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Review Article

VITAMIN B COMPLEX: A REVIEW of Different Types and Activities

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Abstract

B complex vitamins are a group of water-soluble compounds essential for numerous physiological functions in the human body. Comprising eight distinct members, including B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate), and B12 (cobalamin), these vitamins play pivotal roles in energy metabolism, DNA synthesis, and red blood cell formation. Thiamine, for instance, is crucial for converting carbohydrates into energy, while riboflavin supports tissue maintenance and growth. Niacin contributes to skin health and aids in the metabolism of fats. Pantothenic acid is essential for synthesizing fatty acids and amino acids, while pyridoxine supports neurotransmitter function. Biotin is vital for skin, hair, and nail health, and folate is integral for DNA synthesis and cell division. Cobalamin, often associated with nerve function, assists in the formation of red blood cells. These vitamins are commonly found in a variety of foods, and their deficiency can lead to various health issues, including anemia, fatigue, and neurological problems. We discuss the pharmacological activities, metabolism, and Structure-Activity Relationship (SAR), as well as the derivatives and uses of vitamins B1, B2, B3, B5 and B12.

1. Introduction

The micronutrients known as vitamins can be taken from a balanced, healthful diet and are either fat- or water-soluble. The B-complex vitamins exemplify water-soluble nutrients, easily absorbed from a healthy stomach and promptly excreted by the kidneys. They are important for maintaining optimal health and are necessary for their essential physiological functions. Hence, when any of the B vitamins are deficient, a well-balanced diet containing the full spectrum of these nutrients is typically required.[9] B vitamins directly affect cell metabolism, brain function, and body energy levels. There are eight types of vitamins in vitamin B complex; thiamine B1, riboflavin B2, niacin B3, pantothenic acid B5, pyridoxine B6, biotin B7, folate B9 and cobalamin B12.[10]

2. Vitamin B1 (Thiamine)

Thiamine, existing as thiamine pyrophosphate in the human body, holds significance for various tissues, especially in high concentrations within skeletal muscle, liver, heart, kidneys, and the brain. In its active form, thiamine diphosphate, it functions as a cofactor for enzymes primarily involved in carbohydrate catabolism. Thiamine (vitamin B1) plays a crucial role in facilitating the conversion of carbohydrates and fat into energy. Upon cellular entry via thiamine kinase, activated by Mg^{2+} ions, it undergoes phosphorylation into its active form, diphosphothiamine (DPT or cocarboxylase). **[Figure 1]**.[2]

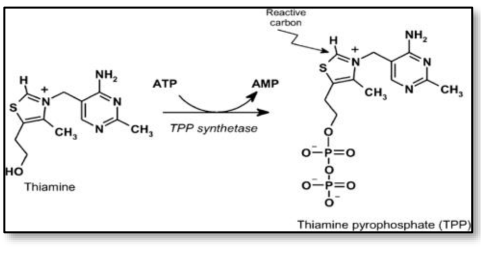


Figure 1: Thiamine activation[2]

2.1. Pharmacological activity of vitamin B1

Being water-soluble, thiamine doesn't accumulate in the body, necessitating daily intake. Sources of thiamine include meats (particularly pork), wheat germ, liver, poultry, eggs, fish, beans, peas, nuts, and whole grains.[11] Poor dietary intake or long-term alcoholism might hinder thiamine absorption and use.[12] Beriberi was the first illness linked to thiamine deficiency.[13] In pregnancy, thiamine is transferred to the fetus through the placenta, and pregnant women, especially in the third trimester, have an increased need for this vitamin. Thiamine plays a crucial role not just in the development of mitochondrial membranes but also in synaptic membrane function. Furthermore, a deficiency has been linked to impaired brain development in infants and is considered a potential factor in sudden infant death syndrome.[14, 15]

2.2. Metabolism of vitamin B1

In blood, the thiamin diphosphokinase enzyme converts thiamin into its active form, thiamin pyrophosphate (PP). TPP plays different roles during different steps of metabolism, glycolysis, Krebs cycle, and pentose phosphate pathway.

- Thiamin pyrophosphate (TPP) collaborates with enzymes in the metabolism of carbohydrates, lipids, and branched-chain amino acids.
- TP acts as a cofactor at several steps during glycolysis and oxidative decarboxylation of carbohydrates.
- TPP acts as a coenzyme for the mitochondrial enzyme complexes such as a-ketoglutarate dehydrogenase and pyruvate dehydrogenase. These enzymes have a critical role in the Krebs cycle and tricarboxylic acid cycle. **[Figure 2]. [16]**

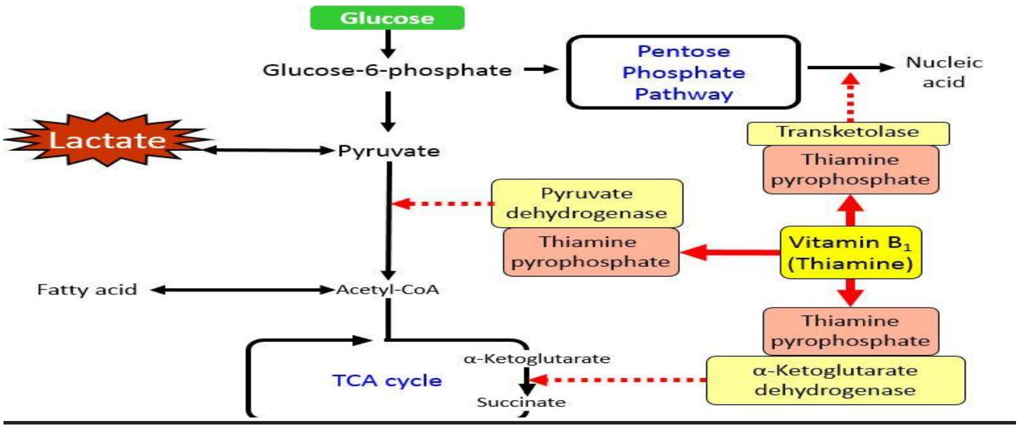


Figure 2: Thiamine metabolism[4]

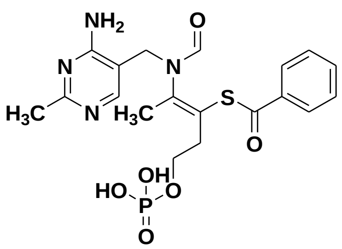
2.3. Structure activity relationship of vitamin B1:[17]

Thiamine molecule is composed of pyrimidine (4-amino-2-methylpyrimidine) and thiazolium (4-methyl-5-(2-hydroxyethyl)-thiazolium) rings which are linked by a methylene bridge between C3 carbon atom of pyrimidine ring and N3 nitrogen atom of thiazolium ring. **[Figure 3]**.[18]

2.4. Derivatives of vitamin B1:

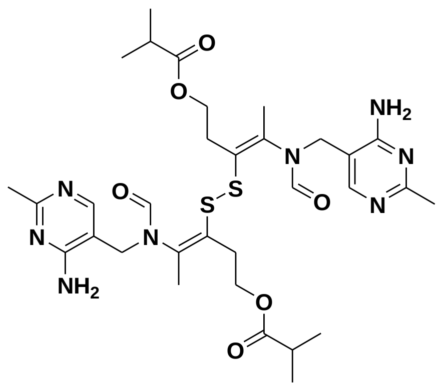
2.4.1. Benfotiamine (1):

Benfotiamine (BFT) differs from thiamine in its chemical structure by having an open thiazole ring. Following ingestion, BFT is converted to S-benzoyl thiamine, which is extremely lipophilic and easily diffuses through biological membranes, by the ecto-alkaline phosphatases found on the gut brush border membrane. Erythrocytes capture the majority of S-benzoyl thiamine in the blood and turn it into active thiamine.[19]



2.4.2. Sulbutiamine (2):

Sulbutiamine is a synthetic compound related to vitamin B1 in function (thiamine). sulbutiamine dissolves in lipids, as opposed to vitamin B1, which dissolves in water. Thiamine concentrations in the brain can be raised by sulbutiamine . It has undergone a variety of tests since its discovery to see if it may treat various illnesses, with varying degrees of success. In retrospect, sulbutiamine was initially employed in neurochemical research and, more recently, it has been demonstrated to reduce fatigue in MS patients who were already taking medication for the condition.[15]



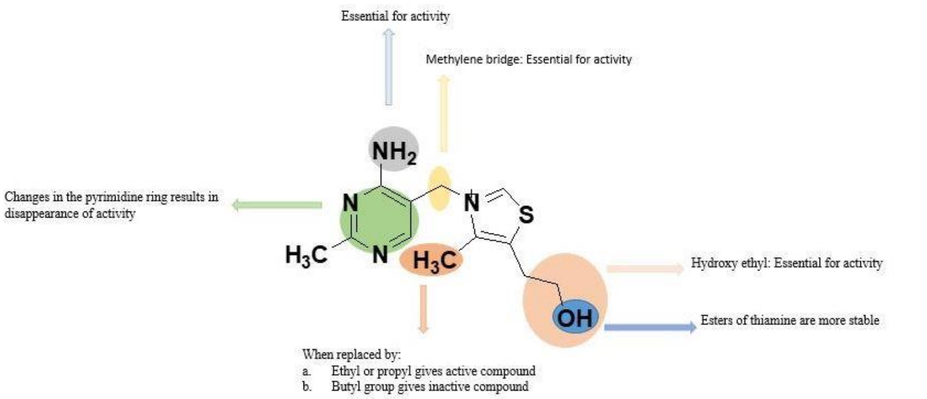


Figure 3: SAR of thiamine

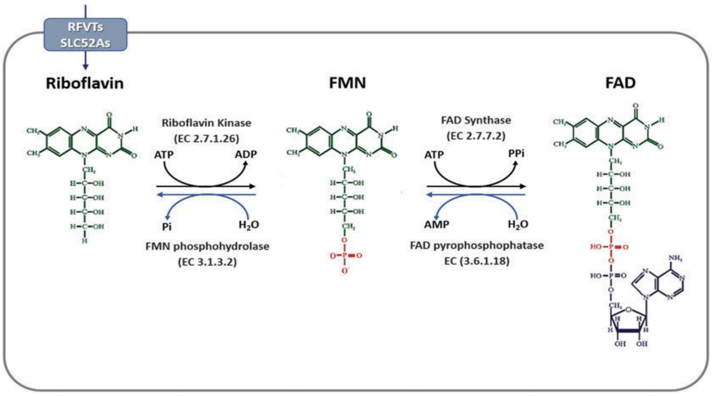
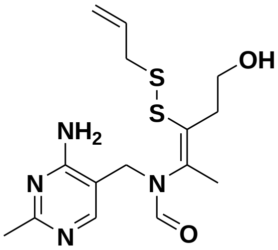


Figure 4: Riboflavin metabolism[6]

2.4.3. Allithiamine (3):

It has been found that in the hyperglycemia-induced increase in the level of AGEs, pro-inflammatory changes were significantly suppressed by allithiamine 3. However, allithiamine could not enhance the activity of transketolase, but it exerts a potent antioxidant effect. Collectively, there are data suggest that allithiamine could alleviate the hyperglycemia-induced endothelial dysfunction due to its potent antioxidant and anti-inflammatory effect.[20]



3. Vitamin B2 (Riboflavin)

In 1879, the English chemist A. Wynter Blyth isolated a yellow-orange substance from cow milk, which he named lactochromo. Later, scientists identified the same substance in various sources and named it riboflavin due to its fluorescent property. In 1937, Theorell and in 1938, Warburg and Christians elucidated the chemical structure of the coenzymes derived from riboflavin: flavin mononucleotide (FMN) and flavin-adenine dinucleotide (FAD), respectively.[21]

3.1. Pharmacological activity of vitamin B2

Riboflavin, or vitamin B2, is a readily absorbed, water-soluble micronutrient crucial for maintaining human health. Playing a key role in energy production, it assists in metabolizing fats, carbohydrates, and proteins. Vitamin B2 is essential for red blood cell formation, respiration, antibody production, and the regulation of human growth and reproduction. It contributes to healthy skin, nails, hair growth, overall well-being, and helps regulate thyroid activity. Additionally, riboflavin is implicated in preventing or treating various eye disorders, including certain cases of cataracts.[22, 23]

3.2. Metabolism of vitamin B2

Vitamin B2, often known as riboflavin, is a water-soluble vitamin made up of an isoalloxazine ring, also known as 7,8-dimethyl-10-(-1-D-ribityl). Although it is the precursor to both FMN and FAD **[Figure 4]**, the co-enzymatically active forms, free riboflavin is not the active form. An ATP-dependent flavokinase process produces FMN. FAD synthase catalyzes a process that converts FMN into FAD.[24, 25] Biosynthesis of the flavin coenzymes from riboflavin is controlled by thyroid hormones.[26]

3.3. Structural activity relationship of vitamin B2

- Riboflavin contains 7,8-dimethyl isoalloxazine ring attached to D-ribitol by a nitrogen atom.
- Ribitol is an open chain form of sugar ribose with aldehyde group is reduced to alcohol.
- Sugar alcohol called ribityl group is attached at 10th position it is essential for activity.
- The phosphorylation of sugar gives the active form.

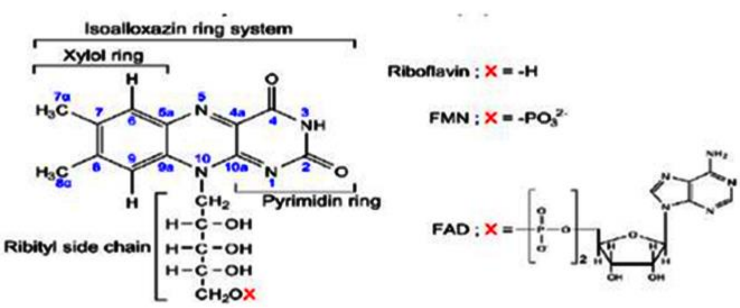


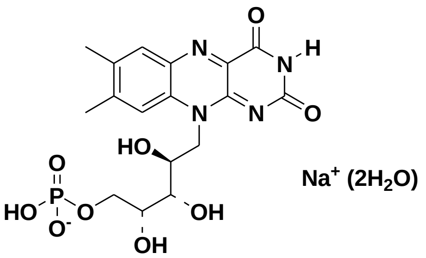
Figure 5: SAR of Riboflavin[3]

- The distinctive structural features of a flavin crucial for its protein binding ability lie in the segment of the molecule extending from the 5'-hydroxy group to the 3-imino group.
- The attack with nicotinamide or any aromatic compounds makes the solubility of riboflavin increased.
- The carbonyl group at the N 6-position of uracil (orotic acid) showed a significantly smaller enhancement in O_2 photogeneration compared to the amino group at the 5- or 6-position. In contrast, 5-methyl uracil (thymine) and 6-methyl uracil did not produce more O_2 than uracil.[27, 28] **[Figure 5]**

3.4. Derivatives of vitamin B2

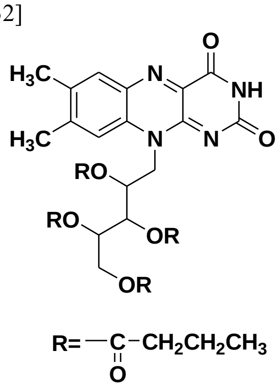
3.4.1. Riboflavin 5'-monophosphate (4):

It's a Vitamin B_2 phosphate & its crystalline solid. Riboflavin 5'-monophosphate (FMN) is a coenzyme that is tightly bound to enzymes catalyzing oxidation and reduction reactions in a variety of biosynthetic pathways.[29, 30] FMN also binds the FMN riboswitch (RFN element) on RNA to alter gene regulation.[31]



3.4.2. Vitamin B2 Tetrabutyrate (5):

Riboflavin butyrate, a derivative of vitamin B2, is extensively used in Japan and is a common ingredient in multivitamin complexes. It is employed for the relief of various symptoms, including stomatitis, glossitis, perleche, cheilitis, rough skin, acne, dermatitis, eczema, rash, and sores. It is a supply of Vitamins B2 and B6 in the following situations: physical fatigue, pregnancy/lactation, decline of physical strength during or after illness.[32]



4. Vitamin B3 (Niacin)

Niacin, once known as vitamin B3, is a water-soluble vitamin. The term "niacin" encompasses both nicotinic acid and nicotinamide, which share a fundamental structure of pyridine-3-carboxylic acid. Free niacin isn't the active form but acts as a precursor for nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), the co-enzymatically active forms.[33, 34]

4.1. Pharmacological activity of vitamin B3 Niacin coenzymes are necessary for all human energy synthesizes, including cytosolic glycolysis and the mitochondrial oxidativephosphorylation/citric acid cycle, and are involved in hydrogen transfer.**[35]** Antioxidant against oxidative damage in rat brain, study was conducted on rats where Nicotinamide showed significant inhibition of oxidative damage induced by (ROS) generated by photosensitization systems in rat brain mitochondria.As it protects against both protein oxidation and lipid peroxidation, at milli molar concentrations.**[36]** Niacin is an effective hypolipidemic agent for reducing the circulating lipid concentrations and, hence decreasing cardiovascular events. This hypolipidemic effect is thought to be mediated by inhibition of lipolysis in adipose tissue& inhibition of VLDL synthesis.**[37]** Nicotinamide improved glucose tolerance and urinary glucose excretion was significantly reduced when daily doses of nicotinamide were given to partially depancreatized rats. In human insulin- dependent type I diabetes, the administration of nicotinamide prolonged insulin-free remission after initial disease control with insulin therapy.**[38]**

4.2. Metabolism of Vitamin B3

Niacin undergoes predominant liver metabolism along two major pathways:

Pathway 1: (low affinity, high capacity) involves niacin conjugation with glycine, forming nicotinic acid, and is linked to flushing.

Pathway 2: (high affinity, low capacity) results in the formation of nicotinamide, NAD, and other metabolites. These metabolites are associated with liver enzyme elevation and other manifestations of hepatotoxicity.[39] **[Figure 6]**

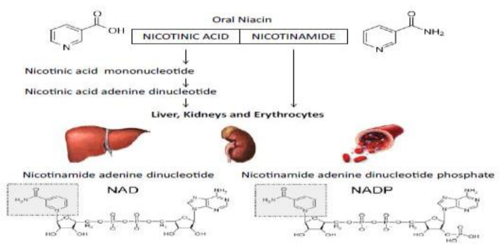


Figure 6: Niacin metabolism[5]

4.3. Structural activity relationship of vitamin B3

Niacin is a pyridine monosubstituted carboxylic acid in which the hydrogen at position 3 is replaced with a carboxylic group (pyridine-3-carboxylic acid).[40] [**Figure 7]**

4.4. Derivatives of vitamin B3

4.4.1. Nicotinamide (6):

The (OH) group in niacin is replaced by NH2 which is a main amide group is connected to a pyridine ring in the meta position. It is effective in treating pellagra

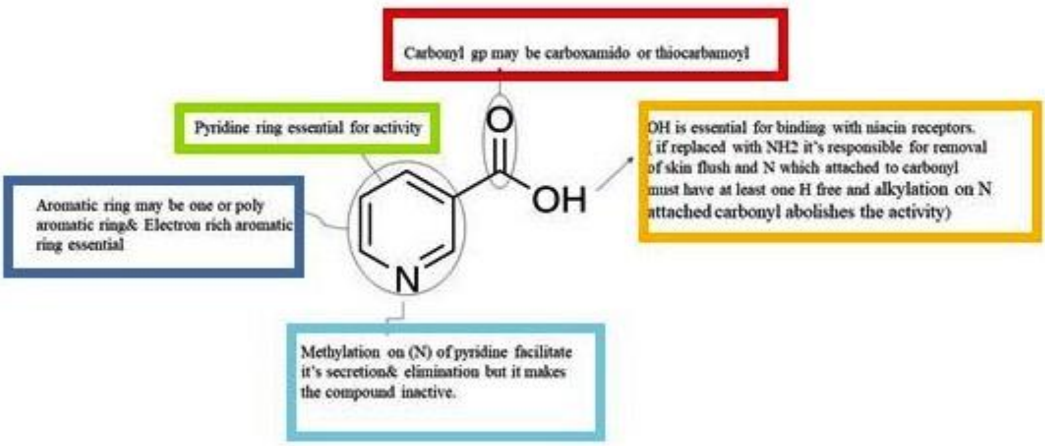
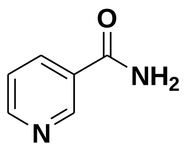


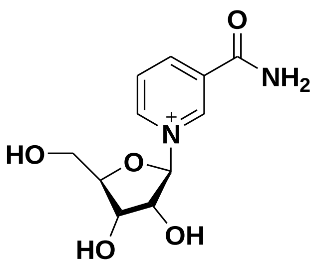
Figure 7: SAR of Niacin

and arthritis. Skin flushing is not a side effect of nicotinamide.



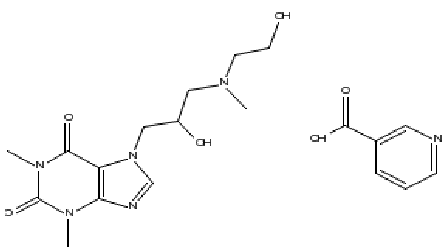
4.4.2. Nicotinamide riboside (7):

A pyridine nucleoside containing nicotinamide and a 1-position -D-ribofuranosyl moiety. It's an important intermediate in the process of NAD biosynthesis.[37]



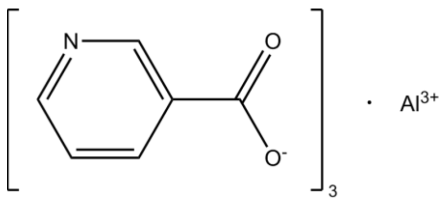
4.4.3. Xanthinol Nicotinate (8):

Xanthinol Nicotinate, acting as a vasodilator, has the ability to directly affect the smooth muscle of small arteries and capillaries. It promotes the expansion of blood vessels, enhances blood rheology, and reduces peripheral vascular resistance.[41]



4.4.4. Aluminum nicotinate (9):

It seems to be a safe peripheral vasodilator, especially effective in reducing serum cholesterol levels when they are notably elevated.[42]



5. Vitamin B5 (Pantothenic acid)

Vitamin B5, also known as pantothenic acid, is a crucial B vitamin among the eight. It is abundantly present in both plants and animals, including meat, vegetables, cereal grains, legumes, eggs, and milk.[43] Vitamin B5 is susceptible to destruction through boiling, like other water-soluble vitamins. It undergoes conversion into 4'-phosphopantetheine, subsequently forming co-enzyme A (CoA) through adenosine triphosphate. Pantothenic acid plays a regulatory role in epidermal barrier function and keratinocyte differentiation through CoA metabolism. It is integrated into co-enzyme A, providing protection against peroxidative damage by elevating glutathione levels, making it essential for maintaining healthy skin, hair, eyes, and liver.[44]

5.1. Pharmacological activity of Vitamin B3

Categorized as the "anti-stress vitamin" or pantothenate, vitamin B5 (VB5) serves as the precursor to coenzyme A, an important component of all microorganisms. A large number of amides of pantothenic acid develop strong antibacterial properties. Pantothenic acid has the ability to enhance the skin barrier and speed up the healing of surgical wounds. Reduced cortisol production increased arthritic pain, myalgia, exhaustion,

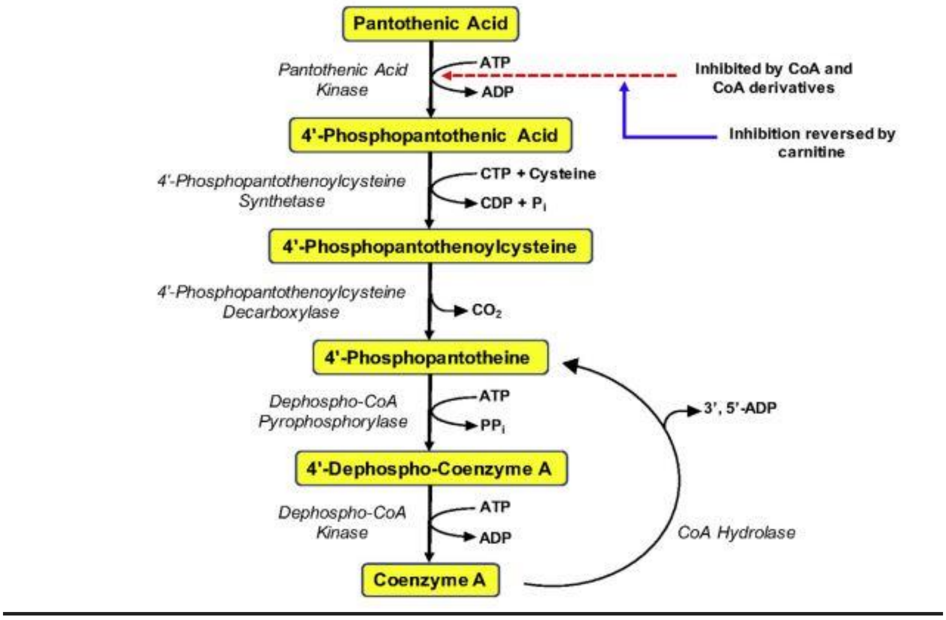


Figure 8: Metabolic conversion of pantothenic acid to coenzyme A.[1]

headaches, depression, insomnia, and systemic "proinflammatory" impacts on the immune system are the results of its shortage. VB5 is a multifunctional protein that stimulates immune cells to generate cytokines.[45]

5.2. Metabolism of Vitamin B5

The initial stage in CoA synthesis involves the phosphorylation of pantothenic acid to 4'-phosphopantetheine, a reaction facilitated by pantothenic acid kinase. This reaction acts as the main control point in the pathway. Notably, feedback inhibition of pantothenic acid kinase by CoA or its derivatives serves as a crucial regulatory mechanism, significantly controlling the flow of substrate through subsequent steps and establishing the upper limit for intracellular CoA cofactor levels.[1] **[Figure 8]**

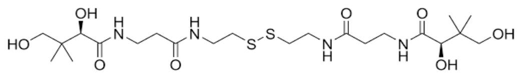
5.3. Structure activity relationship of Vitamin B5

β-alanine and 2,4-dihydroxy-3,3-dimethylbutyric acid (pantoic acid) are essentials for activity.[46] **[Figure 9]**

5.4. Derivatives of vitamin B5

5.4.1. Pantethine (10):

It consists of 2 molecules of pantothenic acid linked by amide bond to cysteamine disulfide group. Most potent form of vitamin B5 (produced by add of cysteamine or oxidation of pantetheine). Disulfide gp necessary to reduce platelet response which play role against cerebral malaria and used also as nutritional supplement.[47]



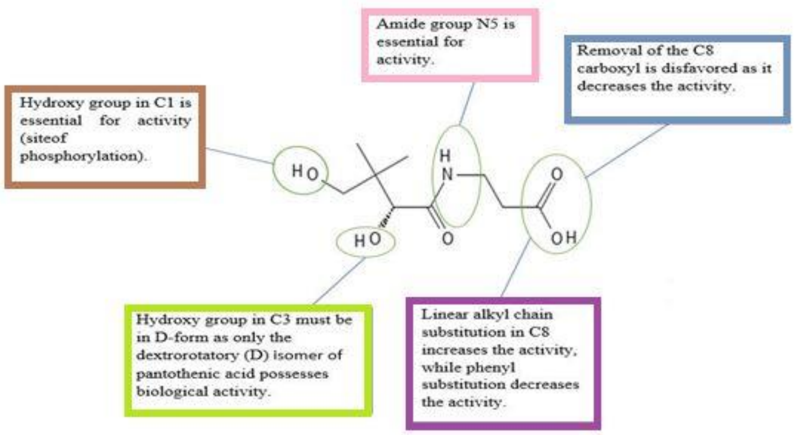
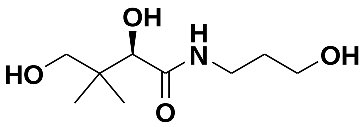


Figure 9: SAR of Vitamin B5

5.4.2. Panthenol (11):

Panthenol is an alcohol derivative of pantothenic acid. D-Panthenol exhibits a distinct dermotropic action, effectively distributing in the skin and mucosae. This property makes it valuable in dermatology for treating various dermatoses and dermatitis resulting from intoxication, infection, metabolic disorders, and radiation. It is employed in the treatment of eczemas from diverse origins, burns, and various types of wounds. Additionally, Panthenol is utilized in cosmetics designed for addressing skin and scalp disorders associated with a deficiency of pantothenic acid.[48]



6. Vitamin B12 (Cobalamin)

Vitamin B12 is a vitamin that is present highly in meat, fish and dairy products. It can alsobe created in a lab and is frequently used along with other B vitamins.[49] The brain, nerves, and blood cells are just a few of the bodily parts that need vitamin B12to function and develop. Vitamin B12's active form is methylcobalamin. Vitamin B12 is widely used to treat cyanide poisoning, vitamin B12 insufficiency, and high blood homocysteine levels. It is also used to treat a variety of other conditions, such as fatigue, canker sores, cataracts, osteoporosis, and Alzheimer's disease.[50, 51]

6.1. Pharmacological activity of vitamin B12

A synthetic vitamin B12 molecule called cyanocobalamin is primarily used to treat vitamin B12 deficiency. It is a crystallizable cobalt complex that is a member of the chemical group known as "corrinoids." The cyanide group that is connected to the molecule gives it the name "cyanocobalamin".[52] Vitamin B12 is used as a protective agent against neurotoxicity brought on by glutamate, Increased intake of vitamin B12 through diet and supplements may be crucial in the prevention of neurological and psychological diseases, even if the mechanism by which vitamin B12 has an impact on the nervous system is not fully understood. Glutamate, is present in the brain in extremely high amounts. Physiologically, enough glutamate release is necessary for optimal neuronal function, such as the development of learning and memory or brain plasticity. In contrast, excessive glutamate release has been linked to a variety of neuropathological illnesses, including chronic psychiatric and neurodegenerative diseases like Alzheimer's disease as well as acute traumas like stroke. Inhibiting glutamate release from nerve terminals could therefore have significant effects and serve as a possible mechanism for neuroprotective effects.[53] It is believed that folic acid can have harmful clinical effects on persons who are cobalamin deficient. As a result, when cobalamin deficiency is diagnosed, high serum folate levels are linked to neurological abnormalities, and treating people with folic acid who are cobalamin deficient can increase or cause neurological symptoms and indications.[54]

6.2. Metabolism of vitamin B12

When cyanocobalamin enters the body, it undergoes conversion to either methylcobalamin or adenosylcobalamin, which are the two active forms of vitamin B12 in humans. When cyanocobalamin is absorbed, it converts to hydroxocobalamin (which means discarding of the cyanide in the process) and also to methylcobalamin and adenosylcobalamin.[55] **[Figure 10]**

6.3. Structure activity relationship of vitamin B12

Three components make up the composition of vitamin B12. The modified tetra pyrrole that binds the center cobalt ion comes first (Corrin ring). Second, the molecule that has a nucleotide loop that houses an uncommon base called dimethylbenzimidazole in vitamin B12, the higher ligand to the cobalt ion, in vitamin B12is

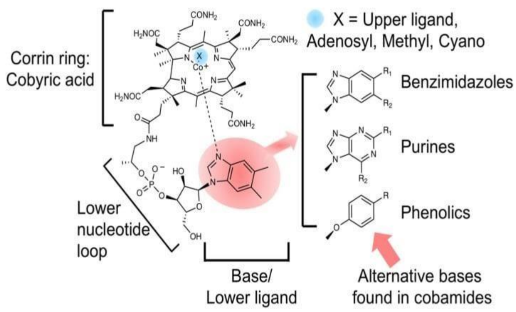


Figure 11: Components of vitamin B12[8]

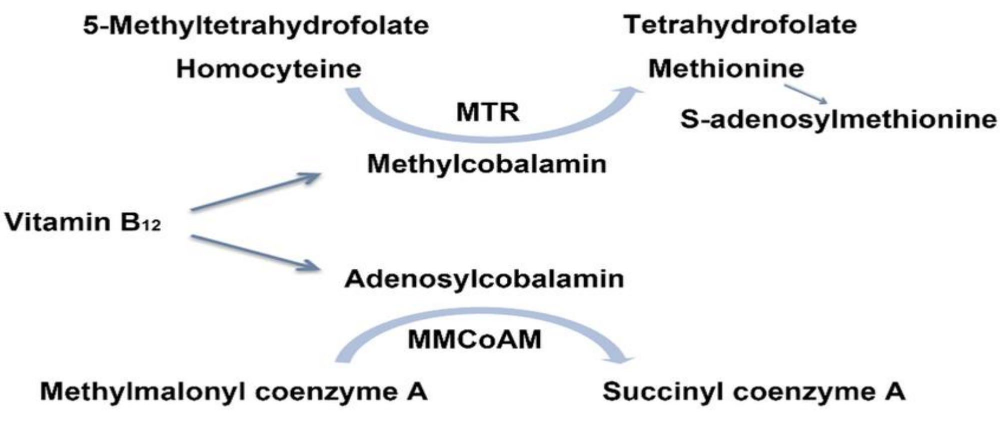


Figure 10: Metabolism of vitamin B12[7]

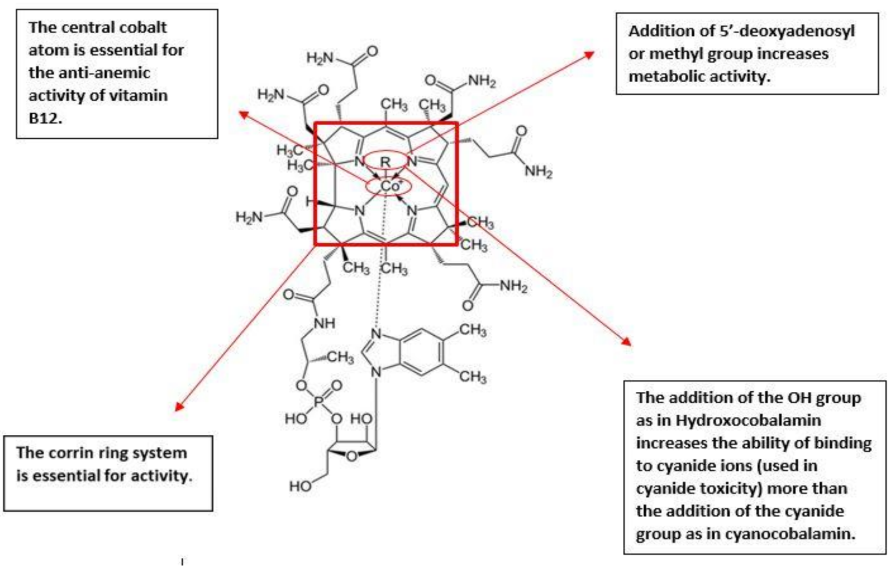


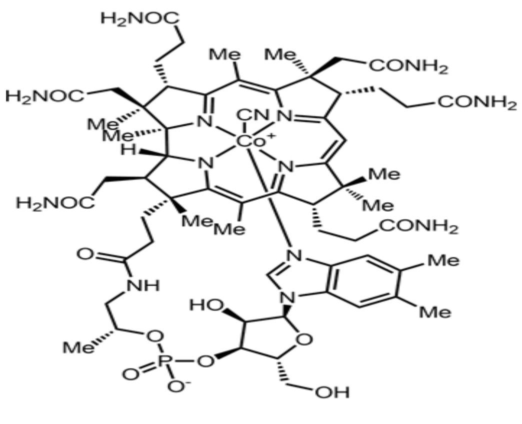
Figure 12: SAR of vitamin B12[8]

which can be OH, CN, CH_3 or 5-Deoxyadenosyl, is the third component of vitamin.[8, 56] **[Figure 11 & 12]**

6.4. Derivatives of vitamin B12

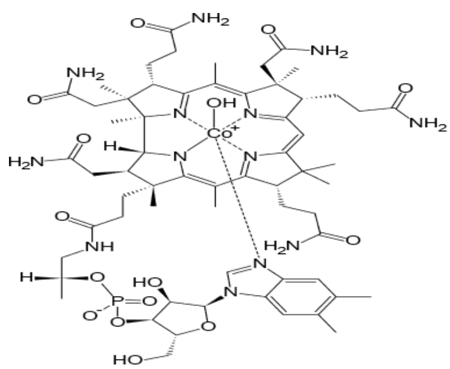
6.4.1. Cyanocobalamin (12):

Cyanocobalamin is industrially produced through bacterial fermentation. Various microorganisms involved in fermentation generate a mixture of methylcobalamin, hydroxocobalamin, and adenosylcobalamin. This mixture is then transformed into cyanocobalamin by adding potassium cyanide in the presence of sodium nitrite and heat.[57]



6.4.2. Hydroxocobalamin (13):

A cobalamin (Vitamin B12) derivative called hydroxocobalamin is created by first submitting cyanocobalamin to catalytic hydrogenation, which creates cobalamin, which is then oxidized to create hydroxocobalamin.[51]



7. Conclusion

This review covers different types and activities of vitamin B complex which are a group of water-soluble vitamins. It discusses five types in details: thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), and cobalamin (vitamin B12). These vitamins play diverse roles in the nervous, endocrine, and cardiovascular systems, as well as in energy metabolism, DNA metabolism, cell signaling, and various metabolic reactions. Furthermore, the review sheds light on the potential pharmacological activities of B vitamins, which may have implications in the development of therapeutic agents. Understanding the metabolism and action of these vitamins, as well as exploring their structure-activity relationship, can aid researchers in designing more effective drugs or formulations that harness the beneficial properties of these vitamins. Also, researchers can further explore the roles of these vitamins in human health and potentially develop innovative interventions to improve well-being and address related health conditions.

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