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MINIREVIEW ARTICLE

Plant amino acid-derived vitamins: biosynthesis and function

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Abstract Vitamins are essential organic compounds for humans, having lost the ability to de novo synthesize them. Hence, they represent dietary requirements, which are covered by plants as the main dietary source of most vitamins (through food or livestock's feed). Most vitamins synthesized by plants present amino acids as precursors (B_1, B_2, B_3, B_5, B_7, B_9 and E) and are therefore linked to plant nitrogen metabolism. Amino acids play different roles in their biosynthesis and metabolism, either incorporated into the backbone of the vitamin or as amino, sulfur or one-carbon group donors. There is a high natural variation in vitamin contents in crops and its exploitation through breeding, metabolic engineering and agronomic practices can enhance their nutritional quality. While the underlying biochemical roles of vitamins as cosubstrates or cofactors are usually common for most eukaryotes, the impact of vitamins B and E in metabolism and physiology can be quite different on plants and animals. Here, we first aim at giving an overview of the biosynthesis of amino acid-derived vitamins in plants, with a particular focus on how this knowledge can be exploited to increase vitamin contents in crops. Second, we will focus on the functions of these vitamins in both plants and animals (and humans in particular), to unravel common and specific roles for vitamins in evolutionary distant organisms, in which these amino acid-derived vitamins play, however, an essential role.

Keywords Thiamine · Riboflavin · Nicotinic acid · Pantothenate · Pyridoxal · Biotin · Folic acid · Tocopherol

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Abbreviations

AIR	5-Aminoimidazole ribonucleotide (5-amino-1-(5-phospho-D-ribosyl)imidazole)
ATP	Adenosine-5′-triphosphate
CoA	Coenzyme A
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide (Riboflavin-5′-phosphate)
GTP	Guanosine-5′-triphosphate
HET-P	4-Methyl-5-β-hydroxyethylthiazole phosphate
HMDH-PP	6-Hydroxymethyl-dihydropterin diphosphate
HMP-PP	2-Methyl-4-amino-5-hydroxymethylpyrimidine diphosphate
$NAD(P)^+$	Nicotinamide adenine dinucleotide (phosphate)
PABA	*p*-Aminobenzoate
PLP	Pyridoxal 5′-phosphate
PRPP	5-Phospho-α-D-ribose 1-diphosphate
ROS	Reactive oxygen species
SAM	*S*-adenosyl-L-methionine
THF	Tetrahydrofolate

Introduction

After Funk (1912) isolated and described the first essential organic micronutrient as an anti-beriberi factor in rice bran (later characterized as thiamine) the term used was *vitamine* ("vital amine"), because at the time it was assumed that these essential compounds responsible for many "deficiency diseases" contained amine groups (Combs 2012). Soon this final "e" was dropped, but the involvement of amino acids in vitamin biosynthesis and metabolism has been found to be very significative.

The term "vitamin" was defined empirically, based on animal/human requirements, emphasizing the loss of the ability to synthesize these compounds de novo and thus the diet requirement of these or their immediate precursors for good health and normal development (Combs 2012). Vitamin category is therefore only defined by its essentiality, caused by its function in human physiology. While one particular vitamin may play multiple metabolic and biochemical roles, others present quite narrow—but at the same time, essential—biochemical functions as cofactors, cosubstrates or through non-enzymatic mechanisms (Rébeillé et al. 2007) (see Table 1). Some vitamins have a role as antioxidants (vitamins B_6, C and E; provitamin A) and several act as cofactors or cosubstrates in redox reactions (vitamins B_2, B_3, B_5, B_6, C, E and K_1). Two vitamins (A and D) are hormonal precursors in animals; vitamin A acts as a photoreceptive cofactor in animal vision, and vitamin B_2 is a chromophore for blue light photoreceptors (Briggs 2006). Many vitamins (B_2, B_3, B_5, B_7 and B_9) are also involved in post-translational modification of enzymes, transcription factors and histones (Ryšlavá et al. 2013). Structural roles in membrane conformation have been proposed for vitamins B_1 and E, possibly affecting the membrane-associated processes like signaling, cellular trafficking, vesicular transport and the activity of proteins associated with the membrane and membrane microdomains (Bâ 2008; Brigelius-Flohé 2009).

The scope of this review is limited to those vitamins synthesized by vascular plants in whose biosynthesis amino acid metabolism is involved, namely vitamins B_1, B_2, B_3, B_5, B_7, B_9 and E. Thus, vitamins A, B_{12}, C, D and K will not be covered in this review. Here, we aim at providing an overview of the biosynthesis of amino acid-derived vitamins in plants, and how vitamin contents can be increased

Table 1 Vitamin main precursors, active forms and biochemical functions (based on in-text citations)

Vitamin	Main active forms	Vitamers (and provitamins)	Biochemical function	Main precursors
trans-Retinol (A)	–	Retinal, retinoic acid (α-carotene, β-carotene, β-cryptoxanthin)	Animal hormonal precursor Vision Antioxidant	GGPP
Thiamin (B_1)	Thiamin pyrophosphate (TPP)	Thiamin, thiamin-P, thiamin-PP, thiamin-PPP, adenosine thiamin-PPP	Decarboxylation and group transfer in carbon metabolism	AIR, Gly, NAD^+
Riboflavin (B_2)	Flavin adenine mono/dinucleotide (FMN/FAD)	–	Electron transfer Hydride transfer	D-Ribulose-5-P, GTP
Nicotinic acid (B_3)	Nicotinamide adenine dinucleotide (phosphate) ($NAD(P)^+$)	Nicotinamide	Electron transfer Hydride transfer	Asp, PRPP
Pantothenic acid (B_5)	Coenzyme A (CoA) 4′-Phosphopantetheine	–	Acyl group transfer	β-Ala, Val
Pyridoxal (B_6)	Pyridoxal 5′-P (PLP)	Pyridoxal (PL), Pyridoxine (PN), Pyridoxamine (PM); and their phosphorylated forms	Amino acid metabolism	D-Glyceraldehyde-3-P, D-ribose-5-P, Gln
Biotin (B_7)	–	–	Carboxylase	Pimeloyl-CoA, Ala
Folates (B_9)	Tetra-hydrofolic acid - Glu_n	Di- and tetra-hydrofolic acid mono- and polyglutamates	Methyl group transfer	Chorismate, GTP Glu
Cobalamin (B_{12})	Adenosylcobalamin Methylcobalamin	–	1,2-Shift of hydrogen atoms	Glutamyl-tRNA
Ascorbate (C)	Ascorbic acid	(Mono-) Dehydroascorbate	Mono-/di-oxygenase Antioxidant	Mannose
Cholecalciferol (D)	1,25-Dihydricholecalciferol	Ergocalciferol (D_2), Cholecalciferol (D_3)	Animal hormone precursor	Cholesterol
α-Tocopherol (E)	α-Tocopherol	α-, β-, γ- and δ-Tocopherol; α-, β-, γ- and δ-Tocotrienol	Antioxidant	Tyr, GGPP
Phylloquinone (K_1)	Menaquinones (K_2)	–	Electron carrier Disulfide bound formation Gamma-carboxilation	Chorismate, GGPP

AIR 5-amino-1-(5-phospho-D-ribosyl)imidazole, *Ala* alanine, *β-Ala* β-alanine, *Asp* aspartate, *CoA* coenzyme A, *GGPP* geranyl–geranyl diphosphate, *Gln* glutamine, *Glu* glutamate, Glu_n polyglutamate, *Gly* glycine, *GTP* guanosine-5′-triphosphate, NAD^+ nicotinamide adenine dinucleotide, *PRPP* 5-phospho-α-D-ribose 1-diphosphate, *Tyr* tyrosine, *Val* valine

in crops. Later, we will focus on the functions of these vitamins in plants and animals (with a particular focus on humans), defining common and specific roles for vitamins in these evolutionary distant organisms.

Amino acids in vitamin biosynthesis

A number of α-L-amino acids constitute the backbone of different vitamins (Table 1; Fig. 1). Glycine is incorporated into the thiazole moiety of thiamine—vitamin B_1—and into 5-aminoimidazole ribonucleotide (AIR)—precursor of a number of vitamins (see below), including the pyrimidine moiety of thiamine (Zrenner et al. 2006; Jurgenson et al. 2009; Goyer 2010). Aspartate is incorporated into niacin—vitamin B_3—(Katoh et al. 2006); alanine into biotin—vitamin B_7—(Alban et al. 2000); glutamate into folates (Hanson and Gregory 2011); and tyrosine into tocochromanols—vitamin E—(Garcia et al. 1999). Vitamin B_3 is de novo synthesized from tryptophan in animals, from aspartate in plants and from tryptophan or aspartate in bacteria. There is a controversy whether some grasses can also synthesize vitamin B_3 from tryptophan (Roje 2007). Curiously, pantothenate—vitamin B_5—main precursors are derived from amino acid metabolism: 2-oxoisovalerate and β-L-alanine. 2-Oxoisovalerate, as valine's 2-oxoacid, is an

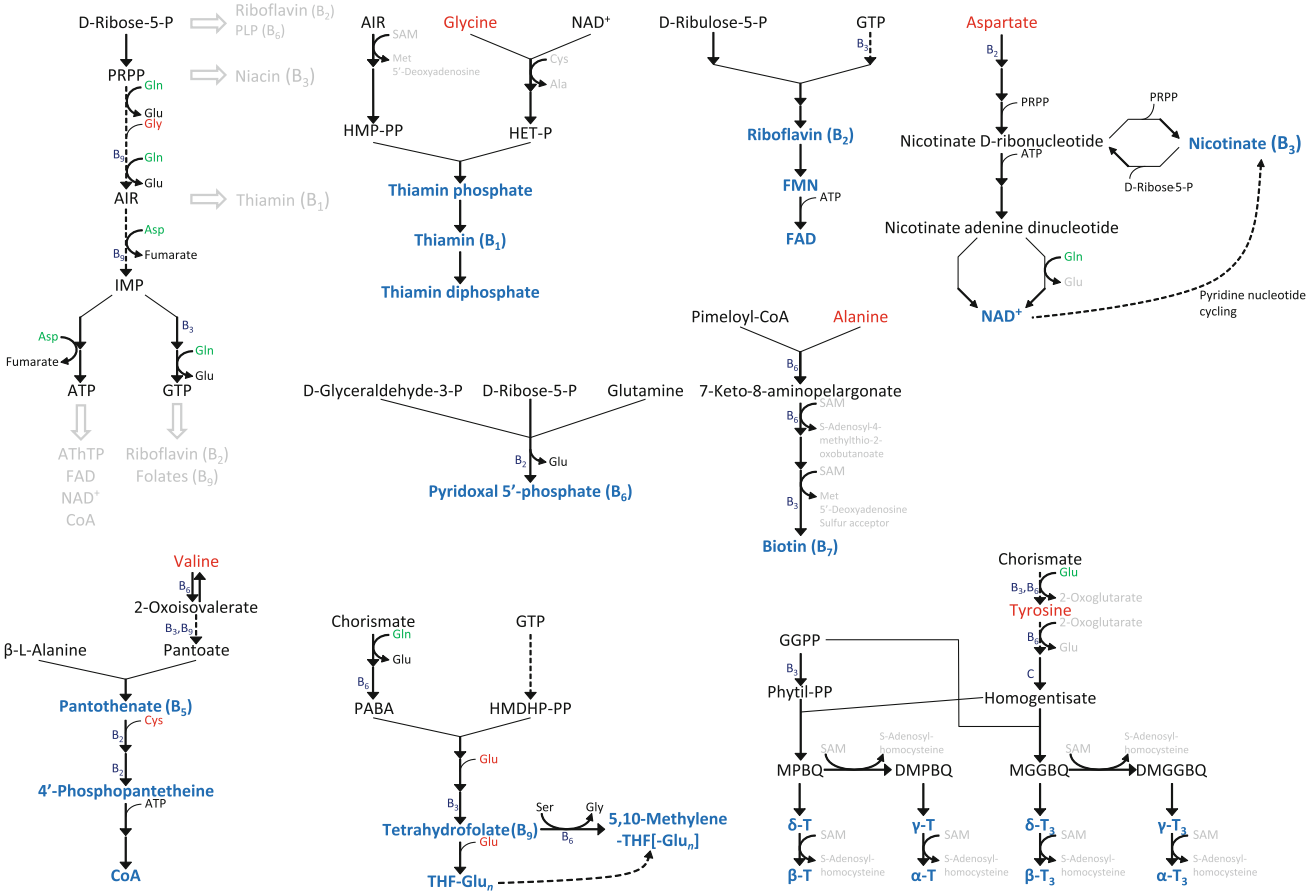

Fig. 1 Schematic plant amino acid-based vitamins and purine de novo biosynthesis pathways. *Red* denotes amino acids incorporated to the backbone of the synthesized vitamin; *green* colored, amino acids as amino group donors; and amino acids and their related compounds with other function appear in *grey*. *Light blue* points out the vitamins and their main biologically active forms, while their active forms as either cofactors or cosubstrates are indicated in *dark blue*. Unless otherwise stated, all amino acids are α-L-amino acids. *AIR* 5-amino-1-(5-phospho-D-ribosyl)imidazole, *Asp* aspartate, *AThTP* adenosine thiamine triphosphate, *ATP* adenosine-5′-triphosphate, *CoA* coenzyme A, *Cys* cysteine, *DMGGBQ* 2,3-dimethyl-5-geranylgeranyl benzoquinol, *DMPBQ* 2,3-dimethyl-6-phytyl-1,4-benzoquinol, *FAD* flavin adenine dinucleotide, *FMN* riboflavin-5′-phosphate, *Gln* glutamine, *Glu* glutamate, Glu_n polyglutamate, *Gly* glycine, *GTP* guanosine-5′-triphosphate, *HET-P* 4-methyl-5-β-hydroxyethylthiazole phosphate, *HMDHP-PP* 6-hydroxymethyl-dihydropterin diphosphate, *HMP-PP* 2-methyl-4-amino-5-hydroxymethylpyrimidine diphosphate, *IMP* inosine-5′-monophosphate, *Met* methionine, *MGGBQ* 2-methyl-6-geranylgeranyl benzoquinol, *MPBQ* 2-methyl-6-phytyl-1,4-benzoquinol, NAD^+ nicotinamide adenine dinucleotide, *PABA* *p*-aminobenzoate, *PLP* pyridoxal 5′-phosphate, *PRPP* 5-phospho-α-D-ribose 1-diphosphate, *SAM* *S*-adenosyl-L-methionine, *Ser* serine, *T* tocopherol, T_3 tocotrienol, *THF* tetrahydrofolate. Based on BRENDA (Schomburg et al. 2013), TAIR (Lamesch et al. 2011), and PlantCyc and MetaCyc databases (Caspi et al. 2012), and references in the text (color figure online)

intermediary of both its synthesis and degradation (Webb et al. 2004; Chakauya et al. 2006). In plants, there is evidence for the synthesis of β-alanine (a non-protein amino acid) from a number of precursor pathways: polyamine degradation, uracil degradation and synthesis from propionate (Kupke et al. 2003; Raman and Rathinasabapathi 2004; Chakauya et al. 2006).

Amino acids can also be dynamically incorporated and removed from a vitamin with a regulatory role. Tetrahydrofolates present a γ-polyglutamyl tail, essential for folate (vitamin B_9) metabolism and function. Folate-dependent enzymes generally prefer the polyglutamated forms—actually the complete loss of polyglutamation capacity is embryo-lethal (Mehrshahi et al. 2010; Zhou et al. 2013a)—, while membrane transporters prefer monoglutamyl forms (Suh et al. 2001). Because protein-bound folates are protected from hydrolization, the polyglutamyl tail not only regulates their function and compartmentation but also their catabolism (Suh et al. 2001).

Another main role of amino acids is amino group donation, being the pair glutamine/glutamate the main donor. Through a number of transaminases, this pair donates amino groups for the synthesis of many vitamin precursors from the de novo purine nucleotide pathway—AIR, GTP, ATP (see below, see also Table 1) (Zrenner et al. 2006)—and the synthesis of NAD^+ (active form of vitamin B_3 and precursor of the thiazole moiety of thiamine) (Roje 2007; Goyer 2010). In contrast, the glutaminase activity of the pyridoxal phosphate (PLP) synthase complex deaminates glutamine to glutamate to supply nitrogen for closing the PLP heterocycle (Mooney and Hellmann 2010). Other amino acids involved in vitamin metabolism as amino group donors are the pyridoxamine-pyruvate aminotransferase, requiring the pair Ala/pyruvate for the interconversion of pyridoxal and pyridoxamine (Huang et al. 2011), and the pair Glu/2-oxoglutarate in the synthesis of tyrosine and its downstream processing for the biosynthesis of the chromanol head of vitamin E (DellaPenna and Pogson 2006). The aspartate/fumarate pair also acts as donor of amino groups through the successive actions of a synthase and a lyase in purine de novo synthesis pathway (Zrenner et al. 2006), whose intermediates and final products are common precursors for a number of vitamins.

AIR is a common precursor for a number of vitamins. The synthesis of this shared precursor requires two transaminations (Gln/Glu), and the incorporation of one glycine molecule. Downstream, purine biosynthesis requires a first amino group from the aspartate/fumarate pair, incorporated by the successive action of a synthase and a lyase; and a second amino group from Gln/Glu transamination for GTP biosynthesis. Instead, for ATP synthesis two amino groups are incorporated from Asp/fumarate (Zrenner et al. 2006). The intermediate AIR is the immediate precursor for the pyrimidine moiety of thiamine (HMP-PP) (Goyer 2010). GTP is a common precursor for riboflavin and folates (Fischer and Bacher 2005; Roje 2007) and the ATP backbone is required for the synthesis of FAD, $NAD(P)^+$ and CoA (active forms of vitamins B_2, B_3 and B_5, respectively) (Jordan 2007). Another adenylated form of a vitamin has been described—adenosine thiamine triphosphate—but its biological role remains unclear (Bettendorff et al. 2007; Frédérich et al. 2009; Tanaka et al. 2011).

Sulfur metabolism is also involved in vitamin biosynthesis, mediated by the amino acid cysteine. Cys plays two different roles in vitamin biosynthesis: as a sulfur donor in thiamine synthesis (Goyer 2010) and as a part of the backbone of 4′-phosphopantetheine (active form of vitamin B_5) (Webb et al. 2004). Further, amino acids also act as one-carbon donors in vitamin metabolism. The methylation of tetrahydrofolate (THF), a key reaction of C_1 metabolism, is mainly catalyzed by serine hydroxymethyltransferase (SHMT) and the glycine decarboxylase complex (GDC)—two PLP-dependent enzymes—with the pair Ser/Gly as the methyl group donor (Hanson and Roje 2001; Schirch and Szebenyi 2005). One of the metabolic roles of THF is the re-methylation of homocysteine to methionine. Methionine can be adenosylated to *S*-adenosyl methionine (SAM), a donor of methyl groups in many reactions (Roje 2006), like in the last steps of vitamin E synthesis (Cheng et al. 2003; Mène-Saffrané and DellaPenna 2010). SAM involvement in vitamin biosynthesis also includes other functions of this compound as a cofactor/cosubstrate. For the synthesis of the pyrimidine moiety of thiamine, SAM is reduced to give an adenosyl radical required to isomerize AIR to HMP-P (Jurgenson et al. 2009). SAM is also involved in two steps of biotin biosynthesis. While it first acts as an amino group donor for the diaminopelargonic acid aminotransferase (Cobessi et al. 2012), it also generates an adenosyl radical and acts as a sulfur donor closing the thiophene ring of biotin by the insertion of a sulfur atom in the last step of the pathway (biotin synthase) (Patton et al. 1998; Roje 2006). Therefore, either incorporated to its backbone or as donors of amino, sulfur or methyl groups, amino acids play crucial roles in vitamin biosynthesis.

Variation in vitamin contents

Two main strategies have been exploited to increase the contents of vitamins B_1, B_2, B_3, B_5, B_7, B_9 and E in crops: (a) plant breeding and (b) metabolic engineering strategies (Tester and Langridge 2010; Fitzpatrick et al. 2012). Metabolic engineering is based on the modification of genes involved in the biosynthesis, stability, recycling, transport and catabolism of the compound of interest, or its regulation. This approach and its application to vitamins

have been widely reviewed elsewhere (Zhu et al. 2007; Fitzpatrick et al. 2012; Bock 2013) and will not be discussed here. Other factors affecting nutritional quality should, however, be additionally considered: climatic factors, plant nutrition, harvest time, processing, storage, food and feed processing and bioavailability (Welch and Graham 2004; Kumar and Aalbersberg 2006; Lešková et al. 2006; Martin 2013; Miller and Welch 2013).

Levels of vitamins B_1, B_2, B_3, B_5, B_7, B_9 and E can vary greatly between plant species and within species—among varieties and cultivars—, thus implying potential for nutritional enhancement through the exploitation of micronutrient enrichment traits (Welch and Graham 2004). Nowadays, exploiting this natural variability relies on the combination of comprehensive molecular mapping and high-throughput (and preferably cheap, simple, fast and reliable) phenotyping methods—vitamin determination—to implement an efficient selection process (Welch 2002; Ibrahim and Juvik 2009; Tester and Langridge 2010). But this approach can be limited by the heritability of the vitamin content, which can be low in some cases (Shewry et al. 2011). Approaches to increase the concentrations of these vitamins should also consider the possibilities offered by the manipulation of environmental factors (temperature, light exposure, mild abiotic stresses) through agronomic practices (Poiroux-Gonord et al. 2010; Miller and Welch 2013).

Treatments with plant growth regulators and/or elicitors are also an approach to increase the contents and stability of vitamins in vegetables. For example, foliar applications of methyl jasmonate, absciscic acid or salicylic acid increase folate levels up to twofold, while increasing its storage stability, in coriander (*Coriandrum sativum* L.) (Puthusseri et al. 2012). Likewise, ethylene activates *p*-hydroxyphenylpyruvate dioxygenase during the ripening of climacteric fruits, thus increasing vitamin E levels (Singh et al. 2011).

Most of the enzymes involved in the de novo synthesis of these vitamins have been identified and the respective genes are cloned in plants, usually after the identification of genes homologous to those previously described in prokaryotes and fungi. The regulation of these pathways is a fast advancing research field. On the other side, *salvage* pathways and its regulation, interconversions between vitamin forms, and the intracellular trafficking of vitamins and their intermediates are largely unknown despite its potential importance in the control of metabolic fluxes and contents within the cell (Asensi-Fabado and Munné-Bosch 2010; Gerdes et al. 2012; Morandini 2013). As discussed above, amino acids and purine de novo biosynthesis pathways, together with metabolites generated by different glycolysis pathways (see Table 1; Fig. 1), are the main precursors of vitamins. Nitrogen status (deprivation, fertilization) or different N sources (ammonia, nitrate) have therefore an impact on the amino acid profile (Scheible et al. 2004; Foyer 2010; Marschner 2012). Besides, although the de novo synthesis of purines is tightly regulated, it dynamically varies with developmental and environmental cues (Zrenner et al. 2006). Ultimately, the regulation of vitamin biosynthetic pathways is less understood in plants than in bacteria or yeast. In the latter organisms, their regulation has been thoroughly studied, especially in those species used for the production of vitamins by fermentation for food and feed biofortification, or as a raw material for cosmetic and other industries (Eggersdorfer et al. 2012). Although most elements of these biosynthetic pathway are conserved between plants and bacteria and/or yeast, its regulation is usually not identical (Webb et al. 2007; Goyer 2010). In general, the main regulatory mechanism of vitamin pathways in plants is feedback inhibition by final and/or intermediate products (Roje 2007). Hence, many metabolic engineering approaches might have been limited by lack of knowledge about this and other limiting control mechanisms (Morandini 2013).

Inorganic nitrogen fertilization is known to increase the concentrations of vitamin B_1 in field assays, while effects on vitamin B_2 are less consistent (Mozafar 1993). However, other studies indicate that there are no major differences on any vitamin content under different fertilizer dosages in both natural and agricultural environments (Brandt et al. 2011). Besides, meta-analyses of organic fertilization and its effects on vitamin content, especially under organic production practices, report few well-controlled studies capable of making valid comparisons or classify these as insufficiently documented (Mozafar 1994; Woese et al. 1997; Bourn and Prescott 2002; Hunter et al. 2011). It should be noted that most field studies only evaluate a limited number of vitamins; actually, the most commonly analyzed are β-carotene, ascorbate and tocopherols (vitamins A, C and E). Among the vitamin B group, the most evaluated are thiamine and riboflavin. Only vitamin C seems to be consistently enhanced by organic fertilization, while the effects on β-carotene (provitamin A) and tocopherols levels are more disparate. Few studies have analyzed the effects on other vitamins, but surprisingly there is evidence of an increase of B_1 and B_{12} (being B_{12} not synthesized by plants). This phenomenon has been explained by the use of some organic fertilizers (manure, sewage sludges) that often contain high concentrations of vitamins that plants are able to uptake (Mozafar 1994; Bito et al. 2013).

In developed countries, supplementation with vitamins and other micronutrients of some foods and feeds is common, or even compulsory. It is the case of all white flour in Australia, the UK or Canada [in the last case mandatorily

enriched with thiamine, riboflavin, niacin, folic acid and iron (Food and Drug Regulations 2013)]. Nowadays, even with easier and cheaper production by chemical synthesis or fermentation, such postharvest supplementation remains mostly inaccessible or too expensive to people and farmers in developing countries (Eggersdorfer et al. 2012).

As discussed below, biotic, abiotic and developmental stressors significantly raise the levels of certain vitamins in varieties resistant to those stresses, with potential roles in the mitigation of their effects. The application of moderate stresses through agronomic practices (without effects on production) is an especially cost-effective approach to enhance the nutritional quality of products. At the same time, the rise of certain vitamin contents can confer crops an increased resistance to many biotic and abiotic stresses, with a better production both quantitatively and qualitatively. From metabolic engineering to old and novel agronomic practices, nutritional enhancement of crops for animal and/or human nutrition presents multiple complementary and potentially synergic approaches.

Functions of amino acid-based vitamins in plants

Although the category of vitamins is defined by its essentiality for humans (essential as unable to be de novo synthesized, requiring a dietary intake), vitamins are also "essential" for plants, where they generally play the same essential roles in metabolism plus those characteristic of plant metabolic pathways. Complete loss of function of enzymes required for de novo synthesis of vitamins B_1, B_2, B_3, B_5, B_6, B_7, B_9 and E causes embryo or early-seedling lethal phenotypes if not rescued by supplementation (Patton et al. 1998; Sattler et al. 2004; Fischer and Bacher 2005; Titiz et al. 2006; Katoh et al. 2006; Jonczyk et al. 2008; Goyer 2010; Hanson and Gregory 2011).

Biochemical function and its impact on plant metabolism

Vitamins are required for several central metabolic reactions and can potentially regulate these pathways. For example, it has been suggested that the rate of thiamine biosynthesis drives the activity of thiamine-dependent enzymes and consecutively (a) the rate of glycolysis (by regulating the activity of pyruvate dehydrogenase and pyruvate decarboxylase), (b) Krebs cycle and nitrogen assimilation (2-oxoglutarate dehydrogenase), (c) fatty acid biosynthesis (plastid pyruvate dehydrogenase), (d) branched chain amino acid biosynthesis (acetolactate synthase), (e) methylerythritol 4-phosphate (MEP) isoprenoid pathway (DXPS), and (f) pentose-phosphate pathway and Calvin cycle (transketolase) (Frank et al. 2007; Bunik and Fernie 2009; Goyer 2010; Bocobza et al. 2013). In turn, thiamine synthesis is regulated by its active form thiamine diphosphate levels through a well-described riboswitch (Wachter et al. 2007), by circadian rhythms (Bocobza et al. 2013) and by light through thioredoxin (Goyer 2010). Furthermore, structural (non-cofactor) roles have been suggested, in mammals but not in plants, with thiamine interfering with membrane structure and function (Bâ 2008).

Flavoenzymes (FMN/FAD-dependent enzymes) are cofactors of a wide variety of enzymes (Macheroux et al. 2011), actually representing 0.1–3.5 % of the predicted genes in archaeal, eubacterial and eukaryotic genomes (De Colibus and Mattevi 2006). Most flavoenzymes catalyze redox reactions of primary metabolism: citric acid cycle, photosynthesis, β-oxidation and degradation of amino acids (Fischer and Bacher 2005). However, flavoenzymes are not limited to redox processes, but are also involved in other processes, participating in reactions as diverse as protein folding, nitrogen fixation, terpenoids synthesis (both MEP and mevalonate pathways), light sensing and emission, chromatin remodeling, circadian time keeping, DNA repair and apoptosis (Fischer and Bacher 2005; Mattevi 2006; De Colibus and Mattevi 2006).

Vitamin B_3 (nicotinamide and nicotinic acid) is the precursor of $NAD(P)^+$, a key redox cosubstrate (essential in oxidative phosphorylation and redistributing electron equivalents from catabolism to anabolism), and precursor of signaling compounds and post-translational modifications of enzymes, transcription factors and histones [notably, ADP-ribose (ADPR) and cyclic-ADPR (cADPR) through mono-ADP-ribosyltransferases, poly(ADP-ribosyl) polymerases (PARPs) and sirtuins] (Sauve 2008; Houtkooper et al. 2010). PARP activity has been related to biotic and abiotic stresses, and developmental processes (Block et al. 2005; Schulz et al. 2012). The $NAD(P)^+$ pool and redox state are involved in the regulation through the above-mentioned signaling mechanisms, as a cosubstrate, and through direct activation/inhibition of enzymatic activities of limiting steps of different pathways (Noctor 2006; Houtkooper et al. 2010). In plants, vitamin B_3 is the immediate precursor of pyridine alkaloids, notably trigonelline—an *N*-methyl conjugate of nicotinic acid—accumulated upon stress as an osmoprotectant, and also involved in the control of the cell cycle (Zheng et al. 2005; Matsui et al. 2007).

Pantothenate (B_5) is precursor of the 4′-phosphopantetheine moiety of coenzyme A and the acyl carrier protein (ACP). Vitamin B_5 participates in the Krebs cycle and the biosynthesis of fatty acids, terpenoids (only in the cytosolic mevalonate pathway), polyketides (and depsipeptides), non-ribosomal peptides, cysteine (and hence methionine, CoA, thiamin, SAM and glutathione), and secondary

metabolites derived from both carboxylic and amino acid precursors (notably lignin and flavonoids) (Webb et al. 2004; Chakauya et al. 2006).

Pyridoxal phosphate-dependent enzymes catalyze a wide range of reactions: transamination, aldol cleavage, α-decarboxylation, β- and γ-racemization, and elimination and replacement reactions. With the exception of glycogen phosphorylases, all involve amino compounds—especially amino acids—hence biosynthesis, metabolism and catabolism of amino acids depend on PLP at some point (Percudani and Peracchi 2009; Mooney and Hellmann 2010). Furthermore, PLP-dependent enzymes play key roles in many pathways. For example, most sulfur in plants is incorporated by the reductive sulfate assimilation pathway in which the last enzyme (*O*-acetylserine sulfhydrylase) is PLP-dependent (Mozzarelli et al. 2011). PLP-dependent enzymes, SHMT and GDC, catalyze the methylation of THF through the serine/glycine pair, and hence are one of the bases of one-carbon (C_1) metabolism, linking amino acid and folate metabolism (Schirch and Szebenyi 2005), and participating as well in photorespiration (Jamai et al. 2009). Vitamin B_6 has also shown antioxidative capacities as an in vivo singlet oxygen quencher (Bilski et al. 2000; Denslow et al. 2005; Havaux et al. 2009).

Biotin has two main roles in cell metabolism: as a cofactor, required for the transfer of CO_2 during HCO_3-dependent carboxylation, decarboxylation, and transcarboxylation reactions; and in cell signaling and gene regulation, notably—but not only—through biotinylation of histones (Zempleni 2005; Wolf 2005). Biotin serves as a covalently bound coenzyme for a reduced number of carboxylases: (a) acetyl-CoA carboxylase, the first committed step (and main regulatory point) in the synthesis of fatty acids and also required for the elongation of very long-chain fatty acids, the synthesis of many secondary metabolites (flavonoids, anthocyanins and stilbenoids), and the malonylation and acetylation of some amino acids (including those of histones); (b) 3-methylcrotonyl-CoA carboxylase, involved in Leu catabolism and isoprenoid metabolism ("mevalonate shunt"); (c) propionyl-CoA carboxylase, required for the catabolism of odd-numbered fatty acids and some amino acids (branched- and odd-chain amino acids: Ile, Thr, Met and Val); and (d) pyruvate carboxylase, generating oxaloacetate for a Krebs cycle's anaplerotic reaction and for gluconeogenesis (Alban et al. 2000; Rébeillé et al. 2007). These biotin-dependent enzymes are common in mammals and plants, but there is an additional enzyme in plants—also present in some prokaryotes—geranyl-CoA carboxylase, which is involved in isoprenoid catabolism (Guan et al. 1999; Tong 2013). Furthermore, there is evidence of a biotin-bound protein exclusive of seeds with no catalytic function, but thought to play a role in storing biotin (Dehaye et al. 1997; Job et al. 2001). Biotinylation is one of the covalent modifications of histones that through rearranging the structure of chromatin form the basis of gene regulation, mitotic and meiotic chromosome condensation and DNA repair (Kothapalli et al. 2005). Notably, while biotin concentrations in culture media have only a moderate impact on biotinylation of histones, biotinylation of carboxylases correlates strongly with biotin concentrations in culture media (Manthey et al. 2002; Crisp et al. 2004).

THF and its C_1-substituted derivatives act as carriers for C_1 units in enzymatic reactions that form amino acids (methionine, glycine, and serine), purines, thymidylate, pantothenate, biotin, ethylene, formylmethionyl-transfer RNA and secondary metabolites (notably lignin, alkaloids, and betaines; Hanson and Roje 2001). Thus, folates also participate in photorespiration and through SAM and *S*-methylmethionine cycles in a wide range of reactions, including the biosynthesis/catabolism of all isoprenoids (including carotenoids, vitamin E, gibberellins and abscisic acid), phenylpropanoids, ethylene, Met, biotin, alkaloids, chlorophyll, choline, vitamin K, sterols, plastoquinol-9, ubiquinol-10, purines, pyrimidines, among others (Hanson and Roje 2001).

Vitamin E protects membranes by quenching (physically) and scavenging (chemically) the singlet oxygen, and prevents the propagation of lipid peroxidation (by scavenging lipid peroxyl radicals), therefore maintaining the membrane stability under oxidative stress (Kamal-Eldin and Appelqvist 1996; Maeda and DellaPenna 2007; Falk and Munné-Bosch 2010). No direct enzymatic role as cofactor has been experimentally described for vitamin E, but there is ample evidence of its role in signaling and transcriptional and enzymatic regulation (Brigelius-Flohé 2009; Cela et al. 2011; Mehrshahi et al. 2013), possibly by its effects on membrane conformation and membrane-associated proteins (Atkinson et al. 2008; Brigelius-Flohé 2009).

Abiotic and biotic stress tolerance

Plants subjected to abiotic stress conditions—and specially oxidative stress—accumulate thiamine and TPP, increasing the expression levels of its key biosynthetic enzymes and its activity (Rapala-Kozik et al. 2008, 2012; Tunc-Ozdemir et al. 2009). Vitamin B_1 accumulation enhances tolerance to oxidative stress mediated by abscisic acid (Tunc-Ozdemir et al. 2009; Rapala-Kozik et al. 2012). Thiamine biosynthesis and accumulation are regulated by the circadian clock, and hence its content might depend on harvest time, like that of folates (Puthusseri et al. 2012; Bocobza et al. 2013). Furthermore, thiamine confers systemic acquired resistance (SAR) through priming or elicitation competency (Goyer 2010), depending on salicylic acid,

reactive oxygen species (ROS) and hence cellular redox signaling (Ahn et al. 2005, 2007; Zhou et al. 2013b).

Riboflavin-deficient tobacco plants present compromised radical production (ROS and reactive nitrogen species) and hypersensitive cell death response (Asai et al. 2010), while increased levels of riboflavin act as an elicitor of SAR (Dong and Beer 2000) via the induction of ROS and hormonal signaling transduction pathways, promoting the phenylpropanoid pathway and phenolics accumulation (Zhang et al. 2009; Taheri and Tarighi 2011; Li et al. 2012b). Curiously, diminishing free flavins (through the ectopic expression of a flavin-binding protein) also elevates the levels of H_2O_2 enhancing plant resistance to bacterial pathogens (Deng et al. 2011).

NAD^+ and $NADP^+$ are considered the central metabolites in the control of cellular redox homeostasis, through signaling via the generation and scavenging of ROS and modulating responses to abiotic stresses (Foyer and Noctor 2009; Hashida et al. 2009; Munné-Bosch et al. 2013). Plants' stresses such as drought, high light or heat activate PARP-causing NAD^+ breakdown, releasing nicotinamide and increasing ATP consumption, thus depleting energy resources and ultimately causing cell death. When PARP activity is reduced by means of chemical inhibitors or by gene silencing, cell death is inhibited and plants become more tolerant to a broad range of abiotic stresses such as high light, drought and heat. Plant lines with low PARP activity maintain their growth and energy homeostasis under stress conditions by reducing NAD^+ breakdown and consequently energy consumption. The higher energy-use efficiency avoids the need for increased mitochondrial respiration and consequently reduces the formation of ROS (Block et al. 2005; Schulz et al. 2012). Further, extracellular $NAD(P)^+$ leakage from cells losing their membrane integrity upon environmental stress might also act as an elicitor to activate plant defense responses (Zhang and Mou 2009).

Little is known about the involvement of vitamin B_5 in different stresses and the associated responses. Severely reduced CoA levels delay catabolism of storage lipids during seedling establishment, causing severely impaired plant growth and seed production, while high levels of CoA enhance vegetative and reproductive growth, salt/osmotic stress resistance, and increase storage oil accumulation in seeds (Rubio et al. 2008). 4′-Phospho-pantothenoylcysteine decarboxylase, an enzyme involved in the conversion of pantothenate to coenzyme A, is highly induced by salt stress and improves salt tolerance in cellular cultures, increasing the level of proline, a major compatible solute in plants (Nakayama et al. 2005). Indeed, metabolic engineering for β-alanine (a limiting B_5 precursor) over-production confers higher thermotolerance (Chakauya et al. 2006).

Abiotic stresses (chilling, UV radiation, high irradiance, osmotic stress and drought) result in significant increases of PLP levels (Denslow et al. 2005; Huang et al. 2013). While mutants deficient in vitamin B_6 are hypersensitive to oxidative stress (Chen and Xiong 2005; Titiz et al. 2006), vitamin B_6-enhanced lines show increased resistance to oxidative stress (Raschke et al. 2011). Moreover, the expression of PLP biosynthetic genes decreases following pathogen inoculation (Denslow et al. 2005). Indeed, high levels of vitamin B_6 interfere with the hypersensitive response, increasing disease severity (Denslow et al. 2005).

Biotin-deficient plants accumulate H_2O_2 and show up-regulation of defense and ROS signaling-related genes, with a constitutive expression of pathogenesis-related (*PR*) genes. Interestingly, this increase in defense gene expression is not accompanied by enhanced resistance to bacterial pathogens, possibly because this increased transcription is not correlated with an accumulation of the corresponding protein (Li et al. 2012a).

Folate synthesis and levels are stimulated by light, following diurnal cycles. Part of the folates synthesized in the light might contribute to photorespiration process, but most are accumulated in the cytosol, while photorespiration requires folates in the peroxisome (Jabrin et al. 2003). Actually, it is established that folate requirements vary greatly through development, but the regulation of folate homeostasis is largely undescribed (Loizeau et al. 2008; Hanson and Gregory 2011; Zhang et al. 2012).

Vitamin E levels are largely responsive to abiotic stress in plants, the kind of stress, stress intensity, plant physiological state, and species-specific sensitivity to stress playing an essential role in the extent of tocopherol accumulation (Munné-Bosch 2005). Not only high light intensity, water stress, salt stress, heavy metal stress, temperature stress, ozone and UV-B stress, but also early and late developmental stages, cause increased vitamin E levels in plants (Lushchak and Semchuk 2012; Juvany et al. 2013). Tocopherols protect the plant against photooxidative stress, associated with all these abiotic stresses (Munné-Bosch 2005). The role of tocopherols in biotic stress has still not been investigated in detail.

Two amino acid-derived vitamins, vitamin B_1 (thiamine) and vitamin B_2 (riboflavin), but also vitamin K_3 (menadione), are known to induce SAR against fungal, bacterial and/or viral infections. *p*-Aminobenzoic acid (PABA) (a folate precursor) has also been effective in eliciting induced resistance (Song et al. 2013). This implies a big potential for crop protection against pathogens by vitamin treatments, due to its safety and cost effectiveness (Lyon 2007). Mild abiotic stressors (light exposure, temperature, and partial drought) can enhance the vitamin content of crops, and even indirectly confer limited protection against pathogens.

Functions of plant amino acid-based vitamins in humans

Dietary requirements of some amino acid-based vitamins (B_5, B_7) are low, being found ubiquitously in most diets, hence no severe deficiencies have been observed, other than genetic diseases and drug–vitamin interactions (Marquet et al. 2001; Zempleni et al. 2008). The major, but not exclusive, sources of plant amino acid-based vitamins (vitamins B_1, B_2, B_3, B_5, B_7, B_9 and E)—in balanced diets—are vegetables, grains and derived products (oils) (Hiza et al. 2008; Combs 2012).

Thiamine role as a cofactor has been correlated with lipid disorders in certain types of diabetes (Babaei-Jadidi et al. 2004), preventing the progression of hyperglycemia in others (Alaei Shahmiri et al. 2013), and in cancer progression (Lu'o'ng and Nguyen 2013). Thiamine deprivation is related to nervous function, causing polyneuritis and neurological disorders, as beriberi and Wernicke–Korsakoff syndrome. These physiological and developmental disorders have been associated with an impaired energy metabolism (Gibson and Zhang 2002; Butterworth 2003), and also with structural roles of thiamine in membranes (Bâ 2008).

FAD is an electron acceptor in fatty acid β-oxidation, thus B_2 deficiencies report an overall reduction of β-oxidation and altered fatty acid profiles, while essential fatty acids are accumulated (Powers 2003). This has been associated with the excretion of various dicarboxylic acids, from microsomal and peroxisomal fatty acid catabolism, leading to aciduria (Powers 2003; Lienhart et al. 2013). In humans, flavoenzymes are involved in the synthesis of many cofactors and hormones: coenzyme A, coenzyme Q, heme, pyridoxal 5′-phosphate, steroids and thyroxine (Lienhart et al. 2013). Hence, flavin deficiencies are associated with disorders in iron metabolism, neurodegeneration and peripheral neuropathy (possibly through thyroxine metabolism) (Bell et al. 1992; Lienhart et al. 2013). Dihydroflavin (produced by flavin reductase) is required for heme cofactor biosynthesis, hence associated with variegate porphyria (Lienhart et al. 2013). Flavoproteins are also important for C_1 metabolism, regulating interconversion of various folate metabolites and SAM cycle enzymes (Lienhart et al. 2013). Furthermore, riboflavin plays a dual role in animal vision: deficiency has been related to cataracts and riboflavin-dependent receptors (cryptochromes), with riboflavin deficiency leading to night blindness and circadian rhythms disorders (Powers 2003).

Large doses of nicotinic acid are administered to lower serum lipids and cholesterol (Schachter 2005), leading to reduced lipidemias, reduced progression of coronary disease and reduced mortality (Capuzzi et al. 2000). Different serum lipotypes show different dose–response profiles, suggesting the participation of different mechanisms (Sauve 2008). Thus, four basic mechanisms have been proposed: inhibition of lipolysis in lipidic tissues, increased HDL levels (by its removal inhibition), lowering of serum lipoprotein(a), and inhibition of the synthesis and secretion of VLDL in protein (Capuzzi et al. 2000; Kamanna and Kashyap 2000). Elevated doses of nicotinamide have been recommended for the prevention of type 1 diabetes and degenerative diseases, but long-term clinical studies have failed to show decreases in its incidence (Gale 2004). PARP activity consumes NAD^+, generating ADP-ribosylated proteins and nicotinamide. Nicotinamide inhibits PARP, leading to decreased NAD^+ turnover in degenerative states or acute stresses where PARP activity is over activated (Virág and Szabó 2002). The use of nicotinamide for the treatment of ischemia takes advantage of this PARP inhibition activity. After the removal of the stroke blockage, the oxygen-deprived tissue is re-perfused; the sudden re-oxygenation causes the production of oxygen and nitrogen reactive species. This oxidative burst can lead to extensive tissue damage (ischemia reperfusion injury), but this damage is not strictly oxidative. The extensive oxidation of DNA highly up-regulates PARP activity, depleting most of the cellular NAD^+ (Virág and Szabó 2002; Hassa et al. 2006). Consecutively, NAD^+ must be resynthesized through the NAD^+ recycling pathway using high-energy precursors like ATP and PRPP, placing serious strains to cell's energy resources, causing cell death from energy depletion. Against this fatal sequence, nicotinamide plays a double role: protective, especially by PARP inhibition; and also as NAD^+ precursor (Virág and Szabó 2002; Hassa et al. 2006). Furthermore, this complex signaling associated with ADP ribosylation (of histones, transcription factors and PARP itself) is sensitive to vitamin B_3 dietary status (Kirkland 2009). Nicotinamide has also been related to other pathophysiological disorders through these and other mechanisms: blocking cellular inflammatory cell activation (Maiese et al. 2009), preventing neurodegeneration in chronic degenerative diseases and after trauma (Sauve 2008; Houtkooper et al. 2010), and extending life span in model animals (Houtkooper et al. 2010).

Pantothenate biosynthetic pathways and its metabolism in plants and animals have been described; further, its involvement in many pathways as CoA or ACP is also well known. However, pantothenic acid is widely distributed in foods and feeds, thus deficiencies of this vitamin are rare. Animals with induced vitamin B_5 deficiencies show diverse pathophysiological states (e.g., depression, sleep and neurological disorders, cardiac instability, lipid metabolism disorders and dermatitis), but no clear underlying biochemical cause has been identified for them (Rébeillé et al. 2007; Combs 2012).

Vitamin B_6 has the potential to reduce cardiovascular risks (Ishihara et al. 2008) through reducing hypertension and/or homocysteine metabolization (Hellmann and Mooney 2010). PLP might reduce blood pressure through: reducing blood aldehyde levels; by PLP-dependent dopamine synthesis (a vasopressor); or PLP capacity to react with reducing blood sugar and lipids, preventing the formation of glycation or lipooxygenation products (Hellmann and Mooney 2010). Vitamin B_6 is also involved in neurological activity, being required for the synthesis of a number of neurotransmitters like serotonin, dopamine, γ-aminobutyric acid (GABA), epinephrine, norepinephrine and histamine (Hellmann and Mooney 2010; di Salvo et al. 2011). Hence, low levels of PLP have been correlated with depression and brain functional disorders (Hvas et al. 2004; Hoffmann et al. 2007).

In the case of biotin, the most common hereditary deficiencies are involved in biotin recycling, with organic aciduria being the main consequence. Other disorders are often associated with B_7 deficiency (e.g., dermatitis, conjunctivitis, ataxia, neurological disorders, developmental delay), but no underlying biochemical cause has been described (Wolf 2005; Suzuki et al. 2005; Rébeillé et al. 2007). Biotinylation depends on prior DNA methylation (Zempleni et al. 2011), creating epigenetic synergies between biotinylation and methylation events that might offer an explanation to these disorders (Zempleni et al. 2012). Furthermore, there is a correlation between human tumors and alterations in biotin cycling, probably associated with histone biotinylation impairment (Zempleni et al. 2011).

One of the most prevalent vitamin deficiencies is caused by folate, causing a reduction of the cell capacity to synthesize DNA, impairing purine and thymidine synthesis. Furthermore, it is also correlated with high cellular dUMP/dTMP ratio due to thymidylate impairment (Rébeillé et al. 2007). This rise results in higher incorporation of dUTP in DNA, generating point mutations, single- and double-strand breaks, and finally chromosomal breakage and apoptosis (Kim 1999; Li et al. 2003). These damages are important risk factors for cancer (Nazki et al. 2014). Another metabolic pathway impaired by folate deficiency is methionine synthesis. High plasmatic levels of homocysteine and its immediate precursor are associated with coronary and cardiovascular diseases (Stover 2004) and are a risk factor for dementia and Alzheimer (Seshadri et al. 2002). Indirectly, SAM deficiency can limit methyltransferase reactions, resulting in problems including neuropathy due to impaired myelin biosynthesis and major deregulation of gene expression due to hypomethylation of DNA (Rébeillé et al. 2007).

Homocysteine—an important risk factor for cardiovascular and neurodegenerative diseases—is metabolized by two vitamin-dependent routes, trans-sulfuration (dependent on B_6) and re-methylation to methionine (B_2, B_9, B_{12}) (Powers 2003). It should be noted that it is not generally accepted that vitamin supplementation actually reduces blood homocysteine levels (Martí-Carvajal et al. 2013).

Vitamin E has beneficial effects on atherosclerosis and cholesterol metabolism (Kaga et al. 2013); its deficit has been related with ataxia, diabetes, other associated neuronal defects and female reproductive failure (Brigelius-Flohé 2009). Supplementation of the growth medium with α-tocopherol increased oxidative stress while decreasing the cell lifespan in *Saccharomyces cerevisiae* (Lam et al. 2010). Besides, there is no consistent beneficial effect of vitamin E on lifespan in model organisms consistent with reports in human intervention studies (Ernst et al. 2013). Meta-analyses of randomized clinical trials of pharmacological dosage report negative or no effect on mortality/lifespan (Abner et al. 2011), no effects on cancer (Goodman et al. 2011), but positive effects on prevention of cardiovascular disease (Lee et al. 2005; Ye and Song 2008).

Furthermore, suboptimal intake of vitamins with antioxidant function (vitamin E, but also vitamin C and provitamin A) have been associated with oxidative stress-related degenerative diseases such as atherosclerosis, cardiovascular and neurodegenerative disease, chronic inflammation and some cancers (Bjelakovic et al. 2012; Mathew et al. 2012). Diets rich in plant foods (especially fruit and vegetables) have been associated with moderately lower overall mortality rates and lower death rates from cardiovascular disease and some types of cancer (Stanner et al. 2004). The major meta-analyses of randomized trials of antioxidant supplements for primary and secondary mortality, degenerative illness or cancer prevention fail, however, to confirm a protective role for a single or combined group of antioxidants (Bjelakovic 2007; Fortes and Boffetta 2011; Bjelakovic et al. 2012, 2013; Mathew et al. 2012). Indeed, some studies even suggest that treatment with vitamin E may increase mortality (Bjelakovic 2007; Bjelakovic et al. 2013).

While the role of vitamin B_6 as an antioxidant in animal systems has been explored for as long as in fungi and plants (Jain and Lim 2001; Nagaraj et al. 2002), it has been only sparsely included in dietary and supplemental, neither observational nor interventional studies. Besides, vitamin B_6 intake and blood PLP levels have been inversely associated with the risk of colorectal and breast cancer (Larsson et al. 2010; Wu et al. 2013). The design and methodology of these kinds of studies have raised a number of controversies: lack of good biological rationale for selecting specific agents of interest; limited number of agents tested; use of pharmacological, rather than dietary, doses; and insufficient duration of intervention and follow-up

(Goodman et al. 2011; Bast and Haenen 2013). Even it is known that high dosages of any vitamin have undesired toxic effects (Rutkowski and Grzegorczyk 2012), for example, vitamin E is metabolized along the same routes as xenobiotics and induces drug-metabolizing enzymes (Brigelius-Flohé 2007). Other reasons for these differences between dietary and pharmacological studies—intrinsic to foodstuff—have been suggested: micronutrients' synergistic effects or food matrix effects on bioavailability (Martin 2013).

Flavins, niacin, pantothenate, biotin and folate have an independent, and possibly synergistic, impact on chromatin structure through post-translational modifications of histones (Ryšlavá et al. 2013) and other mechanisms (e.g., DNA repair), with different sensitivity to dietary status, causing effects on transcriptional regulation, genomic stability, cell division, differentiation, apoptosis, mitotic and meiotic chromosome condensation and DNA repair. The literature relating vitamins to all these processes and cancer is quite complex. As has been only briefly discussed here, some studies point that deficiencies of a certain vitamin increase the risk of certain cancers, whereas others mark possible preventive or genotoxic stress attenuation effects by the same deficiency. Thus, opposite effects can be reported for the same vitamin, reflecting not only the heterogeneity of the diverse pathologies labeled together as "cancer" but also the different effects of diverse vitamers and dosages (Powers 2003; Fortes and Boffetta 2011; Goodman et al. 2011; Lu'o'ng and Nguyen 2013; Sosa et al. 2013).

Concluding remarks and perspectives

The biosynthesis of most vitamins is intrinsically related to amino acid metabolism. A common response in both humans and plants, to most types of stressors, is to increase the biosynthesis of some vitamins, which have a protective role. The role of vitamins in defense responses has concentrated many efforts, but several questions still remain unsolved. If the final goal of vitamin research is to mitigate or eradicate deficiencies and associated disorders, future efforts on research should consider a comprehensive approach from multiple fields. Molecular bioengineering should be concurrent to traditional breeding and agronomic practices. Further basic research is also required to elucidate plant vitamin pathway regulation, vitamin salvage pathways and compartmentation. Of particular relevance will also be the future research on better understanding the dietary effects of vitamins in humans. Finally, it is essential that plant and mammal physiologists work together with nutritionists and medical doctors to better understand the essential role that vitamins play in evolutionary distinct organisms; filling gaps in different disciplines can help us better understand the basic and applied biology of this important group of compounds.

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