Microbial Production of Vitamins

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Abstract

Vitamins are important nutrients for humans and animals. Their requirement is rising worldwide in different areas such as therapeutic and food industries. Vitamins are naturally produced by several microorganisms. However, its biosynthetic mechanisms are well coordinated as its requirements are just in tracer quantities and the synthesis of some vitamins is limited to few microorganisms. Recently, large scale productions of vitamins have been more concentrated on microbial fermentation as compared to chemical synthesis. Because many steps are required in the chemical synthesis of vitamins, which makes it expensive. So, industrial microbial fermentation is utilized to produce large amounts of vitamins to accomplish the global yearly demands. Further, recent advancement in the fields of systems and synthetic biology would provide an opportunity to engineer the microbial metabolic pathway for the increased production of vitamin. It can lead over to chemical synthesis methods, but scientific difficulties might persist. Further scientific and regulatory concerns remain, which need to be resolved before extended to the user.

Keywords

Vitamins · Microbial · Biosynthesis · B_{12} · *E. coli*

9.1 Introduction

For the normal functioning of organisms, vitamins play a vital role in various physiological reactions. On the basis of the solubility nature of vitamins, it has been classified into two groups such as water-soluble (B, C group) and fat-soluble

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V. Singh et al. (eds.), *Engineering of Microbial Biosynthetic Pathways*,
https://doi.org/10.1007/978-981-15-2604-6_9

(A, D, E, and K). Microbes and plants are producing these different types of vitamins naturally; however, animals get the vitamins from these sources. Intriguingly, vitamins are needed in a small amount in various pathophysiological and other conditions because it acts as a coenzyme in different metabolic reactions in all organisms. Vitamins are sensitive to heat, light, pH, and oxygen, and its content decreased during food processing and preservation (Vandamme and Revuelta 2016). Presently more than 10 tons of vitamin B_{12} are produced per year from different bacterial species (Martens et al. 2002). The worldwide production of fermented vitamin has been increased from 5 to 75% from 1999 to 2012 (Schwechheimer et al. 2016).

Two fungi *Candida maltose* R42 and *Botrytis allii* NRRL 2502 have been utilized for the microbial transformation of vitamin D_3. 1α-Hydroxyvitamin D_3 was produced as a metabolite (Ahmed et al. 2014). The study has shown that CYP105A1 can convert vitamin D_3 (VD_3) to its active form 1α,25-dihydroxyvitamin D_3 (1,25D3). A site-directed mutagenesis method has utilized to construct double variants (R73A/R84A and R73A/R84V) of CYP105A1. An activity of the double variants has shown 100-fold higher as compared to the wild type of CYP105A1 (Yasuda et al. 2017).

Vitamin K [Menaquinone-8 (MK-8)] is comprised of a polar head group and a non-polar side chain. For the production of vitamin K, *Escherichia coli* has been utilized. Overexpression of *E. coli* DXR, IDI, or IspA has enhanced MK-8 quantity up to twofold. However, MenD or MenA has significantly enhanced MK-8 quantity than the wild type (Kong and Lee 2011). Previously, a study has demonstrated that overproduction of menaquinone (MK) was achieved using mutated *Bacillus subtilis*. Menaquinone has been produced by menadione-resistant mutant 30% more as compared to its parent strain (Sato et al. 2001). Some bacterial strains can synthesize various vitamins such as vitamin B_1, B_2, B_3, B_5, B_6, B_7, B_9, and B_{12} as shown in Table 9.1.

9.2 Microbial Production of Vitamin B_1, B_2, B_3, and B_5

Vitamin B_1 (Thiamin) biosynthesis is mainly regulated by thiamine pyrophosphate (TPP) riboswitches in bacteria and a transcriptional repressor in archaea (Hwang et al. 2017). TPP is a vital cofactor in amino acid and carbohydrate metabolism (Eggersdorfer et al. 2012). A riboswitch-based biosensor enabled the discovery (Genee et al. 2016) and metabolic engineering (Bali et al. 2018) of thiamine transporters, and an improved thiamine production in *E. coli* overexpressing thiFSGHCE and thiM or thiD combined with transposon mutagenesis (Cardinale and Sommer 2017).

Vitamin B_2 (Riboflavin) is used in food industry as food colorant and also as food supplement. *E. coli* RF05S-M40 strain has been utilized for the production of vitamin B_2 and the study demonstrated a 12-fold (2702.8 mg/L) higher production than other strains of *E. coli* RF01S (Lin et al. 2014). Initially, riboflavin manufacturing has been enhanced by an amalgamation of conventional mutagenesis

Table 9.1 Vitamins-producing bacterial strains

S. no.	Vitamins	Microorganisms	References
1.	B_1 (thiamin)	*Lactobacillus rhamnosus* strain GG (LGG) *Bifidobacteria* *Leuconostoc* *Bacteroides fragilis*	LeBlanc et al. (2017) Hou et al. (2000) Kneifel et al. (1992) Magnúsdóttir et al. (2015)
2.	B_2 (riboflavin)	*L. lactis* LGG *Bacteroides fragilis* *Clostridium difficile* *Lctobacillus plantarum* *Ruminococcus lactaris*	Burgess et al. (2004) LeBlanc et al. (2017) Magnúsdóttir et al. (2015) Juarez Del Valle et al. (2016) Russo et al. (2014)
3.	B_3 (niacin)	*Ruminococcus lactaris* *Clostridium difficile* *Helicobacter pylori*	Deguchi et al. (1985)
4.	B_5 (panthothenic acid)	*Bacteroides fragilis* *Ruminococcus lactaris* *Ruminococcus torques*	Magnúsdóttir et al. (2015)
5.	B_6 (pyridoxin)	*Bifidobacterium longum* *Collinsella aerofaciens* *Bacteroides fragilis*	Deguchi et al. (1985) Magnúsdóttir et al. (2015)
6.	B_7 (biotin)	*Campylobacter coli* *Lactobacillus helveticus* *Bacteroides fragilis*	Shah and Patel (2014) Magnúsdóttir et al. (2015)
7.	B_9 (folic acid)	LGG *Bacteroides fragilis* *L. Plantarum WCSF1* *Fusobacterium varium* *Prevotella copri* *B. adolescentis* DSM 18350	LeBlanc et al. (2017) Magnúsdóttir et al. (2015) Santos et al. (2008) D'Aimmo et al. (2012) Rossi et al. (2011) Strozzi and Mogna (2008)
8.	B_{12} (cobalamin)	*Prevotella copri* *Bacteroides fragilis* *L. fermentum* CECT 5716 *Fusobacterium varium*	Deguchi et al. (1985) Magnúsdóttir et al. (2015) Cardenas et al. (2015) Lee and O'Sullivan (2010)

and genetic engineering. A study has suggested that *Bacillus megaterium* can be utilized for the production of biotechnologically important molecules. Another study has demonstrated that the microbial fermentation of riboflavin can be achieved through genetically modified *Ashbya gossypii (A. gossypii*). The RIB genes contribute to the production of riboflavin in *A. gossypii*. An RIB-gene-modified *A. gossypii strain* has produced 5.4-fold more riboflavin than the wild type (Ledesma-Amaro et al. 2015). *B. subtilis* is widely used as vitamin B_2 (riboflavin)-producing strains. A biosynthetic mechanism of riboflavin in *B. subtilis* has been well-established, and a study has demonstrated it through the combined approaches of metabolomics and transcriptomics and ^{13}C metabolic flux analysis under various dissolved oxygen (DO) tension states. In ResD-ResE system, DO has been utilized as the signal receiver to analyze the differences between riboflavin synthesis and biomass (Hu et al. 2017).

Vitamin B_3 (Niacin) occurs in three forms that are enzymatically changed into the important cofactors (Rajman et al. 2018). An industrial fermentation process for vitamin B_3 is still not established (Chand and Savitri 2016) although biocatalytic methods exist that use 3-cyanopyridine as a first material that is hydrolyzed to niacin by a nitrilase or hydrated to niacinamide by a nitrile hydratase (Chuck 2009). Vitamin B_5 (D-Pantothenic acid) is widely used, and its microbial production mainly depends on the pantothenate synthetase (PS) enzyme. A recent study has utilized different phylogenetically dissimilar PS-encoding genes, from *B. subtilis*, *E. coli*, *Bacillus thuringiensis*, *Bacillus cereus*, *Enterobacter cloacae*, and *Corynebacterium glutamicum (C. glutamicum)* to overexpression in *E. coli.* The maximum specific activity (205.1 U/mg) and turnover number (127.6 s^{-1}) have been shown by *C. glutamicum* (Tigu et al. 2018). A notion of phylogenetically distant based study should offer support to other researchers that are thinking similar planned work.

9.3 Microbial Production of Vitamin B_6, B_7, and B_9

Vitamin B_6 (pyridoxine) is a biologically very important nutrient, which acts as a cofactor for several enzymes. However, vitamin B6 is synthesized by microorganisms and plants. For the production of pyridoxine, *B. subtilis* has been utilized. The strain produced 14 mg/L pyridoxine in a small-scale production assay. On the other hand, by improving the growth environments and co-feeding of deoxyxylulose and 4-hydroxy-threonine, the yield has been improved to 54 mg/L (Commichau et al. 2014).

Vitamin B_7 (or biotin) is a vital cofactor for carboxylation reactions. Biotin intermediate pimelic acid is produced by two different ways (Lin and Cronan 2011). Previously, efforts for engineering biotin synthesis strains using random mutagenesis and antimetabolites encountered insufficient achievement. The maximum biotin titer described is 500 mg/L with *Serratia marcescens* after 10 days of fermentation (Streit and Entcheva 2003). Vitamin B_9 (Folic acid) is the common name of folates that play a vital function as cofactors in one-carbon transfer reactions. Folates are contributed to the metabolism and biosynthesis of different biomolecules such as hormones, lipids, DNA, and proteins. A recent study has shown the production of folic acid through a fungus *A. gossypii.* Engineered strains of *A. gossypii* has produced a 146-fold vitamin B_9 as compared to the wild type (Serrano-Amatriain et al. 2016). However, folic acids are mostly synthesized through chemical methods.

9.4 Microbial Production of Vitamin B_{12}

Vitamin B_{12} is an important nutrient, which is essential for vital metabolic activities in humans. Presently vitamin B_{12}-producing lactic acid bacteria (LAB) have been considered significantly because of the generally recognized as safe (GRAS) position. Recent study has demonstrated the production of vitamin B_{12} (adenosylcobalamin) from the engineered *E. coli* strain. A study has shown about 250-fold increase in the production of vitamin B_{12} using recombinant *E. coli* strain (Fang et al. 2018). It has presumed that adenosylcobinamide (AdoCbi) is synthesized through the attachment of (R)-1-amino-2-propanol (AP) to AdoCby to yield AdoCbi in a single step reaction, which is catalyzed by a two-component system (designated as α and β in *Paracoccus denitrificans*) (Fig. 9.1).

A very significant coenzyme vitamin B_{12} (cobalamin) in the cell metabolism has been broadly used in therapeutic and food industries. The broad biosynthesis of VB_{12} requires about 30 genes; nevertheless, overexpression of these genes did not result in an estimated rise in VB_{12} production (Cai et al. 2018). *Propionibacterium*

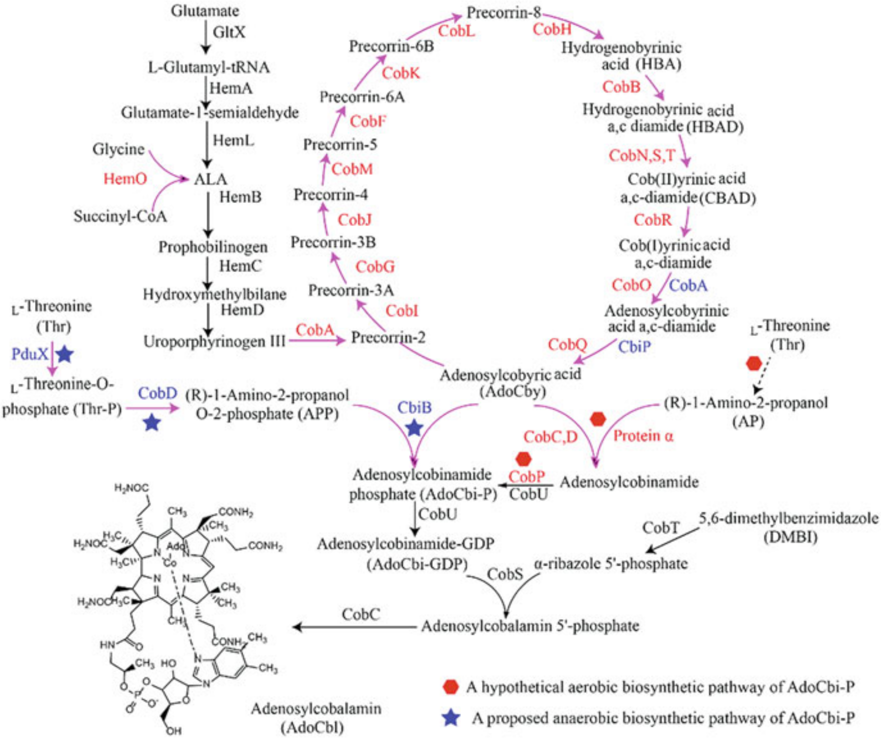

Fig. 9.1 Biosynthetic pathway of adenosylcobalamin. Endogenous enzymes from *E. coli* are shown in black. Enzymes from aerobic bacteria such as *Brucella melitensis*, *Rhodobacter capsulatus*, *Sinorhizobium meliloti*, and *Rhodopseudomonas palustris* are shown in magenta. Enzymes from *Salmonella typhimurium* are shown in blue. Ado represents the abbreviation of adenosyl (Fang et al. 2018. *Adapted with permission*)

freudenreichii has been utilized for overexpression of fusion enzyme BluB/CoBT2. This enzyme is responsible for the biosynthesis of the 5,6-dimethylbenzimidazole, which plays a vital role in the biosynthetic pathway of vitamin B12 (Deptula et al. 2015). *Gluconobacter oxydans* NBRC3293 strain produces 2,5-diketo-D-gluconate (2,5DKG) from D-glucose via D-gluconate and 2-keto-D-gluconate (2KG). This compound acts as an intermediate for the production of vitamin C (Kataoka et al. 2015).

Liquid chromatography-selected reaction monitoring mass spectrometry assays (LC-SRM-MS) has been utilized to investigate the proteins involved in vitamin B_{12} production from marine microbial populations. Use of this technique is helpful to analyze the nutritional status of microbial community members with respect to vitamin B_{12} production (Bertrand 2018). For the production of vitamin B_{12}, *Sinorhizobium meliloti* has been utilized using the novel mutation technique of atmospheric and room temperature plasma (ARTP). In this study, a riboswitch element has been used from *Salmonella typhimurium*, and it provides a convenient high-throughput assessment technique for increasing high VB_{12}-yield strains (Cai et al. 2018). Recent new technologies such as DNA microarray, proteomic, and metabolic investigations have been utilized to enhance the production of riboflavin using *A. gossypii* (Kato and Park 2012). *Ketogulonigenium vulgare* (*K. vulgare*) strain has been utilized for the overproduction of 2-keto-L-gulonic acid (2-KGA) that is a precursor of vitamin C. L-sorbosone dehydrogenase (SNDH) is one of the key enzymes for the biosynthesis of 2-KGA. As per whole genome sequence analysis of *K. vulgare*, it has been demonstrated that two genes were encoding sorbosone dehydrogenases, one derived from the chromosome (named as sndhg) and the other from the plasmid (named as sndhp) (Chen et al. 2016a). For the improvement of the production of 2-KGA, in silico approach has been utilized. In the study, L-sorbose dehydrogenases (SDH) genes of *K. vulgare* has been modeled. For molecular docking, six SDHs have been used for the prediction of binding mode with cofactor pyrroloquinoline quinone (PQQ). After docking, these genes were overexpressed in *K. vulgare* HKv604 and found significant enhancement (7.89–12.56%) (Chen et al. 2016b). Previously genomics- and proteomics-based studies have investigated SDH and SNDH from *Gluconobacter oxydans* T-100 strain. These two enzymes have the ability to convert D-sorbitol to 2-keto-L-gulonate (2-KLGA). Significant production from D-sorbitol to 2-KLGA (130 mg/mL) had been achieved through recombinant *Gluconobacter* using fermentation (Saito et al. 1997).

Akkermansia muciniphila involves in the degradation of mucus sugars into oligosaccharides. After degradation and release of oligosaccharides, it becomes available for various intestinal microbes for microbial synthesis of vitamin B_{12} and other organic molecules (Belzer et al. 2017). Squalene is a triterpene compound and usually found in numerous organisms such as bacteria, fungi, algae, plants, and animals. It acts as a precursor for the synthesis of vitamins (Ghimire et al. 2016). *Bacillus megaterium* has been utilized to produce a large scale of vitamin B_{12}. After providing an essential supplement, it has reached up to 204.46 μg/mL of the B_{12} production as compared with control (0.26 μg/mL) (Mohammed et al. 2014).

Several studies have utilized *Lactobacillus* and *Enterococcus* for the microbial production of vitamin B_{12}. A study has utilized five *Enterococcus* strains isolated from infant feces for the production of vitamin B_{12}. *Enterococcus faecium* LZ86 has shown the highest B_{12} production (499.8 ± 83.7 μg/L), among all five strains of *Enterococcus* (Li et al. 2017a). Similarly, another study has demonstrated vitamin B_{12}-producing *Lactobacillus* strains and their characteristics in tolerance to environmental stresses, gastric acid, and bile salts. Two isolates *Lactobacillus plantarum* LZ95 and CY2 exhibited great extracellular B_{12} production of 98 ± 15 μg/L and 60 ± 9 μg/L, respectively (Li et al. 2017b). Anaerobic biosynthesis of the lower ligand of vitamin B_{12} 5,6-dimethylbenzimidazole (DMB) has been investigated in the obligate anaerobic bacterium *Eubacterium limosum* (Hazra et al. 2015).

Propionibacterium freudenreichii subsp. shermanii has been grown on the spent media previously used by lactic acid bacteria (LAB) for the production of vitamin B_{12}. A study has demonstrated that utilized media could be reused for the production of *Propionibacterium* and metabolites, depending on the LAB strain that was earlier grown. Media remediation is needed to improve the production of vitamin B_{12}, particularly by immobilized cells (Gardner and Champagne 2005). This investigation presents a possibility of reutilizing the used media generated by the producers of LAB or producers of fermented vegetables. It is an attractive procedure from cost-effective and eco-friendly positions.

9.5 Concluding Remarks

Vitamins are not synthesized by humans and animals, and therefore it is required from other sources. Trace amounts (~1 μg/day) of vitamins are required for the nourishment of humans. However, vitamin deficiency is a critical problem of micronutrient malnutrition affecting billions of individuals globally. Consequently, the supplement of some vitamins into food has been adapted as compulsory in several nations, therefore, adding to a rising need of vitamin. Vitamin B_{12}-producing *Enterococcus faecium* strain LZ86 and *Lactobacillus plantarum* LZ95 have essential probiotic properties, and may help as a good candidate for vitamin B_{12} enrichment in the food industry. Furthermore, there is a need to identify a better microbial strain, which can produce large quantities of vitamins to fulfill the current demands. To identify the better microbial strain, we can explore the different omics approaches such as metagenomics, metatranscriptomics, metaproteomics, and metabolomics.

Competing Interests: There is no competing interest.

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