP chromatography has been extensively used, relying on several mobile phases and counter ions. End-capped columns have been demonstrated to provide more efficient vitamin separation, as well as more precise peak shapes (Akiyama et al., 1990; Rizzolo et al., 1991).

The speed of the analysis can be increased through the use of high temperature or ultrahigh-pressure systems; however, some vitamins present significant instability under high temperatures, thus making it necessary to avoid the use of high-column-temperature methods (Zhang et al., 2018).

Methanol–water and acetonitrile–water appear to be the most commonly used mobile phases, modified with acids, such as acetic, formic, or acetate acid (Zhang et al., 2018). In addition, HPLC analysis of vitamins is often performed by applying an elution gradient (Zhang et al., 2018).

HPLC combined with mass spectrometry (MS) is also an efficient mean of analysis. Indeed, HPLC–MS/MS, which can be considered as a confirmatory method, has become the main technique used to perform vitamin identification, because it presents higher selectivity and sensitivity than other methods (Zhang et al., 2018). HPLC–MS/MS analysis of vitamins is most frequently performed using electrospray ionization, the source being operated in positive ionization mode (Zhang et al., 2018). However, this method presents the drawback of exhibiting significant matrix effects that compromise its quantitative accuracy and selectivity (Zhang et al., 2018). High contents of organic compounds displayed by wine matrixes in this case would compete with the analytes, affecting their maximum evaporation efficiency and ionization (Zhang et al., 2018). Therefore, matrix effects should be taken into account before performing HPLC–MS/MS analysis of vitamins in wine samples, in order to adapt the method accurately.

Methods developed for vitamin analysis through HPLC procedures are described in Table 9.

Gas chromatography

Contrary to the HPLC-based method, although highly sensitive, gas chromatography (GC) analysis of water-soluble vitamins is used only infrequently (Eitenmiller et al., 2007). Most of the techniques developed to perform such analyses allow only the specific quantitation of a vitamin alone, and very few methods can be used for the concurrent determination of several vitamins. Indeed, GC is mainly used in the separation of small amounts of analytes. In addition, GC presents, with regard to grape musts and wines, the disadvantage of not allowing biotin analysis, because the molecule is polar (Dasgupta, 2019). It must therefore be taken into account that simultaneous analysis of vitamin contents in grape products in studies including biotin cannot be done with GC methods.

Thiamine is a heat-sensitive and nonvolatile compound, and therefore cannot be directly analyzed using GC techniques, which require indirect methods that involve sulfite pretreatments to split thiamine (Rizzolo & Polesello, 1992). In comparison, direct nicotinamide determination by GC using flame ionization detector appears possible, though it lacks sensitivity (Rizzolo & Polesello, 1992).

High-performance thin-layer chromatography

High-performance thin-layer chromatography presents the advantage of relatively low consumption of the mobile phase per sample basis, therefore saving analysis cost and time (Panahi et al., 2008). It also allows for the simultaneous assay of several compounds in a complex matrix (Kulkarni & Amin, 2000), thus proving very interesting for the analysis of vitamins in grape products. In addition, thin-layer chromatography methods have been proved to be efficient for the analysis of hydrophilic vitamins in biological samples containing large amounts of nonvitamin materials (Ponder et al., 2004).

6.2.3 | Other methods

Spectroscopy-based methods

Infrared spectroscopy, comprising both the near-infrared (NIR) and mid-infrared (MIR) regions of the electromagnetic spectrum, has been proved efficient in characterizing food composition, by offering precise, rapid, and nondestructive quantifications (Magwaza et al., 2012, 2014) of compounds containing polar functional groups (Blanco & Villarroya, 2002; Nicolaï et al., 2007; Obsorne et al., 1993), and, therefore, stands as suitable for analysis of water-soluble vitamins in grape products. As such, infrared spectroscopy methods have been used to process simultaneous determination of several B-groups vitamins in

TABLE 9 HPLC procedures for water-soluble vitamin analysis

Vitamin	Matrix	Column	Mobile Phase	Elution	Injection	Detection	Reference
Riboflavin Thiamine Niacin Pyridoxine	Okra (*Abelmoschus esculentus*)	RP-HPLCAgilent ZORBAX Eclipse Plus C18	A: Methanol (MeOH) B: 0.023 M H_3PO_4	Isocratic, 33:67 A:B	Flow rate: 0.5 mL/min Injection: 20 µL	UV detection (270 nm) ambient temperature	Sami et al., 2014
Thiamine Riboflavin	Beer, cider, white wine, red wine	HPLC Varian Pursuit C18 5 µm fitted with a Security Guard Cartridge C18	A: 10 mM phosphate buffer (KH_2PO_4/K_2HPO_4 at pH 6.5B: MeOH	Gradient elution 0 to 0.5 min 95:5 A:B 0.5 to 10 min 65:35 A:B 10 to 15 min 65:35 A:B15 to 16 min 95:5 A:B	Flow rate: 1 mL/min Injection: 10 µL	Fluorescence (360/425 nm for thiamine; 270/516 for riboflavin)30 °C	Hucker et al., 2011
Thiamine NiacinPyridoxine RiboflavinFolic acid	Sun-dried raisins	RP-HPLC Purospher® star RP-18 end-capped	A: 0.05% (v/v) H_3PO_4B: MeOH	Gradient elution 0 to 5 min: 1:0 A:B (isocratic) 5 to 15 min: 90:10 A:B 15 to 47 min: 67:33 A:B47 to 50 min: 1:0 A:B	Flow rate gradient: initial: 0.8 mL/min 0.6 mL/min in 5 min 0.6 mL/min for 45 min 0.8 mL/min in 3 min.Injection: 10 µL	UV detection (210/270 nm)	Panagopoulou et al., 2019
Ascorbic acid	Fruits, vegetables	RP-LCPLRP-S 5 u 100 A	A: 1.8% tetrahydrofuranB: 0.3% metaphosphoric acid		Flow rate: 0.5 mL/minInjection 10 µL	UV detection (244 nm)	Bushway et al., 1988

(Continues)

TABLE 9 (Continued)

Vitamin	Matrix	Column	Mobile Phase	Elution	Injection	Detection	Reference
Ascorbic acid Niacin pantothenic acidPyridoxine	Merlot and Cabernet grapes	RP-UPLC 1.7 µm 2.1 × 100 mm Acquity UPLC BEH C18	A: 1 % acetic acid in waterB: 1% acetic acid in acetonitrile	Linear gradient elution 0 to 2 min: 99:1 A:B 2 to 3 min: 45:55 A:B 3 to 6 min: 99:1 A:B6 to 12 min: 99:1 A:B	Flow rate: 0.5 mL/minInjection: 2 µL	Mass spectrometry (UPLC–ESI–MS/MS)Triple quadrupole probe	Kıvrak et al., 2016
NiacinInositol	Tea leaves	RP-HPLC 200 mm × 4.6 mm 5 µm i.d Hypersil BDS C8 column-Temperature: 30 °C	A: 15% acetonitrile in water (including 30 mM $HCOONH_4$ buffer solution)B: 95% acetonitrile	0 to 15 min: 30% to 75% B 15 to 20 min: 75% to 100% B20 to 25 min: initial	Flow rate: 1.0 mL/minInjection 10 µL	Fluorescence (λ_{ex} = 290 nm, λ_{em} = 290 nm)	Fan et al., 2018
Thiamine Riboflavin Niacin pantothenic acidPyridoxine	Bread, sourdough	Acquity UPLC HSS C-18 1.8 µm (2.1 × 150 mm)	A: 0.1% formic acid in waterB: 0.1% formic acid in acetonitrile	Gradient elution 0 to 3 min: 1:0 A 3 to 8.5 min: 80:2 A:B 8.5 to 10 min: 5:95 A:B10 to 15 min: 1:0 A:B	Flow rate: 2.5 mL/minInjection: 5 µL	Mass spectrometry (ESI–TOF–MS)	Mihhalevski et al., 2013

(Continues)

TABLE 9 (Continued)

Vitamin	Matrix	Column	Mobile Phase	Elution	Injection	Detection	Reference
Folic acid	Bread, white, wholemeal, multigrain	Acquity UPLC HSS C-18 1.8 µm (2.1 × 150 mm)	A: 0.1% formic acid in milli-Q waterB: acetonitrile	Gradient elution 0 to 0.2 min: 99.5:0.5 A:B 0.2 to 2.2 min: 65:35 A:B 2.2 to 3.0 min: 30:70 A:B 3.0 to 3.2 min: 30:70 A:B3.2 to 6.0: return to initial	Flow rate: 200 µL/minInjection: 20 µL	Mass spectrometry (tandem quadrupole MS in positive ion ESI mode)	(Chandra-Hioe et al., 2011)
Thiamine Riboflavin	Fortified corn extrudates	µ-Bondapak C18 column (3.9 × 300 mm, 10 µm)	A: WaterB: Methanol	Isocratic, 30:70 A:B	Flow rate: 1 mL/min Injection: 20 µLTemperature: 30 °C	Fluorescence (365/435 nm for thiamine; 450/510 nm for riboflavin)	Bilgi Boyaci et al., 2012
Thiamine Riboflavin	Complex cereal foods	Purospher® STAR RP-18e (250 × 4 mm, 5 µm particle size)	A: 12.5 mM sodium acetate in methanol:water (25:75) B: 2.4 mM sodium heptanesulfonate		Flow rate: 0.9 mL/min	UV–Vis at 268 nm	San José Rodriguez et al., 2012

(Continues)

TABLE 9 (Continued)

Vitamin	Matrix	Column	Mobile Phase	Elution	Injection	Detection	Reference
ThiamineRiboflavin Niacin Pantothenic acid PyridoxineFolic acid	Dates	Waters Symmetry C18 (250 × 4.6 mm, 5 µm particle size)	A: 5 mL trimethylamine + H_3PO_4 in 940 mL DI water at pH 3.0B: Methanol	Isocratic elution A:B at 96:4	Flow rate: 1 mL/min	UV–Vis at 210 and 280 nm, bandwidth 5 nm	Aslam et al., 2013
ThiamineRibofla NiacinPyridoxine	Feed, premixes, and supplements	Supelco C18 column (250 × 4.6 mm); 5 µm particle size	A: 4% acetonitrile in 11 mM phosphate buffer at pH 2.5B: acetonitrile	Gradient elution 0 to 6.5 min: 93:7 A:B 6.5 to 9 min: 93:7~82:18 A:B 9 to 13 min: 82:18 A:B 13 to 17 min: 82:18~50:50 A:B 17 to 19.5 min: 50:50 A:B 19.5 to 22 min: 50:50 to 93:7 A:B22 to 25 min: 93:7 A:B	Flow rate: 1 mL/min	UV at 260 and 280 nm	Rudenko & Kartsova, 2010
ThiaminePyridoxine	Apple juice, fortified fruit juices, salmon, oysters, scallop	Supelco C18 column (250 × 4.6 mm); 5 µm particle size	A: Methanol:phosphate buffer (10:90) B: 0.018 M trimethylamine at pH 3.55.	Isocratic elution	Flow rate: 1 mL/min	Electrochemical detector coupled with dual analytical cell and guard cell before injection port	Lebiedzińska et al., 2007

(Continues)

TABLE 9 (Continued)

Vitamin	Matrix	Column	Mobile Phase	Elution	Injection	Detection	Reference
Thiamine Riboflavin Niacin Pantothenic acid Folic acid Ascorbic acid (+ fat-soluble vitamins)	Green leafy vegetables	ACE-100 C18 column (100 × 2.1 mm, 3 µm particle size)	A: 10 mM ammonium acetate at pH 4.5 B: 0.1% acetic acid in methanol C: 0.3% acetic acid in methanol	HPLC–MS/MS via ESI interface	Flow rate: 1 mL/min Injection: 10 µL	DAD recording spectra from 200 to 680 nm	Santos et al., 2012

various matrixes (Wojciechowski et al., 1998; Xiao et al., 2012). Similarly, the technique has allowed for precise quantification of ascorbic acid contents in several fruits and fruit juices (Alamar et al., 2016; Andrianjaka-Camps et al., 2015; Arendse et al., 2018; Blanco-Díaz et al., 2014; Liu et al., 2015; Yang & Irudayaraj, 2002), and therefore, appears promising for extension toward the grape must and wine matrixes. Such an analysis could either be performed in the NIR–visible region of the spectrum, at wavelengths between 400 and 2500 nm (Alamar et al., 2016; Blanco-Díaz et al., 2014; Caramês et al., 2017; Liu et al., 2015), or at MIR wavelengths, comprised between 2000 and 10,800 nm (Andrianjaka-Camps et al., 2015; Arendse et al., 2018).

Electrophoresis-based separation

Capillary electrophoresis (CE) techniques are efficient quantitative methods used for the analysis of vitamins (Aurora-Prado et al., 2010; Cataldi, Nardiello, De Benedetto, et al., 2002; Cataldi, Nardiello, Scrano, et al., 2002; da Silva et al., 2013; Marshall et al., 1995; Sánchez & Salvadó, 2002; Ward et al., 1997; Yin et al., 2008), mainly used in the case of limited available amounts of samples. These methods have proved to be fast and low solvent consuming, and in which separation is performed according to compound sizes and charges (Zhang et al., 2018). CE methods are electrodriven separation procedures using a buffer to separate charged or neutral compounds, relying on their electrophoretic mobility and hydrophobicity (Yin et al., 2008). Water-soluble vitamins, such as B or C group, which can be found in grape and in wine products, possess an acidic function that allows their separation using capillary zone electrophoresis (Fotsing et al., 1997), micellar electrokinetic chromatography (Ong et al., 1991), and microemulsion electrokinetic chromatography (Yin et al., 2008).

Because wine is a complex matrix, characterized by a direct acidic and ethanolic constitution, it requires the adaptation of CE methods to ensure their efficiency, whereas modifications of ethanol contents are not required for grape-derived samples such as musts (Coelho et al., 2016). Phosphate or borate buffers characterized by an appropriate ionic strength and pH are the most commonly used electrolytes for separating numerous wine compounds, including vitamins (Coelho et al., 2016).

Capillary zone electrophoresis suffers from the low sensitivity of the absorbance-based detectors that are traditionally used in association with it, an issue that can be avoided through the use of laser-induced fluorescence detection, which is recognized to be highly sensitive (Cataldi, Nardiello, De Benedetto, et al., 2002; Cataldi, Nardiello, Scrano, et al., 2002). Accordingly, although wine electrophoresis mostly relies on UV detection (Coelho

et al., 2016) in the case of vitamins, which are present at trace levels in wine, laser-induced fluorescence appears to be a more powerful detector (Cataldi, Nardiello, De Benedetto, et al., 2002; Cataldi, Nardiello, Scrano, et al., 2002). In addition, some intrinsically fluorescent vitamins, such as riboflavin, benefit from the technique, as they can be detected directly in very low amounts in an alkaline phosphate buffer (Cataldi, Nardiello, Scrano, et al., 2002). The lack of sensitivity when using traditional detection must also be overcome through concentration steps, or the use of internal standards

Micellar electrokinetic capillary chromatography has been used for the determination of total ascorbic acid in beers, wines, and fruit drinks, and proved to present the same order of precision as HPLC, while being faster and less expensive to operate (Marshall et al., 1995).

Biosensors

Biosensors are analytical devices that are able to convert biological responses into quantifiable and processable signals (Lowe, 1984), composed of bioreceptors that specifically bind to the analytes, an interface architecture, and a transducer element. Upon transduction, the signal is converted into an electronic signal, therefore becoming usable for further processing (Grieshaber et al., 2008). Biosensors have been proved efficient in the detection of wine-related vitamins in several matrixes, including biotin (Kergaravat et al., 2012; Martín-Yerga et al., 2017; Polese et al., 2014), folic acid (Arvand & Dehsaraei, 2013; Boström Caselunghe & Lindeberg, 2000; Jamali et al., 2014), inositol (Rajaram et al., 2020; Yang et al., 2006), pyridoxine (Mostafa, 2003; Vaze & Srivastava, 2008), riboflavin (Caelen et al., 2004; Khaloo et al., 2016), and thiamine (Akyilmaz et al., 2006; Halma et al., 2017), as well as the determination of ascorbic contents in several samples, including wine, relying on the use of platinum and carbon paste electrodes (Pisoschi et al., 2011). Methods relying on the use of biosensors capable of the simultaneous detection of B- and C-group vitamins have been established, although limited in number (Baghizadeh et al., 2015; Baś et al., 2011; Gao et al., 2008; Nie et al., 2013, 2014; Revin & John, 2012). However, such techniques present interesting perspectives for the future of vitamin content analysis in must and wine samples.

Immunoassays

Immunoassays are based on the specific reaction existing between an antibody and its associated antigen. Such assays have been shown to be highly specific, highly sensitive, and simple, capable of detecting low contents of residues in short time periods (Zhang et al., 2018). Among immunoassays, enzyme-linked immunosorbent assays (ELISA) appear to be the most widespread, presenting the advantage of high sample throughput (Zhang et al., 2018). Such methods have been developed for the analysis of certain wine-related vitamins in several samples, such as biotin (Chang et al., 1994), folic acid (Hoegger et al., 2007; Iyer & Tomar, 2013), pantothenic acid (Bertelsen et al., 1988; Finglas et al., 1988; Gonthier, Boullanger, et al., 1998; Gonthier, Fayol, et al., 1998; Morris et al., 1988), and riboflavin (Ravi & Venkatesh, 2017; Zeng et al., 2018). What is more, commercial ELISA tests appear unable to detect certain thiamine forms that occur (Edwards et al., 2017). Simultaneous detection of wine-related vitamins using ELISA or electrochemiluminescence immunoassays has not been reported (Chen et al., 2020).

7 | PERSPECTIVES

Most of the studies focusing on vitamins in grape musts and wines were lead in the past decades, and essentially occurred between 1940 and 1970, and, to a lesser extent, between 1980 and 2000. As such, both the age of those investigations and the ancientness and imprecision of the methods used then only provide for obsolete information forming the current knowledge about vitamins in grape products. However, the more sensitive analytical methods that were developed in the recent years to investigate vitamin contents in other food matrixes open up a broad range of prospects in the wine science field and would allow for refined, more precise, and accurate quantification of vitamins and their vitamers in grape musts and wines. This would support a better comprehension of yeast requirements in vitamins in winemaking context, and as such, finer modulations of the processes.

In addition, the involvement of vitamins in the development of wine aromas remains mostly unexplored, and offers ground for in-depth investigation, notably through the metabolic connections existing between vitamins and aromatic molecules. As such, pyridoxine and niacin metabolisms have been proved to be directly linked to butanoate metabolism, and therefore, to the subsequent key wine aromatic compounds derived from it, such as ethyl butanoate and ethyl 2-methylbutanoate, that have been described as significant odorants of several wines (Aznar et al., 2001; Chisholm et al., 1994; Ferreira et al., 2000; Moio et al., 1995), both characterized by fruity and sweet descriptors (Aznar et al., 2001; Berger et al., 1989; Klesk & Qian, 2003; Schieberle et al., 1990), and therefore suggesting a positive effect on the product. Likewise, niacin metabolism is linked to propanoate metabolism, leading the suspicion that a link also exists with derived ethyl-propanoate. The compound has been described as responsible for the increase of fruitiness and complexity when in high levels in wines (Renault et al., 2015), and

could, similarly, evoke a positive effect of the vitamin on wine aromas. However, such involvements remain only assumptions as yet, and, as such, open the door to studies investigating their extent.

8 | CONCLUSION

Vitamins are important compounds in wine-related yeast metabolism, intervening in several key reactions, and have been proved to have major impacts on the winemaking processes. However, most of the research investigating this topic in ancient decades has resulted in imprecise knowledge on vitamin contents in grape musts and wines, as well as on their evolution during winemaking. Similarly, precise quantification of wine yeast requirements in the course of these processes has not yet been determined, and the significance of vitamins in wine sensory properties remains obscure. The broad diversity of techniques developed in recent years provides numerous perspectives for investigating the effects that vitamins have on grape musts and wine.

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M. Evers performed the bibliographical investigation and drafted the manuscript. H. Alexandre and C. Roullier-Gall contributed to the manuscript's construction, and provided bibliographical resources and critical and complementary elements to the manuscript. C. Morge, C. Sparrow, and A. Gobert provided critical and complementary elements to the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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