

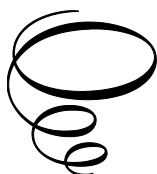
A Guide to Vitamins and Their Effects on Diseases

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Edited by

Ahmet Ata Alturfan
and Ebru Emekli-Alturfan

**Cambridge
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Dedicated to our teachers and parents, who are our first and foremost teachers.

Teachers are the one and only people who save nations
—*Mustafa Kemal Atatürk*

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PREFACE

Vitamins are substances which are necessary for a healthy life, and they can be effective even in very little amounts. Since antiquity, the importance of vitamins has been known, and their effects on diseases and required doses have been researched. Hippocrates, a philosopher who lived between 460 and 370 B.C., stated that “your food is your medicine”, and this remark still rings true.

Vitamins and minerals work together in a close manner: minerals are required for the absorption and stimulation of some vitamins.

In this book, you will find up-to-date information about vitamins, vitamers, vitamin-like substances, vitamin-related minerals, and their basic and specific roles in diseases. We believe that this book will be valuable to the entire scientific community.

We hope you enjoy reading the book.

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SECTION 1:
OVERVIEW AND CLASSIFICATION
OF VITAMINS

CHAPTER 1

OVERVIEW AND CLASSIFICATION OF VITAMINS

AHMET ATA ALTURFAN

History

Vitamins are organic compounds that cannot be synthesised or produced in the required amount by humans. They must be ingested daily through diet for growth, reproduction, immune function, cell differentiation, and other functions. The absence of a vitamin is called avitaminosis. In case of deficiencies, organ, tissue, and growth disorders can be seen in young animals. In adults, decreases in daily activities, resistance to infections, and sexual disorders may develop.

It was determined that night blindness (nyctalopia) due to malnutrition disappeared after regular ingestion of cooked liver. Also, in the past, a disease characterised by bleeding and swollen gums, tooth loss, and impaired healing of wounds was common among sailors who had been away from land for a long time. British sailor James Lind added citrus fruits to the diets of ship crews and observed a protective effect against the disease.

In 1901, Dutch physician Grijns was the first scientist to identify beriberi disease. Beriberi affects the nerves, diminishes muscle function, leads to oedema and visual disturbances, and impairs heart functions. It is life-threatening if left untreated. Natives who lived in the Java region mostly consumed polished rice. It was the Polish biochemist Casmir Funk who found that the biomolecule thiamine was lost when brown rice was polished, leading to beriberi. Funk isolated this vitamin from the rice husk in 1912. It was the same researcher who named this substance “vita amines” (vita means life in Latin), which means a nitrogenous substance that gives privilege to thiamine because it contains nitrogen. Later, the suffix “e” at

the end of the word amine symbolizing nitrogen was dropped and vitamin became a term used for all other nutritional factors.

In 1912, British biochemist Frederick Hopkins found that normal development was impaired in rats fed a synthetic and dairy-free diet consisting of carbohydrates, fat, protein, and mineral salts. However, he demonstrated that growth was normalized by adding milk to their diet. Similarly, rats fed a milk-supplemented diet had stunted growth by removing milk from the diet. Hopkins concluded from these observations that other factors besides carbohydrates, protein, fat, and minerals were needed for the growth access of the animals. These factors necessary for growth and survival are referred to as vitamins. He won the Nobel Prize in Medicine in 1929, together with the Dutch medical doctor and physiology professor Christiaan Eijkman.

Properties of vitamins

- All vitamins are organic substances. They have a variety of biochemical tasks.
- Vitamins are also known as micronutrients and the daily requirement of the body is usually expressed as milligrams, micrograms, or International Units (IU).
- Vitamins are considered substances that are essential for metabolism.
- All living creatures usually meet their vitamin needs by consuming plants. Various diseases may develop in the case of vitamin deficiency.
- Some vitamins are synthesised by organisms. Except for vitamin D and niacin, vitamins are synthesised by plants and intestinal microflora.
- Vitamins exist in molecular or ionic forms. For this reason, they directly access the small intestine without being subjected to chemical digestion and participate in the bloodstream.
- While vitamins A, D, E, and K are fat soluble and can be stored in the body, B vitamins and ascorbic acid dissolve in water and cannot be stored.
- Vitamins have auxiliary and effective tasks in the functioning of enzymatic reactions. The vast majority of vitamins (B complex vitamins) play crucial roles as cofactors or precursors in enzymatic reactions.
- Vitamins function as a regulator of tissue and cell differentiation and growth.
- Vitamins can regulate mineral metabolism and may act like a hormone.
- Vitamins can function as antioxidant molecules.
- Excess intake (except water-soluble vitamins) and deficiency of vitamins may lead to serious health issues.

- Vitamins also play roles in immune function, vision, coagulation, wound healing, hormone, erythrocyte, and DNA production, and maintaining the central nervous system and mucous membranes integrity.

Reasons for and conditions that cause vitamin deficiency

- Daily insufficient intake, poor digestion, increased excretion, poor food inhabsits (starvation, poverty);
- Alcoholic liver disease;
- Food taboos;
- Malabsorption;
- Pernicious anaemia (intrinsic factor deficiency);
- Diseases such as anorexia and Crohn's disease;
- Liver failure;
- Infection and inflammation of the intestines (inflammatory bowel disease);
- Lack of carrier proteins necessary for the transport of some vitamins;
- Increased need (growth, pregnancy, lactation);
- Increased excretion (kidney function failure);
- Drug-induced deficiency such as the microbial synthesis defects of the intestine due to antibiotic intake and isoniazid-induced niacin deficiency.

Classification of vitamins

Due to the differences in the structure of the vitamins, a precise chemical classification cannot be made. There are 13 main vitamins and eight vitamin-like substances known in the literature. These are mainly divided into two groups: fat-soluble and water-soluble vitamins.

Fat-soluble vitamins

Fat-soluble vitamins encompass the vitamins A (retinol), D (calciferol), E (tocopherols, tocotrienols), and K (phyloquinone). These predominantly nonpolar molecules have many physiological roles in vision, blood coagulation, immunity, bone health, and wound healing. They are absorbed by the gut in the presence of lipids with the aid of bile salts. Accordingly, issues during the absorption of lipids in the body generally lead to an impairment of the absorption of fat-soluble vitamins. For example, conditions such as diarrhea or obstruction of the gall bladder may give rise to a decrease in fat-soluble vitamin concentrations, which can lead to serious

health issues such as haemorrhage, rickets, osteomalacia, night blindness, and oxidative stress. Fat-soluble vitamins are stored in the liver. Vitamin E is also stored in adipose tissue. For this reason, excess intake of these vitamins can be toxic. Fat-soluble vitamins are important for overall health. Most people can obtain sufficient vitamins from a varied diet.

Water-soluble vitamins

Water-soluble vitamins include vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), biotin (vitamin H), vitamin B9 (folic acid), vitamin B12 (cobalamin) and vitamin C (ascorbic acid). They are polar molecules and soluble in water. The storage rate of water-soluble vitamins in the body is relatively low. This is especially true for most of the B vitamins. Symptoms of people with vitamin B deficiency appear in a few days. Vitamin B12 is an exception because vitamin B12 in the liver can be sufficient for a person for almost a year. The absence of vitamin C, another water-soluble vitamin, demonstrates its symptoms in a few weeks. Scurvy, caused by vitamin C deficiency, can result in death within 20-30 weeks. For this reason, water-soluble vitamins (except B12) should be taken in adequate amounts daily. Most of the water-soluble vitamins are involved in enzymatic reactions as coenzymes. Toxic effects of severe hypervitaminosis are not observed in water-soluble vitamins owing to their excretion in the urine.

Vitamin-like substances

There are some compounds apart from the 13 vitamins mentioned above that are effective like vitamins but are not included in the general classification:

- Lipoic acid;
- Coenzyme Q₁₀;
- Bioflavonoids;
- Choline;
- Carnitine;
- Miyoinozitol;
- Para-aminobenzoic acid (PABA);
- Orotic acid (Vitamin B₁₃).

CHAPTER 2

MICROBIAL BIOSYNTHESIS OF VITAMINS

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Overview

Vitamins are organic molecules that function as coenzyme precursors. Their presence is vital to regulate the biochemical processes in living cells needed for survival. However, humans can't synthesize all the necessary vitamins required to have a healthy metabolism. Hence, these vitamins should be obtained from exogenous sources such as the products of human gut microbiota and foods (1). The enormous surface of the human gastrointestinal tract (250–400 m²) is exposed to nearly 60 tonnes of food passing through including the microorganisms from the environment (2, 3). Bacteria, archaea, and eukarya are gut microbiota colonizing the gastrointestinal tract and there is obviously a mutually beneficial relationship between the members of the gut microbiota and the host (4). The estimated number of gut microbiota is 10¹⁴, which is 10 times higher than the number of human cells in the body (5, 6). The gut microbiota has many benefits for the human gastrointestinal tract, such as strengthening the gut integrity (7), supply of energy (8), protection against environmental pathogens (9), and regulating the host immunity (10). However, alteration in the microbial composition of the gut microbiota is known as dysbiosis, and it may disrupt all of these beneficial effects.

The gut microbiota of neonates dominantly has Proteobacteria and Actinobacteria phyla-, but becomes more diverse with the emergence and dominance of Firmicutes and Bacteroidetes after around 2.5 years of age (11-13). The gut microbiota has the capability of *de novo* synthesis of several vitamins which are not produced by the host (14). For instance, vitamin B12 is produced by lactic acid bacteria (14,15). Similarly,

Bifidobacteria could produce folate, an essential vitamin for DNA synthesis and repair (15). Additionally, the gut microbiota can synthesize vitamin K and group B vitamins such as riboflavin, thiamine, nicotinic acid, pantothenic acid, and pyridoxine. Any alteration in vitamin synthesis may lead to metabolic diseases such as obesity and type 2 diabetes (16). Although human gut microbiota is unique for each individual, it shares some common points in healthy individuals. Bacteroidetes with Firmicutes represent 90% of the human gut microbiota. The majority of them are butyrate-producing Gram-positive Firmicutes such as *Faecalibacterium*, *Clostridium*, *Ruminococcus*, etc. and Gram-negative Bacteroidetes are responsible for degrading many complex glycans. Other members of the microbiota are Gram-negative Proteobacteria such as *Escherichia coli* (*E. coli*) and the *Enterobacteriaceae* family, and Gram-positive Actinobacteria such as the genus *Bifidobacterium*, *Fusobacteria* and *Verrucomicrobia* such as *Akkermansia* which represents smaller portions (10%) of the gut microbiota (17,18).

Accordingly, the vitamins mentioned above are essential for bacterial survival. Therefore, deficiencies of said vitamins may have health-threatening consequences. Rats with vitamin K deficiency may develop hemorrhages due to low levels of prothrombin (19, 20). Similarly, suppression of intestinal microbiota by antibiotics reduces prothrombin levels in human serum (21). A highly cited paper describing the vitamin synthesis pathways of the gut microbiota using metagenomics sequencing methods evaluated common gut bacteria genomes. The authors indicated the phylum rates as the producers of each of eight B vitamins [biotin (vitamin B7), cobalamin (vitamin B12), folate (vitamin B9), niacin (vitamin B3), pantothenate (vitamin B5), pyridoxine (vitamin B6), riboflavin (vitamin B2), and thiamin (vitamin B1)] (22). Vitamins taken with foods are generally absorbed in the duodenum, while several vitamins are synthesized by the microbiota in the colon (23).

The gut microbiota is in mutual-benefit cooperation with the host in food digestion and energy recovery, and, most of the bacteria also need these vitamins. Interestingly, in humans, a diet low in vitamin K causes no vitamin deficiency when maintained for short periods, but inhibition of human intestinal microbiota with antibiotics causes a reduction in prothrombin levels. The aforementioned metagenomic study of the genomes of 256 intestinal bacteria for biosynthetic pathways of eight B vitamins (biotin, cobalamin, folate, niacin, pantothenate, pyridoxine, riboflavin, and thiamin) has indicated that the percentages of vitamin-producer gut bacteria phyla. They suggested that each of the eight vitamins

was produced by 40–65% of the 256 human gut microbes (22). It seems that the human gut microbiota has co-evolved relationships that are specific to the gut environment in which the microbiota contributes to the B vitamin pool of the gut and that the host can benefit from the B vitamin biosynthesis of the microbiota. The details will be explained in more detail in the following sections of this article.

Microbial biosynthesis of K and B vitamins

K vitamins

Key Points

- Green vegetables are generally good sources of natural K vitamins (K1, phylloquinone). However, menaquinone (K2, MK) cannot be obtained from green vegetables, it has to be synthesized by the members of the gut microbiota such as the *Lactococcus*, *Lactobacillus*, *Enterococcus*, *Leuconostoc*, and *Streptococcus*. Finally, K3, known as synthetic menadione, is not a natural vitamin (25).
- Vitamin K acts as a γ -carboxylase enzyme co-factor, and the γ -carboxylase enzyme converts glutamyl residues to γ -carboxyglutamyl (Gla) residues. The γ -carboxylated amino acid residues have calcium-binding sites that draw calcium ions. Therefore, the compound can bind with calcium ions and incorporate them into the hydroxyapatite crystals that form the bone matrix. Vitamin K also facilitates blood clot formation (26, 27).

The biosynthesis of Vitamin K

The synthesis of MKs occurs mainly in *E. coli*. In *E. coli*, the naphthoquinone ring is formed by the conversion of chorismate to isochorismate and catalyzed by the six enzymes (gene product of *MenFDHCEB* gene) in the first step of MK biosynthesis. Chorismate is a precursor for the aromatic amino acids and the folate precursor para-aminobenzoate, and the biosynthesis of Vitamin K and folate in plants and microorganisms. The naphthoquinone ring and the isoprenoid side chain are coupled to form 1,4-dihydroxy-2-naphthoate (DHNA). Two enzymes are responsible for the prenylation and methylation of DHNA yielding menaquinones as the end product: 1,4-dihydroxy-2-naphthoate octaprenyltransferase (*menA*) and demethylmenaquinone methyltransferase (*menG*) (28).

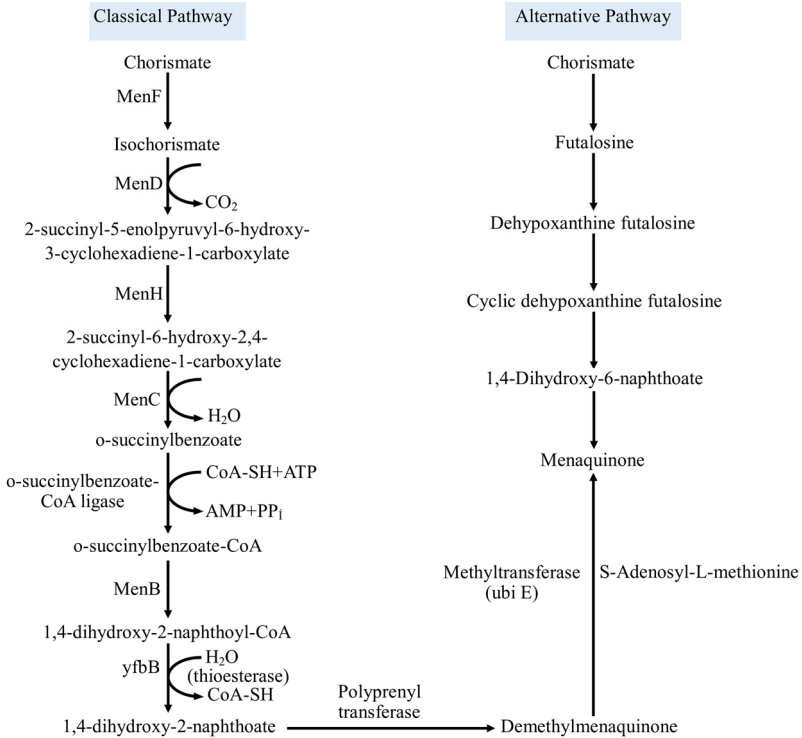


Figure 2.1. The biosynthesis of vitamin K. *menF*: menaquinone-specific isochorismate synthase, *menD*: 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase, *menH*: menaquinone biosynthesis methyltransferase, *menC*: O-succinylbenzoate synthase, *menB*: 1,4-dihydroxy-2-naphthyl-CoA synthase, *yfbB*: 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase, CoA: Coenzyme A.

Formation of isochorismate from chorismate is catalyzed by the isochorismate synthase encoded by menaquinone-specific isochorismate synthase (*menF*). Conjugate addition of α -ketoglutarate with isochorismate to form 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexadiene-1-carboxylate is catalyzed by thiamine diphosphate-dependent 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase (*menD*). Menaquinone biosynthesis methyltransferase encoded by *menH* is responsible for eliminating pyruvate moiety to form 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate. Aromatization of this compound is achieved by the O-succinylbenzoate synthase enzyme encoded by *menC*, which forms o-succinylbenzoate. An o-succinylbenzoate-CoA ligase (*menE* gene product) catalyzes to yield o-

succinylbenzoate-CoA. Then, o-succinylbenzoyl-CoA is converted to 1,4-dihydroxy-2-naphthoyl-CoA by 1,4-dihydroxy-2-naphthoyl-CoA synthase enzyme encoded by *menB*. The hydrolyzation of the last compound forms 1,4-dihydroxy-2-naphthoate (DHNA) catalyzed by 2-succinyl-6-hydroxy-2,4-cyclohexadiene-1-carboxylate synthase (*yfbB*). Then, DHNA is prenylated and methylated by 1,4-dihydroxy-2-naphthoate octaprenyltransferase and demethylmenaquinone methyltransferase, encoded by *menA* and *menG*, respectively, yielding menaquinones as the end product. An alternative futasine pathway was used by microorganisms that don't have these *men* genes. In this pathway, chorismate is converted to MK via four enzymes encoded by futasine synthase (*mqnA*), futasine hydrolase (*mqnB*), dehydropanthinyl futasine cyclase (*mqnC*), 1,4-dihydroxy-6-naphthoate synthase (*mqnD*), Obligate and facultatively aerobic bacteria use the classical menaquinone pathway, while anaerobic bacteria use the futasine pathway.

Vitamin K produced by bacteria is shown as MK-n, "n" indicating the isoprenoid (5-carbon) unit numbers. MK-8 is present in *E. coli*, while MK-9 was utilized by *Mycobacterium tuberculosis* (*M. tuberculosis*) as an electron carrier. *Helicobacter pylori* (*H. pylori*), *Campylobacter jejuni*, and *Lactobacilli* do not carry *men* genes, these bacteria can synthesize MKs by an alternative futasine pathway (29) (Fig. 2.1).

Bacteroides spp. synthesize MK-10, *Eubacterium lentum* produce MK-6 while *Veillonella* generates MK-7, and *Enterobacter* species generate MK-8. All these bacteria are found in the intestinal flora. Most menaquinones (MK-7, MK-6, MK-8, and MK-10) are found in the distal colon, but the best absorption site is the terminal ileum, where there are scarce menaquinone-producing bacteria and bile salts that are needed for solubilization of menaquinones (7, 21). Therefore, although intestinal microflora synthesizes large amounts of menaquinones, the bacterial menaquinone bioavailability is not adequate, and diet is the major source of vitamin K2 (3, 7, 8). Therefore, it is generally accepted that vitamin K deficiency cannot be compensated by human gut microbiota MKs (30).

B vitamins

Microbial biosynthesis of Vitamin B1

Key Points

- Vitamin B1 (thiamine), as a cofactor, is required for enzymatic reactions such as pyruvate dehydrogenase and α -ketoglutarate dehydrogenase in energy metabolism.
- Vitamin B1 deficiency leads to neurological and cardiovascular disorders (31).

The biosynthesis of vitamin B1

Some members of gut microbiota can produce thiamine and thiamine pyrophosphate (TPP) as free forms of vitamin B1. In the colon, free bacterial vitamin B1 is absorbed mainly by thiamine transporters for distribution throughout the body. However, unlike in the small intestine, TPP produced by the gut microbiota is not converted to free thiamine, because alkaline phosphatase is not released in the colon. Instead, TPP is absorbed directly by the colon via TPP transporters (e.g., TPPT-1) that are highly expressed on the apical membrane of the colon. The absorbed TPP enters the mitochondria via MTPP-1, a TPP transporter that is expressed in the mitochondrial inner membrane and is used as a cofactor for ATP generation. This suggests that bacterial TPP is important for energy generation in the enterocytes. Therefore, dietary and bacterial vitamin B1 appear to have different roles in the host, and TPP production by gut microbiota is very critical for colonic energy generation (32).

Thiamine moieties; thiazole and pyrimidine are independently synthesized and are coupled to form thiamine phosphate. Gut microbiota can obtain thiamine from their environment (33). Vitamin B1 is made up of two parts: 2-methyl-6-amino-5 hydroxymethyl pyrimidine (pyrimidine) and 4-methyl-5-hydroxyethyl thiazole (thiazole). The primary sources of thiazole are 1-deoxy-D-xylulose-5-phosphate, tyrosine, and glycine for gut bacteria. Bacteria obtain the pyrimidine moiety from 5-aminoimidazole ribonucleotide, an intermediate in the purine pathway. (34). Biosynthesis of thiazole moiety (THZ-P) and pyrimidine moiety (HMP-PP) occur separately in bacteria. For instance, in *E. coli*, THZ-P is derived from the oxidative condensation of tyrosine, cysteine, and 1-deoxy-D-xylulose 5-phosphate (DXP). The following *E. coli* genes are involved in vitamin B1 synthesis: *thiI*, *thiG*, *thiF*, *thiS*, *thiH*, *iscS*, and *Dxs*. THZ-P biosynthesis in *B. subtilis* is performed by

glycine oxidase encoded by the *ThiO* gene to form dehydroglycine, which utilizes glycine instead of tyrosine to form dehydroglycine to provide the C2-N3 unit for THZ-P (35,36) (Fig. 2.2.).

Hydroxymethyl pyrimidine phosphate (HMP-P) production is the result of the catalyzation of aminoimidazole ribotide (AIR) by the hydroxymethyl pyrimidine synthase (encoded by *thiC*). Following this catalyzation, the phosphorylation of HMP-P to HMP-PP occurs by hydroxymethyl pyrimidine kinase (encoded by *thiD*). Thiamin monophosphate (ThMP) is formed by the coupling of THZ-P and HMP-PP by thiamin phosphate synthase (encoded by *thiE*). Finally, the active form of thiamin (ThDP) is formed by the thiamin phosphate kinase (encoded by *thiL*) reaction. Thiamin can also be produced by a salvage pathway where thiazole alcohol (THZ) is used to form THZ-P (37, 38).

Recent metagenomic studies showed that *Fusobacterium varium*, *Ruminococcus lactaris*, *Bacteroides fragilis*, *Prevotella copri*, *Lactobacillus* spp, *Bifidobacterium* spp., and *Clostridium difficile* are capable of synthesizing vitamin B1. Indeed, many gut microbiota members possess this property. *Lactobacillus casei* can also produce vitamin B1 in milk products. However, *Faecalibacterium* spp. (Firmicutes) lack a vitamin B1 synthesis pathway, even though they require vitamin B1 for their growth. Therefore, these bacteria must obtain their vitamin B1 from other bacteria or the host (39, 22). Genome annotations in the Pub- SEED platform showed that thiamin monophosphate synthesis may be present in most phyla, except for Firmicutes, and mostly seen in Bacteroidetes and Fusobacteria phylum (22).

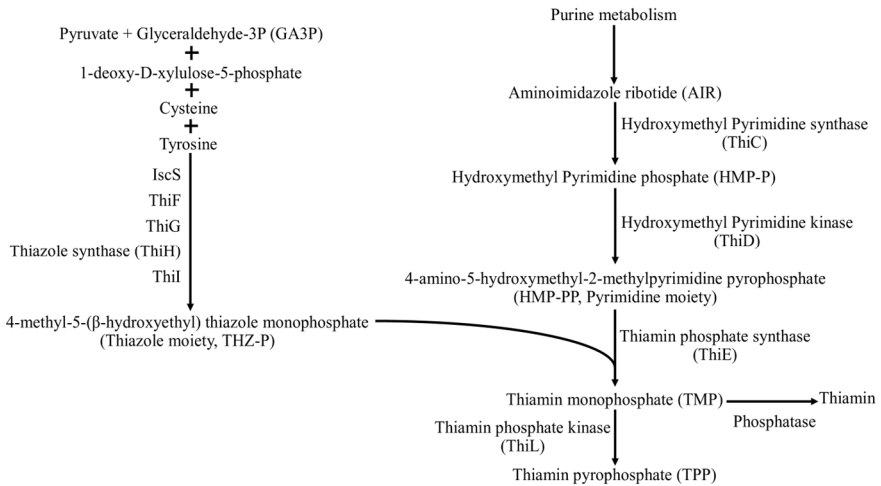


Figure 2.2. The biosynthesis of vitamin B1 in *E. coli*.

Vitamin B2

Key points

- Vitamin B2 (riboflavin) is the precursor for the coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The enzymes that require FMN or FAD as cofactors are termed flavoproteins. Flavoproteins that require these precursors play a critical role in redox reactions (25).
- Vitamin B2 deficiency can lead to glossitis, seborrhea, angular stomatitis, cheilosis, and photophobia (25).
- The free riboflavin conversion of vitamin B2 occurs via FAD pyrophosphatase and FMN phosphatase in the intestine. The adsorption of free riboflavin is facilitated by a riboflavin transporter expressed in the intestine. Free riboflavin is then converted back to FMN or FAD (40).

The biosynthesis of vitamin B2

D-ribulose 5-phosphate and guanosine triphosphate (GTP) are the primary sources of vitamin B2 synthesis (41). One GTP and two ribulose 5-phosphate molecules are required for riboflavin biosynthesis. The imidazole ring of GTP is converted into 5-amino-6-ribitylamino-2,4(1H,3H)-

pyrimidinedione by a sequence of deamination, a side chain reduction, and dephosphorylation. Condensation with 3,4-dihydroxy-2-butanone 4-phosphate obtained from ribulose 5-phosphate leads to 6,7-dimethyl-8-ribityllumazine. The final step in the biosynthesis of the vitamin involves the dismutation of 6,7-dimethyl-8-ribityllumazine catalyzed by riboflavin synthase. *Bacillus subtilis* have the genes for riboflavin biosynthesis (42) (Fig. 2.3).

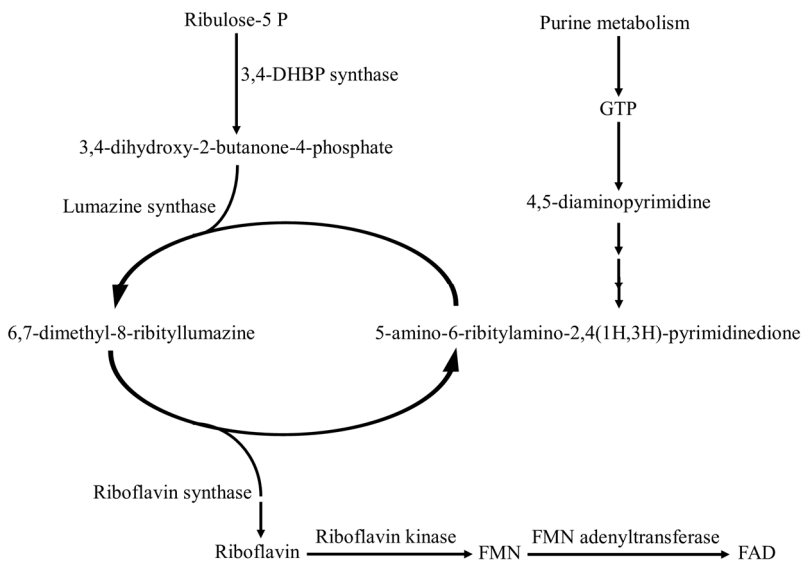


Figure 2.3. The biosynthesis of vitamin B2 in *Bacillus subtilis*. DHBPS: Dihydroxy-2-butanone-4-phosphate synthase, FMN: Flavin mononucleotide, FAD: Flavin adenine dinucleotide.

A metagenomic analysis indicated that gut microbiota bacteria such as *L. fermentum*, *Ruminococcus lactaris*, *Clostridium difficile*, *Bacteroides fragilis*, *Prevotella copri*, and *Lactobacillus plantarum* can synthesize vitamin B2. These microorganisms are the main vitamin B2 source in the intestine. *L. fermentum* isolated from milk products was also found to be capable of synthesizing riboflavin (43). Some *Bacteroidetes* species can synthesize more riboflavin than other phyla such as Firmicutes and Actinobacteria (44). Actinobacteria and Firmicutes phyla I express riboflavin transporter and the enzymes necessary for FAD and FMN generation from free riboflavin. These bacteria can't synthesize vitamin B2 themselves, they require FAD and FMN for their growth and survival (45).

Therefore, there is a competition for riboflavin between the host and the members of the gut microbiota (44).

All Bacteroidetes and Fusobacteria, 92% of Proteobacteria, and 50% of the Firmicutes are predicted to be riboflavin producers. The vitamin B2 pathway is reported to be the most conserved pathway among the eight B vitamins. However, many Actinobacteria and 50% of the Firmicutes phyla don't have this pathway (22).

Vitamin B3

Key points

- Niacin (vitamin B3) is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).
- Both NAD and NADP play critical roles in metabolic reactions by maintaining the redox state of the cell with a central role in aerobic respiration. NAD⁺ and NADP⁺ are the cofactors in lactate dehydrogenase and malate dehydrogenase reactions (46).

The biosynthesis of vitamin B3

Niacin can be derived from tryptophan but with a very low yield. For example, 60 mg of tryptophan is required to produce 1 mg of niacin. The niacin synthesis also needs vitamins B1, B2, and B6. Some bacteria use aspartic acid to produce quinolinic acid. In the NAD biosynthesis pathway, L-Aspartate is converted to nicotinate mononucleotide. There are three enzymes involved in these reactions: L-aspartate oxidase (encoded by *nadB*), quinolinate synthetase (encoded by *nadA*), and quinolinate phosphoribosyltransferase (encoded by *nadC*). Nicotinate mononucleotide (NAM), which is also generated from nicotinate, is subsequently converted to NAD. NAD is degraded by the *E. coli* enzyme. *E. coli* and *Saccharomyces cerevisiae* produce niacin and niacinamide by salvage pathways. Nicotinamide riboside synthesis from NAD is also facilitated by salvage pathway enzymes. Niacin and niacinamide (NAM) are the commercial forms and intermediates in salvage pathways (Fig. 2.4).

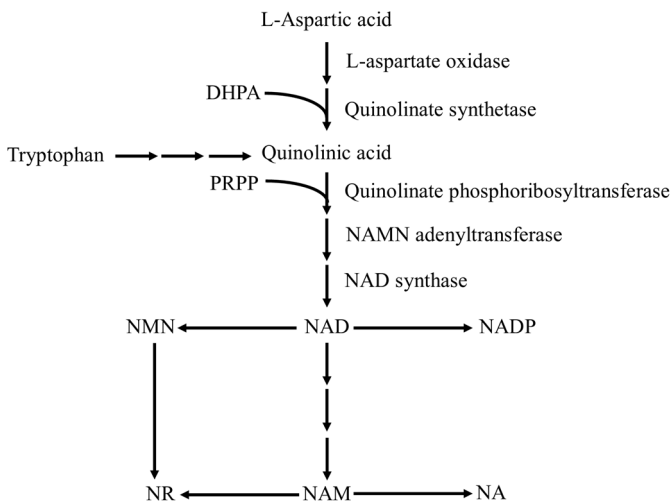


Figure 2.4. The biosynthesis of vitamin B3 in *E. coli*. DHAP: Dihydroxyacetone phosphate, PRPP: Phosphoribosyl pyrophosphate, NAMN: Nicotinamide mononucleotide adenylyltransferase NAM: Nikotinamid, NA: Niacin, NAD: nicotinamide adenine dinucleotide, NADP: nicotinamide adenine dinucleotide phosphate, NM nicotinamide mononucleotide, NR: nicotinamide riboside.

In the Firmicutes phylum, the Bacilli and the Clostridia classes are known as niacin producers. Most Fusobacteria and Proteobacteria are also able to synthesize niacin. The uptake of the nicotinamide and nicotinic acid from the environment is only observed in Actinobacteria, Firmicutes, and a single Proteobacteria. The salvage of N-ribosylnicotinamide is only found in four Firmicutes and 18 Proteobacteria phyla (47,48).

The B3 biosynthesis pathway is observed in the majority of the gut microbiota members. The Actinobacteria and Firmicutes phyla produce much less vitamin B3 than the other phyla. The presence of the niacin salvage pathways is seen in these phyla but not in the Fusobacteria and Bacteroidetes. At the species level, *Fusobacterium varium*, *Clostridium difficile*, *Bacteroides fragilis*, *H. pylori*, *Prevotella copri*, and *Bifidobacterium infantis* are predicted to carry vitamin B3 producer characteristics (49,50).