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A study of microbial synthesis of group B vitamins by sustainable methods

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Abstract
Vitamins are defined as organic components that are necessary for normal growth and nutrition and must be consumed in modest amounts in the diet as they cannot be produced by human body. All living things require these vitamins for proper metabolism, which they naturally produce in plants and microorganisms. At least 30 different types of substances are referred to as "vitamins," more than 20 of which are known to be essential for biological health. Using biotechnology to enrich existing natural sources or develop new ones that are better suited for industrial uses, vitamin output can be increased in an environmentally responsible manner. vitamins are produced industrially and used widely as cosmetics, medicinal agents, health and technical aids, and food and feed additives. most vitamins are produced chemically, industrial bioprocesses have been devised to produce Vitamin B_2 and Vitamin B_{12} successfully. This article reviews some of the microbial biosynthetic means of group B vitamins.

Keywords: vitamins, folic acid, biotin, microbial synthesis, physiological processes

Introduction

Vitamins are defined as organic components that are necessary for normal growth and nutrition and must be consumed in modest amounts in the diet as they cannot be produced by human body. They can be split into two categories based on their chemical makeup: fat-soluble vitamins and water-soluble vitamins. A vitamin that is water-soluble is easily soluble in water and insoluble in organic solvents.[1] Most of these proteins are eliminated with urine after absorption, and very few are stored by the body. Vitamins that can dissolve in fat but not in water are known as fat-soluble vitamins, and they are kept in the liver or other fatty tissues for later use.[2] All living things require these vitamins for proper metabolism, which they naturally produce in plants and microorganisms. In countries where a diversified diet is missing, it is especially critical since the lack of these compounds causes a variety of health issues that have a significant negative economic impact on both people and farm animals. Animals that cannot manufacture enough vitamins on their own or that synthesize insufficient amounts to meet all of their demands depend on vitamins for healthy growth and health.[3] All living things require vitamins as necessary nutrients, yet many plants and microbes can synthesis them spontaneously on their own. Contrarily, in order to maintain good health, people and other animals must consume enough vitamins through their diets or through supplements.

At least 30 different types of substances are referred to as "vitamins," more than 20 of which are known to be essential for biological health.[4] A sizable industry for the manufacture of vitamins has successfully grown over the past few decades all over the world. Such vitamins have historically been created using organic chemical synthesis, but this frequently necessitates a large number of reactions, expensive equipment, and solvents that are typically unwelcome pollutants detrimental to the environment. Using biotechnology to enrich existing natural sources or develop new ones that are better suited for industrial uses, vitamin output can be increased in an environmentally responsible manner.[5] Mutagenesis and metabolic engineering, which can be done through chemical or biological methods, have historically been used to increase vitamin production strains. Through genetic and metabolic engineering, microbes can be changed through biotechnology to produce vitamins. Chemical processes are typically costly, wasteful, waste-prone, and require expensive waste disposal. However, because it is inexpensive, uses little energy, and is simple to recycle trash, the microbial fermentation approach has garnered a lot of interest. Today, vitamins are produced industrially and used widely as cosmetics, medicinal agents, health and technical aids, and food and feed additives.[6] By screening natural vitamin producers, studying the most favorable growth conditions, increasing output, and improving downstream procedures to extract the pure product, biological vitamin manufacturing has been established. Researchers now acknowledge the fermentation method, which is safer and more environmentally beneficial than chemical processes.[7] This review discusses some of the aspects of microbial production of vitamins and significance thereof.

Water soluble Vitamin B:

While most vitamins are produced chemically, industrial bioprocesses have been devised to produce Vitamin B_2 and Vitamin B_{12} successfully.[8] B vitamins are increasingly in demand due to their numerous uses in food, medicine, feed, and other industries.

Vitamin B_1

The first B vitamin discovered is vitamin B_1, usually referred to as thiamine. Thiamine monophosphate (ThMP), thiamine diphosphate (ThDP), thiamine triphosphate (ThTP), adenosine thiamine triphosphate (AThTP), and adenosine thiamine diphosphate are the five phosphate derivatives of vitamin B_1.[9] The active form of thiamine, thiamine pyrophosphate (TPP), can decrease cholinesterase activity, lessen skin irritation, stop seborrheic dermatitis, or eczema, and enhance skin health. Thiamine plays a crucial role in oxidative decarboxylation and transketolase processes, and deficiencies in this substance are linked to imbalances in the status of carbohydrates.[10] Dietary sources of is vitamin B1 include wheat germ, soy beans, dry beans, and peas. Although it is present in many foods, its concentration is frequently low because cooking destroys it. To meet the needs of both humans and animals, vitamin B1 is chemically synthesised. Two different ways of synthesising substances have been developed over time: (1) condensation of the pyrimidine and thiazole rings, and (2) building the thiazole ring on top of a pyrimidine component that has already been created. *B. subtilis* has recently been used to produce high levels of thiamine in medium.[11] Several species of *Bacillaceae, Streptococcaceae, Corynebacteriaceae, Lactobacillaceae* and *Brevibacteriaceae* have been successfully mutated by which thiamine production is deregulated and thiamine products are released from cell.

Vitamin B_2

Riboflavin is another term for vitamin B_2, which gets its name from its yellow hue. Since riboflavin is the primary constituent of the FAD and FMN cofactors, it is crucial for the normal operation of all flavo-proteins.[12] Persistent anemia is a symptom of riboflavin deficiency. Several microorganisms, including ascomycete fungus (*Ashbya gossypii, Eremothecium ashbyii*), yeasts (*Candida flaeri, Candida famata*), and bacteria (*B. subtilis, Corynebacterium ammoniagenes*), naturally synthesize this substance. The purR gene in *B. subtilis* was deleted and the ribA gene was overexpressed specifically in the genetic engineering process, which resulted in the highest possible output of riboflavin. In *Candida famata*, the high riboflavin-producing strain AF-4 was created by combining sef1 and imh3 overexpression with conventional mutagenesis techniques.[13]

Vitamin B_3

Nicotinic acid, nicotinamide, and other substances like inositol hexanicotinate that have a similar biological function make up the vitamin B_3 group.[14] The name "niacin" can group these substances together. The pyridine coenzymes NAD (nicotinamide adenine dinucleotide) and NADP are made from niacin as a precursor (nicotinamide adenine dinucleotide phosphate). It is present in quite high concentrations in the muscle tissues, fruits, and internal organs of animals. Niacin is mostly utilized today in the production of various medications or as a pharmaceutical intermediate in feed additives to improve the utilization of feed protein. In *Rhodococcus rhodochrous*, nitrilase has been overexpressed, resulting in a strain that can almost completely convert 3-cyanopyridine into nicotinic acid.[15]

Vitamin B_5

Pantothenic acid, generally known as vitamin B_5, is made up of pantoic acid and -alanine, a precursor to coenzyme A. In addition to dexpanthenol and calcium pantothenate, which are substances created in a lab from d-pantothenic acid, it is marketed as d-pantothenic acid.[16] It is crucial for preserving the wellbeing of the blood and skin. Its primary role is to help the body produce energy, but it can also regulate how fat is metabolised and is a crucial nutrient for the brain and nerves. Its large-scale manufacturing procedure combines chemical and enzymatic reactions. Chemically, isobutyraldehyde, formaldehyde, and cyanide are converted into pantolactone. Beta-alanine and d-pantolactone are combined to create pantothenic acid. The essential protein for racemic resolution is the fungal enzyme lactohydrolase, which uses d-pantolactone as a substrate but not l-pantolactone.[17] It converts d-pantolactone into d-pantoic acid, which can be easily distinguished from pantolaconte's l-enantiomer. High activity of this enzyme have been observed in *Gibberella*, *Cylindocarpon*, and *Fusarium*. In addition, cells of Fusarium oxysporum have been immobilised in calcium alginate gels, allowing for high conversion rates.

Vitamin B_6

It is a water-soluble vitamin that shows up in the body as phosphate. This vitamin influences the metabolism of proteins and amino acids and keeps blood homocysteine levels stable. Additionally, it contributes to the metabolism of lipids, carbohydrates, and one-carbon compounds. It is necessary for the creation of neurotransmitters and plays a role in the development of gluconeogenesis, glyconeogenesis, immunological system, and haemoglobin.[18] Pyridoxal 5′-phosphate (PLP), which is a cofactor of several proteins and enzymes in all organisms, is the most adaptable form of vitamin B_6.[19] Entire manufacture of this vitamin is by chemical techniques. When certain microorganisms were tested for their ability to manufacture vitamin B6, *Flavobacterium* sp. and *Rhizobium meliloti* were found to be the most effective producers.

Vitamin B_7

It is also called as Biotin. It is important vitamin for human physiological processes especially for the fats and proteins metabolism. This vitamin is has a significant role in normal growth and development of human body. This vitamin is currently produced on industrial scale by synthetic chemical methods. Microbiological synthesis and production of biotin can be achieved but the issues of lowering the production costs have to be resolved. It has been found that *Corynebacterium glutamicum*, *Mesorhizobium loti* and *Ensifer meliloti* can synthesize biotin in sufficient amounts and studies should be focused on the optimization of the production parameters to obtain comparatively higher yields. Some experiments were carried out using random mutagenesis and use of antimetabolites for the strain improvement for synthesis of biotin. *Serratia marcescens* was shown to produces higher amount of biotin through such experiments.[20]

Vitamin B_9

This is also termed as folic acid. Folates are crucial for the metabolism of nucleotides and amino acids. The natural form of vitamin B_9 is polyglutamic acid and its biologically active form is tetrahydrofolate.[21] The sole vitamins are folic acid, folinic acid, and 5-methyltetrahydrofolate (THF). This vitamin plays significant role in the process of hematopoiesis. Megaloblastic anaemia, delayed cell maturation, and decreased haemoglobin concentration in red blood cells can all result from deficiency of this vitamin in human body. Many bacteria have access to the biological precursors glutamate, phosphoenolpyruvate, D-erythrose-4-phosphate, and GTP and therefore it becomes feasible to bio-engineer such bacteria to over-produce this vitamin. It has been proved successfully to develop *Bacillus subtilis* or *Ashbya gossypii* by genetic engineering methods to manufacture folic acid.[22] The chassis strain for the manufacture of folic acid, *A. gossypii* has drawn growing interest as study into it continues. Natural folic acid synthesis by *A. gossypii* can reach 0.04 mg/L, however after metabolic engineering process, it can reach 6.59 mg/L.[23] It has been claimed that yeast strains or modified lactic acid bacteria used in the fortification of dairy products can produce folates. Additionally, this is the largest documented production value to date. 4-6 biosynthesis genes are carried by the folate-related transcription units in *B. subtilis*, whereas seven fol genes are dispersed over the genome in *E. coli*. There is still a long way to go for the fermentation of this product because the commercial chemical synthesis of folic acid is inexpensive, unless the ecologically harmful element of the chemical synthesis process is reduced. It will be difficult to build a bioprocess unless environmental restrictions force it because folic acid's chemical manufacture is extremely inexpensive and its demand is modest.

Vitamin B_{12}

Plants and animals cannot synthesize Vitamin B12. Many microorganisms possess the ability to produce this vitamin through the biosynthetic pathways occurring in their cells. The chemical synthesis of this vitamin was studied thoroughly but these synthetic processes are very complicated and production costs involved are also very high, therefore in most of the instances, microbial synthesis of this vitamin is being practiced. The most commonly used strains for the fermentative production of vitamin B_{12} are *Pseudomonas denitrificans* and *Propionibacterium freudenreichii*.[24] To enhance the production capabilities of vitamin B_{12} for these strains, techniques of random mutagenesis using a variety of chemical mutagens have been studied and worked out in detail. *Propionibacterium shermanii* is another bacteria that has found to produce this vitamin in considerable quantities.[25] In all cases optimization of physico-chemical parameters of fermentation have to be done to obtain the higher yields.

Conclusion

Compared to conventional chemical synthesis techniques, the fermentative production of vitamins utilizing bacteria, yeasts, or microalgae has many benefits. Vitamins produced via biological processes may be more suitable for both internal and external applications in terms of safety, biological activity, absorption rate, etc. Vitamin requirements within cells are rather low, hence their production has not evolved to be very productive in nature. However, logical and conventional metabolic engineering has successfully built commercial bioprocesses for producing vitamin B complex. Even though highly complex biosynthetic pathways, enzymes, and low present manufacturing costs make creating industrially relevant cell factories exceedingly difficult, a number of indicators point to a potential shift toward bio-based processes. Although vitamin B_2 and vitamin B_{12} fermentation has advanced technologically and is used in industrial production, techniques for the other B-group vitamins have not yet been established. The advancement of synthetic biotechnology opens up new possibilities for the development of vitamin cell factories.

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