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Abstract: Vitamins are dietary components which are necessary for life. They play a major role in health and their deficiency may be linked to symptoms of psychiatric disorders. B vitamins are required for proper functioning of the methylation cycle, monoamine oxidase production, DNA synthesis and the repair and maintenance of phospholipids. Vitamin B deficiency could influence memory function, cognitive impairment and dementia. In particular, vitamins B1, B3, B6, B9 and B12 are essential for neuronal function and deficiencies have been linked to depression. We discuss the causes of depression and the neurochemical pathways in depression. In particular, we provide evidence that vitamin B contributes to the complexity of depressive symptoms.

Keywords: Depression, vitamin B, vitamin B6, vitamin B12, vitamin B complex

1. DEPRESSION

Unipolar major depression is the fourth most common disease suffered on a global scale [1] and in the next 20 years will become second only to heart disease as the leading cause of death and disability [2]. Patients suffering from unipolar depression experience an array of symptoms, such as an inability to function efficiently at work and home, feeling overwhelmed, miserable or worthless, experiencing a lack of confidence. Likewise, patients may experience physical manifestations like sleeplessness, fatigue, headache and muscle pain [3]. If left untreated, this disease can lead to functional impairment in both the short and long term. Depression is more prevalent amongst children and younger adults [4], with the greatest rate of suicide in Australia (7 per day) occurring in people aged 15-45 years [3]. However, on a worldwide scale, the World Health Organization reports that suicide amongst the elderly add considerably to the number of suicides, with a threefold rise in suicide rates in people over 75, as compared to those aged 15–24 years [5]. Depression in young people can limit employment and education opportunities, as

well as lead to drug and alcohol dependence. Aggression, violence and other antisocial behaviors are more likely to occur in people suffering depression and this can significantly increase the burden placed on their families, friends and on society in general [4]. The economic load is considerable, with depression and anxiety comprising somewhere between a third and one half of the global cost of mental illness, with was estimated cost of $2.5 trillion in 2010, which is anticipated to increase to over $6 trillion by 2030 [6].

1.1 Causes of Depression

1.1.1. Genetics: Whilst a particular gene has not been identified that may predispose someone to depression, studies in twins have shown that the risk of developing familial clinical depression is as great as 50% [7]. Other studies have shown that epigenetic changes associated with hypermethylation of BDNF (Brain Derived Neutrophic Factor, encoded by the BDNF gene) and TrkB (Tropomyosin Receptor Kinase B, encoded by the NTRK 2 gene) are associated with higher incidence of suicide as a consequence of depression [8]. Likewise, the gene which codes for the serotonin transporter (5-HTT) and selective serotonin reuptake inhibitor drugs (SSRI's) have proven to be effective in treating depression. Even though it is not clear whether polymorphisms within the 5-HTT gene are directly responsible for depression, in some individuals this may regulate the stress response of the the serotonergic system [9]

1.1.2. Illness, Ageing brain: Pre-existing long term illness or chronic pain and discomfort, coupled with a reduced physical capacity and the physical effects of an illness, can contribute to depression [10]. Management of chronic disease can therefore become more difficult when complicated by depression. Recognizing depression early in these patients may facilitate better management of the disease, thereby leading to improved outcomes in health and quality of life [11]. Numerous studies have shown that depression will often be preceded by some incident of significant life stress or coincide with related episodic stress. Animal studies have shown at a biochemical level that exposure to stressors can trigger hyperactivity of the central nervous system and corticotrophin-releasing factor neurons. The firing of these neurons leads to the discharge of corticotrophin, which regulates the endocrine, immune, autonomic and behavioral stress responses [12, 13]

A disruption of the neuronal circuits linking basal ganglia and frontal regions of the brain can be a contributing factor towards depression in the elderly. This disruption is often caused by alterations in blood pressure and sometimes undetected mini-strokes [14]. The ageing brain is more prone to inflammation, immune recruitment and metabolic syndrome, all of which can contribute to neurological disorders such as anxiety and depression [15]. In fact, during ageing, neuropeptides such as brain derived neurotrophic factors and somatostatin can lose up to 50% of their expression, as compared to control subjects [16]. In addition, social isolation and loneliness present other aggravating factors which contribute to depression in the elderly.

2. NEUROCHEMICAL PATHWAYS AND DEPRESSION

B vitamins play an important role in the neurochemical pathways linked to depression; the glutamate and GABA neurotransmittory systems, as well as the serotonergic, noradrenergic, dopaminergic and cholinergic systems. Neurotransmitters, can contribute to depression if they fail to function normally. In fact, reduction in monoamine function plays a key role in depression. In addition, reduction or interruption in serotonin transmission is a likely cause for all types of depression. More specifically, in melancholic or psychotic depression, other neurochemical pathways, such as dopaminergic and pathways for noradrenaline, are more likely to be functioning abnormally (Fig. 1) [14] [17]. The inhibition of serotonin (or 5-hydroxytryptamine; 5-HT) and norepinephrine transporters (in order to increase monoamine transmission) is achieved with selective 5-HT reuptake inhibitors and 5-HT norepinephrine reuptake inhibitors. Therefore, targeting monoamine receptors and additional transporters with multimodal drugs and triple re-uptake inhibitors is the foremost treatment option for depression [18]

3. STRESS, MITOCHONDRIAL DYSFUNCTION AND DEPRESSION

Chronic stress has been widely recognized as a contributing factor to the onset of major depressive disorders [19-21]. The hypothalamic pituitary adrenal axis (or HPA axis) is triggered during periods of stress, resulting in increased levels of cortisol. It is thought that an imbalance between the way cortisol interacts with mineralocorticoid receptors (NR3C2) and glucocorticoid receptors (NR3C1) produces an inappropriate stress response, leading to depression [22]. The HPA axis can be initiated by various triggers. Monoamine neurotransmitters, such as serotonin and noradrenaline, are two such molecules which can trigger overproduction of HPA [22]. Serotonin and noradrenaline are synthesized by a process called one carbon metabolism, which uses co-enzymes derived from the vitamins folic acid, B6, B12 and B2 [23] .

Certain cytokines involved in immune reactions are also responsible for triggering HPA axis activity. Indeed, IL-1, IL-6, IL-10 and TNF-alpha exist in a bi-directional feedback loop which increase cortisol levels. However, if cortisol levels become too high inflammatory, reactions are suppressed as a protective mechanism. Furthermore, chronic stress and increased cortisol can lead to oxidative damage to mitochondrial function. Mitochondria provides a pivotal role in neurotransmitter signaling in brain synapses and damage sustained by oxidation can affect energy production, protein synthesis, lipid mediation, buffering of intracellular calcium and regulation of apoptotic pathways. Vitamin B12 and folic acid are known to protect against oxidative cell damage [22, 24].

4. INFLAMMATION AND DEPRESSION

The immune system consists of an intricate assembly of cells which function in a regulated manner in order to maintain health and well-being. Innate immunity begins immediately after, or within hours of, antigen stimuli. This involves mast cells, basophils, macrophages, dendritic cells, natural killer (NK)-cells, eosinophil's and neutrophils. As a result of their activation, toxic metabolites are secreted, as are cytokines, chemokine's and growth factors [25]. The adaptive immune response soon follows, involving antigen specific interactions by $CD4^+$ and $CD8^+$ T cells, NK-T cells and B cells. Over activation of peripheral immune system leads to increased activation of neurotoxic metabolites resulting from the tryptophan cascade, increased activation of microglial cells caused by circulating cytokines and alteration of brain function by peripheral stimulation of vagal nerve via afferent pathways [26]. As a consequence, this leads to modifications in the function and production of neurotransmitters, in particular serotonin, dopamine and glutamate. This can cause an inhibition of neurogenesis and neuroplasticity, which appears to have an active role in the pathogenesis of depression [27, 28].

5. VAGAL STIMULATION AND THE BRAIN GUT AXIS IN DEPRESSION

Understanding how the immune system affects the brain has gained much attention in recent years, as inflammatory markers and antibodies are unable to penetrate through the blood brain barrier. In fact, the vagus nerve, which connects the brain to the abdomen, may be the key to this puzzle. Inflammatory responses in the gut are thought to send signals to the brain via the vagus nerve, which in turn stimulates the production of inflammatory mediators, acetylcholine and cytokines (such as, IL-6). This leads to an increase in metabolism and a decrease in brain serotonin levels which, through interaction with immune cells, attenuates inflammation. Toxic chemicals, such as nitric oxide, quinolinic acid and kynurenic acid, can also be stimulated for release by vagal signaling. These chemicals cause decreased function of nerve cells [29, 30]. In fact, the gut microbiome and intestinal permeability has mounting evidence linking it to brain development, function and behavior, through the immune, endocrine and neural pathways [31]. Certain probiotic treatments that are capable of controlling the brain-gut microbiota axis, termed psychobiotics, have been shown to deliver health benefits to patients experiencing psychiatric illness. It is thought that such benefits may be due to their anti-inflammatory action [32]. The term '*psychobiotics*' has recently been conceived to encompass the sub-types of probiotics that may be capable of modulating the brain-gut-microbiota axis to have a beneficial effect on mood, anxiety and cognition.

6. VITAMIN B COMPLEX

Vitamin B complex plays an important role in the functioning of the methylation cycle involved in monoamine oxidase production, the synthesis of DNA, RNA, protein and phospholipid's, and in cell

repair. The methylation cycle ensures proper immune function and inflammatory balance, maintains DNA, provides energy, and balances mood behaviors. Lowered methylation function is associated with a range of chronic conditions, including numerous neurological conditions, such as autism, schizophrenia, Alzheimer's disease, psychiatric disorders, mood behaviors and depression [33].

6.1. VITAMIN B AS CO-FACTORS

Vitamin B complex act as co-enzymes in enzymatic reactions. As a group they participate in the metabolism of carbohydrate, protein, lipids, vitamins, minerals and drugs, whilst taking part in a number of other cellular metabolic functions, including DNA synthesis (Table 1).

6.1.1. Vitamin B1 (Thiamine): Thiamine is part of co-enzyme thiamine pyrophosphate, which plays a critical role in normal carbohydrate metabolism whereby it participates in both the decarboxylation of pyruvic and α-ketoglutarate acids and in the utilization of pentose in the hexose monophosphate shunt. Thiamine pyrophosphate also aids the conversion of pyruvate to acetyl CoA in the pyruvate dehydrogenase complex and also plays a part in the α-ketoglutarate-dehydrogenase complex in the TCA (Krebs) cycle, thereby converting a 5 carbon compound into a 4 carbon compound. Deficiency of thiamine in the diet can result in pyruvate not being converted to acetyl CoA. This in turn causes a rise in pyruvate and lactate levels in the blood. In animal tissue within the inner mitochondrial membrane, branched-chain α-ketoacid dehydrogenase complex uses thiamine pyrophosphate in an irreversible step in the catabolism of branched-chain amino acids which function in the Krebs cycle [34-38].

6.1.2. Vitamin B2 (Riboflavin): The two active forms of Riboflavin, Flavin mononucleotide (FMN) and Flavin adenine dinucleotide (FAD), function as cofactors for a number of important metabolic reactions. FAD occurs in two different redox states which it moves between by donating or accepting electrons. FAD is reduced to FAD-H_2 to carry high energy electrons used for phosphorylation. FAD forms part of the complex II of the electron transport chain and is essential in the conversion of pyridoxal (Vitamin B6) to pyridoxic acid by pyridoxine 5' phosphate oxidase and the conversion of retinol to retinoic acid via retinal dehydrogenase. FAD is also necessary for oxidating pyruvate, a-ketoglutarate and branched chain amino acids and reducing the oxidized form of glutathione to glutathione reductase in complex II of the electron transport chain. Fatty acyl Co-a dehydrogenase requires FAD in fatty acid oxidation and $FADH_2$ synthesizes an active form of folate (5- mehtyltetrahydrofolate) from 5,10-methylenetetrahydrofolate.
FMN is an important component in the primary coenzyme form of Vitamin B6 and is required to convert tryptophan to niacin (Vitamin B3) in complex I of the electron transport chain. FMN reduces the oxidized form of glutathione to glutathione reductase in complex II of the electron transport chain [34, 39-43].

6.1.3. Vitamin B3 (Niacin): Niacin and nicotinamide are both precursors of the coenzymes nicotinamide adenine dinucleotide (NAD) and ncotinamide adenine dinucleotide phosphate (NADPH). The enzyme NAD+ kinase phosphorylates NAD to NADPH, both act as coenzymes for many dehydrogenases which participate in hydrogen transfer processes. NAD is likewise a significant contributor to the catabolism of fat, carbohydrate, protein and alcohol, whereas NADPH mostly occurs in anabolistic reactions such as fatty acid and cholesterol synthesis. NAD is also required for cell signalling and DNA repair [34].

6.1.4. Vitamin B5 (Pantothenic Acid): Pantothenic acid, also called pantothenate or vitamin B_5, contributes to the synthesis of fatty acids, cholesterol and acetylcholine and is required for the formation of acyl carrier protein, which is required for fatty acid synthesis. In energy metabolism, it assists pyruvate to enter the TCA cycle as acetyl-Co-A and the transformation of ketoglutarate to succinyl-CoA. CoA participates in acylation, which is important in signal transduction and acetylation, which is vital for enzyme activation and deactivation [34, 39, 44, 45].

6.1.5. Vitamin B6 (Pyridoxine): Also known as: pyridoxine (PN), pyridoxine-5'-phosphate (PNP), pyridoxal (PL), pyridoxal 5-phosphate (PLP), pyridoxamine (PM), pyridoxamine 5-phosphate (PMP) and 4-pyridoxic acid (PA). Vitamin B6 is essential for amino acid metabolism, Glucose metabolism, Lipid metabolism, Hemoglobin synthesis and function and gene expression.

Amino acid metabolism: PLP acts as a cofactor in the synthesis of neurotransmitters serotonin, dopamine, epinephrine, norepinephrine and GABA. It also synthesizes histamine. PLP, along with transaminases, break down amino acids and help move amine groups. The neuromodulator, serine, relies on PLP for synthesis and selenium relies on PLP for conversion into the primary dietary form selenomethionine and for the conversion of selenium into selenoproteins. PLP also aids the conversion of tryptophan to niacin.

Glucose/lipid metabolism: Within glucose metabolism, PLP aids glucogen phosphorylase in the process of glucogenolyis, whilst in lipid metabolism, PLP facilitates the synthesis and the breakdown of sphingolipids such as ceramide [34, 46-52].

6.1.6. Vitamin B7 (Biotin): Biotin is a cofactor in several carboxylase enzymes, including acetyl-CoA carboxylase alpha, acetyl-CoA carboxylase beta, methylcrotonyl-CoA carboxylase, propionlyl-CoA carboxylase and pyruvate carboxylase. Biotin is important in the synthesis of fatty acids, in the catabolism of branched-chain amino acids and gluconeogenesis [34, 53-56].

6.1.7. Vitamin B9 (Folate): Folate in the form of tetrahydrofolate (THF) and other folate derivatives are important in a series of single carbon transfer reactions. It is important in methylation, along with B12 and B6, for recycling homocysteine into methionine and for the synthesis of DNA and the process of cell

division. Folate in the form of 5-MTHF helps to regulate the neurotransmission of monoamines and assists in DNA methylation and NO2 synthesis [23, 34, 42, 46, 51, 57-59].

6.1.8. Vitamin B12 (Cobalamin): Vitamin B12 consist of reactive C-Co bonds which participate in Isomerase and methyltransferase reactions. MUT or methylmalonyl Co-enzyme-A mutase is an isomerase reaction in fatty acid oxidation which converts L-methylmalonyl Co-A to Succinyl Co-A before it enters the citric acid cycle, where it helps to extract energy from proteins and fats. MTR or Methyltransferase uses B12 as a cofactor to transfer a methyl group from 5-MTHFR to homocysteine, in order to generate THF and methionine used in the methylation cycle. If Vitamin B 12 is deficient, it causes an increase in homocysteine levels and folate is trapped in the cycle as 5-methyl-tetrahydrofolate instead of the active form, tetrahydrofolate. This can interfere with DNA production and reduce the body's ability to produce rapid turnover cells, such as red blood cells, which can lead to megablastic or pernicious anaemia. Here Vitamin B12 is needed to re-stablish MTR, or fresh folate is needed in the diet [13, 23, 34, 46, 51, 60-63].

6.2. VITAMIN B AND THE METHYLATION CYCLE

Methylation is the mechanism by which the body deals with stress, toxins and infections. The methylation pathway deals with the balancing of neurotransmitters, the detoxification processes in the body, as well as controlling inflammation. Methylation reactions are involved in almost every chemical reaction undertaken within the body. The result of ineffective methylation reactions within the body are widespread and can result in many health conditions and diseases, including neurological disorders such as anxiety, depression, bipolar disorder, Alzheimer's disease, fibromyalgia, neural tube defects, schizophrenia and sleep disorders [64].

The enzyme methionine synthetase, catalyses the methylation of homocysteine to methionine [57]. The failure of this reaction to take place effectively leads to an increase levels of homocysteine in the blood, which can cause metabolic impairment. Several neurodegenerative disorders, including Parkinson's, Alzheimer's disease and depression, are characterized by increased homocysteine levels [57]. The toxic effect to vascular endothelial and neuronal cells caused by homocysteine elevation is well documented [65-67]. In order for levels of homocysteine to remain low in the central nervous system, an adequate amount of folate is required in the diet, as folate is essential in the methylation of homocysteine to methionine and in the synthesis of S-adenosyl-methionine, which is required for methylation of DNA, proteins and lipids. Low folate levels, especially in pregnancy, can cause neural tube defects, spina bifida, anencephaly, congenital malformations and birth defects in newborns [68]. Homocysteine, which is solely a product of the methylation cycle, acts as a sensitive marker of vitamin B12 and folate deficiency [57]. Numerous studies have linked low folate level to depression, in fact approximately one-third of depressed

patients are folate deficient [69], whilst folate supplementation reduces depressive and somatic symptoms in depressed patients [70].

7. THE EFFECTS OF VITAMIN B COMPLEX IN DEPRESSION

Vitamins play a major role in health and their deficiency is linked to symptoms of psychiatric disorders. Vitamin deficiencies could influence memory function, cognitive impairment and dementia. In particular, vitamin B1, B3, B6, B9 and B12 are essential for neuronal function and deficiencies have been linked to depression (Table 2). In fact, low intake of B vitamins is associated with poor adolescent mental health and behavior [71].

7.1. VITAMIN B1 (THIAMINE)

Thiamine is found most abundantly in yeasts (brewers and bakers) and liver. The most important source in the diet, however, comes from cereal grain [72]. Thiamine is vital for the metabolism of carbohydrates and nerve function. Deficiency can lead to Beriberi, a disease which mainly affects the central nervous system, and Wernicke's encephalopathy, a disease which is mostly associated with chronic alcoholism [35] (Table 3)

Thiamine can be damaged by pH >6, heat, oxidation and ionizing radiation. Thiamine is bound as serum proteins, mainly albumin, and it is absorbed in low concentrations by passive transport in upper small intestine and in high concentrations by active transport, mostly in jejunum and ileum. During metabolism of thiamine, 80% is phosphorylated and most is bound to proteins. Excretion occurs in the urine, as thiamine and acid metabolites (2-methyl-4-amino-5-pyrimidine carboxylic acid, 4-methyl-thiazole-5-acetic acid, and thiamine acetic acid) (Table 3) [73]. Numerous studies have highlighted the importance of adequate thiamine intake in the diet. It was reported over 35 years ago that low thiamin levels were common in newly admitted psychiatric patients. In particular, patients with depression and schizophrenia showed signs of clinical malnutrition and had low levels of thiamine. In 118 geriatric patients, an association with thiamine deficiency and depression was evident [74]. Likewise, in 1,587 older Chinese adults, poor thiamine nutritional status (low thiamine levels) was linked to depression [38]. Experimentally induced thiamine deficiency in dogs resulted in neurologic syndrome, or sudden unexpected death. In particular, symptoms included anorexia, paraparesis, convulsions, muscular weakness and depression [37]. Recently, the importance of adequate thiamin levels in the first year of life was demonstrated in infants with thiamin deficiency, leading to severe syntactic difficulties at age 5 or 9 due to a lack of brain development supporting syntactic abilities [75]. In addition, episodic memory dysfunction can occur sub-acutely in patients as a result of thiamine deficiency [76], and a strong relationship between thiamine

deficiency and peripheral neuropathy exists in people with excessive consumption of alcoholic beverages [77].

Thiamine supplementation for 6 weeks in 80 randomly selected elderly Irish women who were borderline thiamine deficient, resulted in decreased fatigue, improved sleep patterns and improved depression symptoms [78]. Likewise, in geriatric depressed patients, supplementation of thiamine, riboflavin and pyridoxine improved depression and cognitive function scores, compared to a placebo group [47]. Interestingly, a 50 year old male admitted to a psychiatric clinic in the Netherlands with symptoms of depression and a range of neurological disturbances, experienced partial remission of symptoms following thiamine supplementation [79]. In animal models with postpartum depression, the combination of zinc, magnesium and thiamine improved depressive symptoms and anxiety like behaviors [80]. Hence, it is clear that thiamine deficiency is involved in depression and its supplementation improves depressive symptoms.

7.2. VITAMIN B2 (RIBOFLAVIN)

Riboflavin plays a vital role in the intermediary metabolism of carbohydrates, amino acids and lipids. Due to its ability to play a role in both one and two electron transfer processes, deficiency of this vitamin manifests first within tissues of rapid cellular turnover such as skin and epithelium, causing inflammation of membranes of mouth skin eyes and gastrointestinal tract [72] (Table 3). Riboflavin is widely distributed in foods and is sensitive to high temperatures and light [81]. Non-covalently bonded riboflavin includes FMN (Flavin mononucleotide), FAD (Flavin adenine dinucleotide) and free riboflavin, which is well absorbed within tissues. Riboflavin is transported freely in the plasma and bound to plasma proteins, including immunoglobulin IgA, IgG and IgM [72]. Absorption takes place via a Na^+ dependent carrier mediated process and receptor-mediated endocytosis across the placental barrier [40]. Following absorption, riboflavin is converted to its co-enzyme forms FMN and FAD. Excretion is via the urine mainly as free Riboflavin. It is also secreted into milk in amounts dependent on the riboflavin intake of the mother [72].

A meta analysis systemic review of the micronutrient intake of older adults demonstrated that a deficiency of riboflavin and thiamin was linked with poor cognitive outcomes [82]. Interestingly, a link between riboflavin and vitamin D metabolism, an insufficient riboflavin availability and an imbalance of FAD and FMN, results in a distinct alteration in structure within the skeletal and central nervous systems [83].

7.3. VITAMIN B3 (NIACIN)

Brewers yeast is the most significant food source of niacin and ~~it~~ is found in a wide range of foods, including meat and wholegrains. Within food sources, niacin is predominantly bound to proteins in the forms of nicotinic acid, nicotinamide, nicotinamide adenine-dinucleotide (NAD) and nicotinamide-

adenine dinucleotide phosphate (NADP). NAD and NADP are pyridine nucleotides that act as vital cofactors for enzymes in many areas of metabolism (Table 1). Niacin is absorbed in the form of nicotinamide and nicotinic acid in the stomach and small intestine via Na^+ dependent carrier mediated facilitated diffusion, stored predominantly in the liver as NAD^+, NADH and NADPH and excreted in the urine as *N*1-methyl-nicotinamide and its 2-pyridone derivative (*N*1-methyl-2-pyridone-5-carboxamide) [72]. (See table 1)

In the 1950s, niacin (or nicotinic acid) was implicated in the treatment of schizophrenia manic depression, benign depression and tension anxiety conditions. Indeed, numerous studies showed improved depressive and anxiety reactions following niacin supplementation [45]. In recent years, other than niacin effectively treating delusion [84], limited studies have determined the link between niacin and depression. However, in 30 patients with recurrent unipolar depressive disorder, treatment with aqueous niacin skin flushing significantly improved depression, anxiety and somatic symptoms [85]. Further studies are necessary to determine the effectiveness of niacin in depression.

7.4. CHOLINE

A substance is classed as cholinergic if it is capable of producing, altering or releasing acetylcholine. Similarly, a receptor or synapse is cholinergic if it uses acetylcholine as a transmitter (Fig. **1**) [86]. Choline is classed with B vitamins based on its chemical structure, but is not necessarily defined as such [87]. It is important in cell membrane structure and plasma lipoproteins, as it aids in the synthesis of the phospholipid components. In addition, it plays a role in the cell signaling function of membranes. In tissues, choline facilitates movement of fats into cells and prevents fat deposits in the liver. In fact, rats fed a choline-deficient diet develop fatty liver and humans develop hepatosteatosis which can be corrected with choline supplementation [88]. Furthermore, choline is the primary component of acetylcholine, a neurotransmitter used primarily by the parasympathetic nervous system and at neuromuscular junctions and preganglionic neurons. Cytosolic choline levels in the brain, whether deficient or in excess, have been linked to depression and anxiety. Proton magnetic resonance spectra, taken from 17 depressed and 28 healthy adolescents, indicated that choline creatine ratios and choline/N-acetyl aspartate ratios were significantly higher in the depressed group [89]. However, in a large population-based study, choline concentrations were negatively associated with anxiety symptoms, but not depression [90]. Further, rats fed a choline supplemented perinatal diet, out-performed control rats in in an open-water learning maze and forced swim test [91]. Hence, choline supplementation during development may prevent stress and depression. (Table 3)

7.5. VITAMIN B5 (PANTOTHENIC ACID)

Pantothenic acid is widely distributed in foods with the richest source coming from meat (liver, heart), avocado, broccoli and some yeasts. At low concentrations it is transported by facilitated transport

and at high concentrations by passive diffusion. Pantothenic acid of dietary origin has the ability to synthesize coenzyme A (CoA) in most tissues of the body. CoA is an important co-factor for many enzymes involved in intermediary metabolism. Excretion of pantothenic acid occurs mostly in the urine, as free pantothenic acid and some 4'-phosphopanthenate, however 15% of pantothenic acid is also oxidized and excreted through the lungs as CO_2. Several studies to date have reported that amides derived from pantothenic acid possess an antibiotic quality within the body, which may prove to be a novel antibiotic solution to appropriately relevant gram positive bacteria [92] or malarial agents [93]. Higher levels of nutrient intake, including pantothenic acid, results in better mental health scores, as based on the global assessment of functioning scores and the Hamilton depression rating scale [39]. Further studies are required to determine whether pantothenic acid plays a role in mental health disorders, including depression. (Table 3)

7.6. VITAMIN B6 (PYRIDOXINE)

Vitamin B6 constitutes three interrelated isoforms, pyridoxine, pyridoxal, and pyridoxamine. All three pyrimidine derivatives are naturally occurring and are endogenously converted to pyridoxine-pyridoxal- pyridoxamine-5'-phosphate [94]. Vitamin B6 is present in a wide variety of foods, mostly in meats, whole grains, vegetables and nuts. Bioavailability of B6 in food is within a range of around 70-80% and absorption of B6 takes place via passive diffusion in the jejunum and ileum [95].

Vitamin B6 (pyridoxine, pyridoxal and pyridoxamine) is involved in the regulation of mental function and mood. It impacts on neurotransmitters, which control depression, pain perception and anxiety. Its deficiency results in high homocysteine levels and has been linked to seizures, migraines and depression. Indeed, in 140 individuals studied, a clear correlation was noted between depression and low plasma pyridoxal levels [96]. Supplementation of vitamin B6 reduces homocysteine blood levels and improves mood, psychotic symptoms in schizophrenia, fatigue, cognitive function and depression [50]. In addition, reduced depressive symptoms were evident following 4 weeks of pyridoxine administration in schizophrenic patients [97]. Likewise, combined pyridoxine and magnesium supplementation for 4 weeks reduced anxiety-related premenstrual symptoms and depression, and a combination of pyridoxine and estradiol improves major depression in women [48]. Interestingly, pyridoxine intoxication in rats results in severe sensory neuropathy, as substantiated by behavioral deficits [98] (Table 3)

Glutamate in mammals is one of the major excitatory neurotransmitters, which exists in extremely high levels in brain tissue. These levels can be toxic and tight regulation of this system is needed in order to balance the excitatory potential**,** whilst limiting exotoxic damage. The physiology required to maintain the balance of this system is complex and multifaceted [99]. In addition, glutamate takes part in other functions in the body**,** including synthesis of proteins and peptides, energy production and ammonia detoxification.

7.6.1. Vitamin B6 and glutamernergic system: Glutamate is synthesized in the brain by 2 processes; (i) glucose is used as a precursor**,** whereby it enters the Krebs cycle and is transaminated by α-oxoglutarate transaminase to form glutamate, and, (ii) reuptake of glutamate by glial cells**,** where it is converted to glutamine and transported to the neuronal terminal**,** where it is converted back to glutamate**,** packaged into synaptic vesicles and stored for reuse at a later time [100]. Glutamate serves as a metabolic precursor to gamma amino butyric acid (GABA)**,** which is an inhibitory neurotransmitter found in high concentrations in brain tissue and the spinal cord**,** although absent in peripheral nerves [100]. Brain seizure disorders**,** such as epilepsy**,** can be facilitated by a reduction of GABA levels**,** which cause a reduction of neuronal inhibition leading to seizures [100, 101]. Bipolar disorder and major depression are both linked to dysfunction of the glutamate system, which may be due to the degradation of quinolinic acid, a metabolite of tryptophan [102].

In a cohort of patients suffering from depression, significantly lower concentrations of GABA in the lower occipital cortex were noted as compared to controls, whilst mean glutamate levels were considerably increased [103]. In addition, drugs that modulate glutamatergenic synapses produce antidepressant like activities and interfere with glutamate metabolism receptors, which are often linked to depression and suicidality [104]. A correlation between high glutamate levels and anxiety in humans has been reported [105]. Furthermore, vitamin B6 is integral in GABA synthesis and vitamin B6 supplementation is used to treat early onset of epilepsy in children with inborn errors of vitamin B6 metabolism [52]. Recently, it was demonstrated that food poisoning from Ginkgo biloba seeds can cause epilepsy, since Ginkgo biloba decreases vitamin B6 levels**,** which decreases GABA concentrations in the brain [49].

7.6.2. Vitamin B6 and serotonergic system: Serotonin is a signalling molecule found in blood vessels, the gut and other parts of the body. It is produced mainly in the brain in the raphe nuclei**,** which has connections throughout the brain and spinal chord. Serotonin is a modulatory chemical, which can have an effect on a number of conditions**,** including mood, anxiety, circadian rhythms, bowel problems, migraines, memory, nausea, and vasoconstriction/dilation. Serotonin (5-HT) is formed from L-tryptophan. When serotonin is released into the synaptic cleft it is taken up by serotonin receptors on the postsynaptic neuron. Following the binding of serotonin to receptors on the postsynaptic neuron**,** where it performs its function of signal transduction**,** it is then released again into the synaptic cleft. Serotonin can remain in the synaptic cleft or it can be taken up into the presynaptic neuron by serotonin transporters**,** where it is recycled and used again. Both serotonin transporters and monoamine oxidase are targets for anti-depressant drugs [106]. Dietary intake of serotonin is unable to be accessed by the body**,** due to the blood brain barrier. Tryptophan**,** however**,** can cross the blood brain barrier and diets poor in tryptophan or vitamin B6, which act as co-factors to facilitate the conversion of L-tryptophan to serotonin**,** may induce depression [106-108].

Furthermore, low monoamine levels, particularly serotonin, can lead to symptoms of depression. This theory was first postulated in the 1960's [109] and the subsequent studies have developed drugs to raise the synaptic serotonin levels without affecting other monoamines, by working on serotonin receptors [110]. Selective serotonin reuptake inhibitors are now amongst the most commonly prescribed drugs in the treatment of depression. Other studies have demonstrated that a low number of receptors relating to an underlying abnormality in the serotonin system could be a cause for low serotonin serum levels; increasing serotonin levels aids in increasing serotonin receptors, thereby increasing serotonin transmission [109]. Diets rich in vitamin B6 and tryptophan help boost serotonergic neurotransmission in depression observed in various neurodegenerative diseases. In fact, vitamin B6 deficient rats are highly susceptible to seizure disorders [111]. In addition, 140 individuals with symptoms of depression were shown to have significantly low levels of plasma pyridoxal phosphate, the phosphate derivative of vitamin B6 [96]. Furthermore, patients suffering from depression have elevated plasma homocysteine levels, which correlate with low vitamin B6 and folate levels [112].

7.7. VITAMIN B7 (BIOTIN)

Biotin is found in liver, egg yolks, soy beans, fish, whole grains and is important for gluconeogenesis, fatty acid synthesis and amino acid catabolism (Table 3). Avidin, present in egg whites, binds to biotin tightly [53] and prevents its absorption within the tissues. Biotin is synthesized by the normal micro flora of the large intestine and is partly absorbed by colonocytes. Over 30 years ago, it was noted in a patient with severe depression accompanied by delirium, that paresthesia and headache were improved following treatment with biotin [54]. Few studies are available which determine whether biotin plays a role in depression, although recently it was noted that inherited biotinidase deficiency in newborns leads to neurological abnormalities [113] (Table 3).

7.8. VITAMIN B9 (FOLATE)

Vitamin B9 (folate, folic acid, vitamin M, vitamin Bc) is found widely in foods, but is particularly abundant in foods of plant origin. It is closely associated with vitamin B12 and vitamin B6 in maintaining normal metabolic processes. When taken in food, folates are in the form of polyglutamates. Folate reductase enzymatically converts polyglutamates into folate monoglutamates within the mucosa of the jejunum. This process is necessary before absorption can take place in the small intestine by Na^+ - coupled carrier mediated processes (Table 3).

Folate is required for the synthesis, repair and methylation of DNA and is important for a number of biological reactions. Low folate levels have been linked to depression, according to 11 different studies with a total of 15,315 participants [114]. Low plasma or serum folate has also been found in patients with

recurrent mood disorders being treated by lithium. Interestingly, in Hong Kong and Taiwan populations with rich folate diets, there is a low incidence of major depression. Patients who respond poorly to anti-depressant medication are usually those with low folate levels; folic acid supplementation improves responses to medication, as reviewed in [115]. In 517 Japanese adults (21-67 years) folate supplementation showed an inverse and linear association with depressive symptoms in males, but not females [42]. Riboflavin, pyridoxine, cobalamin and omega-3 intake showed no correlation. However, folate intake had no effect on the risk of postpartum depression, although moderate consumption of riboflavin showed evidence of protection against postpartum depression [51]. In the Finnish male population, 2,682 participants were recruited and those with the lowest intake of folate had a higher risk of being depressed, compared to those with the highest folate intake [116]. A more recent Australian review and meta analyses on folate and B12 in depression suggests that increasing these two vitamins in the diet does not lessen the severity of depressive symptoms in the short term, but may assist in the ongoing management of depression in select populations [117]. However, in a Turkish cohort there was no difference in serum folate and B12 levels between depressive and non-depressive post-menopausal women and that supplementation of folic acid and B12 did not reduce depressive symptoms [118]. On the basis of this data, further studies are required to determine the effects of folic acid supplementation to improve treatment outcomes in depression. In fact, folic acid supplementation affects noradrenalin and serotonin receptors in the brain, suggesting its ability to have antidepressive effects.

7.8.1. Folate and dopaminergic system: Folate is needed in the brain for the synthesis of dopamine. [70]. Dopamine, a catecholamine-classed neurotransmitter, is found in numerous areas of the midbrain, including the substania nigra, retrorubral and ventral mesencephalon. The dopaminergic pathway, extending from these regions, innervates the forebrain of mammals and other peripheral tissue (on which it performs an exocrine or paracrine function) [119]. Dopaminergic neurons are responsible for higher motor function and goal orientated behavior, including reward, motivation and working memory, as well as learning and prediction [120]. Motor diseases, such as Parkinson's, and neuropsychological conditions, including obsessive compulsive behavior and schizophrenia, depression and drug addiction, are associated with the selective loss of dopamine neurons, or interruption to the dopaminergic system (Fig. **1**) [121-123]. Pharmacologically, decreasing dopamine levels in patients has been shown to result in an induction or deepening of depression symptoms [124]. Likewise, the firing capabilities of dopaminergic neurons in an animal model of depressed rats showed decreased neuron-bursting activity, hence lower dopamine release into the synapse compared to normal rats [123]. Interestingly, this area of research has led to deep brain stimulation in an attempt to increase dopamine levels, currently used in the treatment of Parkinson's [123]. Recently, it was noted that an increase in cholinergic levels in mice resulted in depression, according to the tail suspension test and forced swim test, whilst increased dopamine levels led to mania-like behavior [125].

7.9. VITAMIN B12 (COBALAMIN)

Vitamin B12 is a generic description for all compounds which contain a cobalt centered corrin nucleus. The action of B12 is interrelated with that of folate. The metabolically active form of B12 is cyanocobalamin, however other forms found naturally in biological systems include methylcobalamin, cob(I)alamin, 5'-deoxyadenosylcobalamin and hydroxycobalamin. B12 is stable to heat, soluble in water, but sensitive to light [126]. Vitamin B12 is synthesized by bacteria and stored within the tissue of animals and is therefore not present in plant sources, making the dietary intake of this vitamin a concern for people who follow a vegan diet [62]. Dietary B12 is bound to protein in food and released by hydrochloric acid and gastric proteases in the stomach. Once released from food-binding, proteins then bind to B12, transporting and protecting it from stomach acid and catabolism by intestinal bacteria. Intrinsic factor, secreted by parietal cells in the stomach, complexes with B12 and is absorbed in the small intestine. Following absorption, B12 moves into the circulation and is transferred into a cell via a plasma transporter, transcobalamin II. Once inside the cell, lysosomal activity degrades the transcobalamin II-B12 complex and free B12 is released into the cytoplasm [127]. People who undergo bariatric surgery are at risk of vitamin B12 deficiency due to gastric resection [128, 129]. Likewise, people who follow vegan diets are at risk for B12 deficiency, owing to inadequate intake. Common clinical symptoms suffered due to B12 deficiency include fatigue and weakness, constipation, loss of appetite and weight loss, balance issues, depression and cognitive disturbances, peripheral tingling and soreness of the mouth and tongue [130] (Table 3).

Vitamin B12 (cobalamin) plays a major role in the normal functioning of the brain and the nervous system. It is involved in the synthesis and regulation of DNA and metabolism of amino acids and fatty acids. Vitamin B12 deficiency results in severe symptoms of depression, suicidal behaviors, cognitive decline, irritability, mania and psychosis, thus affecting the health and well-being of individuals. Indeed, vitamin B12 deficiency is found in up to one-third of depressed patients and higher vitamin B12 levels are associated with better treatment outcomes. In addition, low vitamin B12 increases the risk of cognitive decline, dementia and Alzheimer's disease and is linked to a five-fold increase in the rate of brain atrophy. In fact, high B12 levels protects against brain atrophy associated with Alzheimer's disease and cognitive decline [131]. Furthermore, in a Finnish group, low B12 was associated with risk for melancholic depressive symptoms, but not with non-melancholic depressive symptoms [132]; low B12 levels were also associated with bipolar depression [133]. This supports the hypothesis that low B12 is linked with diminished synthesis of serotonin and other monoamine neurotransmitters [132]. In a study of 20 geriatric and 16 alcoholic patients with major depression, deficiency in B12 levels (and riboflavin and pyridoxine levels) were evident [134]. The recent Quebec longitudinal study on nutrition and aging, comprising 1,792 participants, demonstrated that low B12 levels were associated with depression in men and low B6 levels were associated with depression in women [135]. However, in post-menopausal

women, at high risk of depression, there was no correlation between B12 (and folate) levels and depressive symptoms [118].

Given that there is a link between B12 deficiency and depression, B12 supplementation should theoretically improve depressive symptoms. Indeed, in a study comprising 199 patients with depression on antidepressants, B12 injections significantly improved depressive symptoms [136]. Long term supplementation over 24 months of B12 improved cognitive function and depressive symptoms in a study ~~in~~ of 900 depressed adults aged 60-74 years [137]. Further studies are therefore warranted to ascertain the effects of B12 supplementation in depression.

7.9.1. Cobalamin and noradrenergic system: The noradrenergic system participates in the synthesis, storage and release of noradrenaline (norepinephrine). Dysregulation of noradrenergic function, most commonly associated with over activation of this system, can lead to many symptoms of anxiety and depression (Fig. **1**) [138]. Norepinephrine is a monoamine, consisting of a single amine group and a benzene ring with 2 hydroxyl groups. It is released by the sympathetic nervous system and mediates the flight or fight response, preparing the body for "action' by affecting cardiovascular function, bronchodilation, gastrointestinal motility and secretion, and glucose metabolism. Within the central nervous system, norepinephrine is associated with sleep, memory, learning and emotion [139]. Noradrenaline is synthesized in the nerve axon and stored in synaptic vesicles in nerve terminals. It binds to receptors when needed. Noradrenaline that is not stored is degraded by monoamine oxidase [140]. Folate and vitamin B12 aid in the metabolism of monoamine neurotransmitters such as norepinephrine. Indeed, folate deficiency could cause impaired methylation and monoamine metabolism, leading to depression [138]. Patients with major depressive disorder have an inhibition of noradrenergic release [141].

CONCLUDING REMARKS

Depression is a multicausal disorder, being a metabolic disorder, cardiovascular disorder, endocrinological disorder, stress disorder and nutritional disorder. Up to the present time, vitamin B cannot replace medication, especially in severe depressive symptomatology, but could be used as an adjunct treatment. It is clear that vitamin B complex plays a role in depression, however further studies are required to determine the mechanistic effects of vitamin B in depression.

FUTURE PROSPECTS

Depression could manifest as an immunological disorder. Pro-inflammatory cytokines, IL-1-beta, IL-2 receptor, IL-6, IL-8, IL-10, TNF-alpha, IFN-alpha, and, C-reactive protein, haptoglobin, toll like

receptor 4, cyclooxygenase-2, prostaglandin-E2, lipid peroxidation levels and acid sphingomyelins have all been implicated in being involved in the neurobiological manifestation of depression [142]. In fact, anti-TNF-alpha treatment decreased depressive symptoms and improved sleep continuity in resistant major depressive patients with baseline high inflammation [143]. Likewise, curcumin, a natural anti-inflammatory, improves major depressive disorder symptoms [144]. In an English longitudinal study of ageing, consisting of 3,397 participants, high c-reactive protein levels were associated with elevated depressive symptoms [145]. Interestingly, a meta-analysis of 18 studies, comprising 583 depressed patients with suicidality, 315 patients without suicidality and 845 control subjects, demonstrated that high levels of IL-1-beta and IL-6 correlated with patients with suicidality, as compared to patients without suicidality and control subjects. Hence, IL-1-beta and IL-6 may aid in the ability to distinguish between suicidal and non-suicidal patients [146]. The immune-cytokine network has powerful control over the brain, increasing its sensitivity to stress, anxiety and depression, hence it is imperative to further understand the role the immune system plays in depression. Moreover, the effects of vitamin B on immune cell functionality will aid in an understanding of the role vitamin B and immune cells play in depression. The development of an effective prescription of a rich vitamin B source for patients with depression may provide a valuable supplement to existing therapeutic strategies for patients with depression.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ABBREVIATIONS

CoA	=	Coenzyme A
FAD	=	Flavin adenine dinucleotide
FMN	=	Flavin mononucleotide
GABA	=	Gamma amino butyric acid
IFN	=	Interferon
IL	=	Interleukin
NAD	=	Nicotinamide adenine-dinucleotide
NADP	=	Nicotinamide-adenine dinucleotide phosphate
TNF	=	Tumor necrosis factor
5-HT	=	5-hydroxytryptamine

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Fig. (1). Relationship between vitamin B and neurochemical pathways leading to depression (and anxiety).

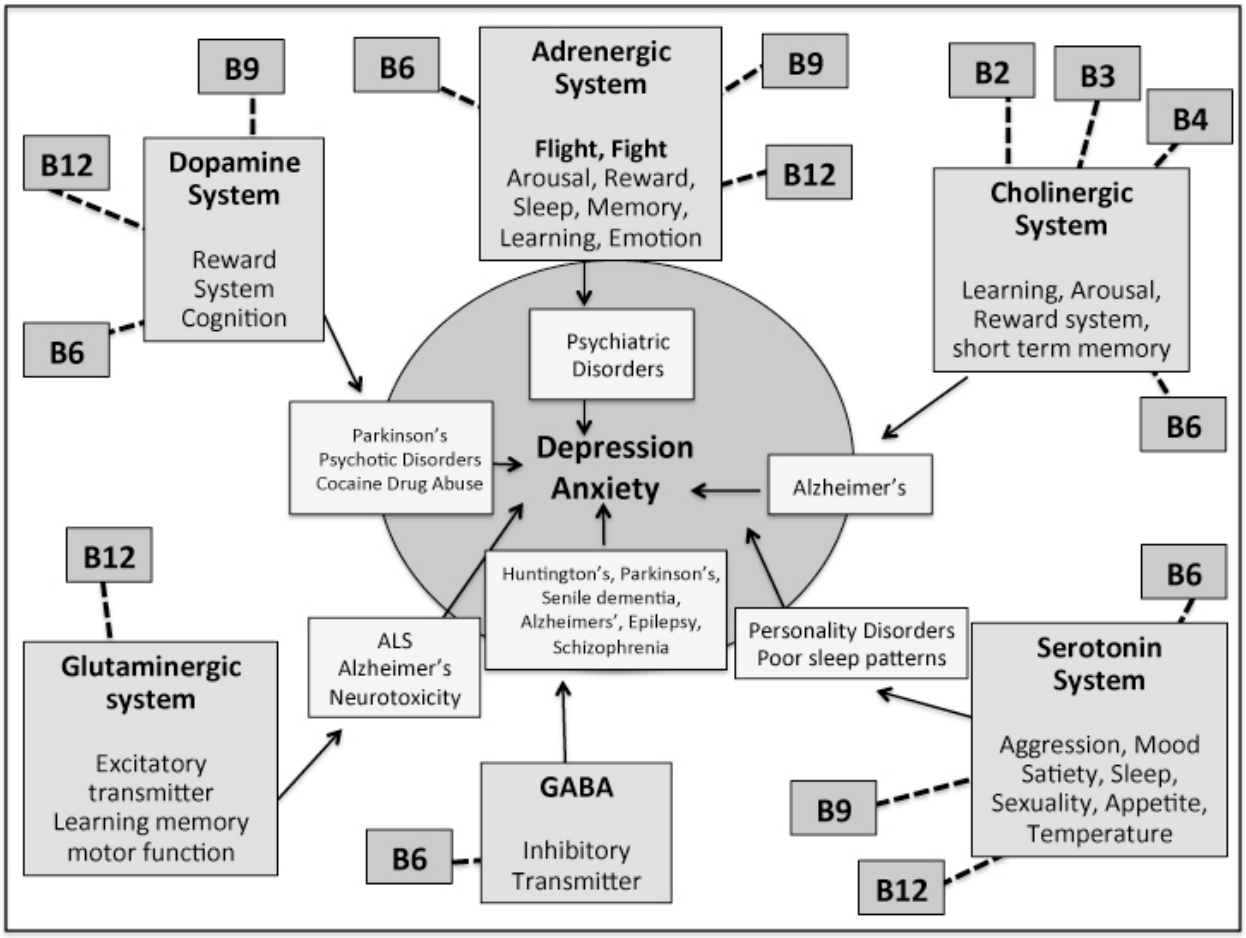


Table 1. B Vitamins as co-enzymes.

B Vitamin	Co-Enzyme	Enzyme	Chemical group transferred	Function
Vitamin B1 (Thiamin)	Thiamine pyrophosphate	Pyruvate dehydrogenase	Aldehydes	• Part of co-enzyme thiamin pyrophosphate, • decarboxylation of pyruvic and α-ketoglutarate acids, • utilization of pentose in the hexose monophosphate shunt. • Aids the conversion of pyruvate to acetyl CoA in the pyruvate dehydrogenase complex • Plays a part in the α-ketoglutarate-dehydrogenase complex in the TCA (Krebs) cycle, converting a 5 carbon compound to a 4 carbon compound. • catabolism of branched-chain amino acids which function in the Krebs cycle
Vitamin B2 (Riboflavin)	Flavin adenine nucleotide (FAD) Flavin mononucleotide (FMN)	Monoamine oxidase	Electrons	• FAD forms part of the complex II of the electron transport chain, • FAD essential in the conversion of pyridoxal (Vitamin B6) to pyridoxic acid by pyridoxine 5' phosphate oxidase • FAD aids conversion of retinol to retinoic acid via retinal dehydrogenase. • FAD is also necessary for oxidating pyruvate, a-ketoglutarate and branched chain amino acids • FAD reduces the oxidized form of glutathione to glutathione reductase in complex II of the electron transport chain. • Fatty acyl Co-a dehydrogenase requires FAD in fatty acid oxidation and $FADH_2$ synthesizes an active form of folate (5-mehtyltetrahydrofolate) from 5,10-methylenetetrahydrofolate. • FMN is an important component in the primary coenzyme form of Vitamin B6 and required to convert tryptophan to niacin (Vitamin B3) in complex I of the electron transport chain. • FMN reduces the oxidized form of glutathione to glutathione reductase in complex II of the electron transport chain
Vitamin B3 (Niacin)	Nicotinamide adenine dinucleotide (NAD+ and NADP+)	Lactate dehydrogenase	Hydride ion ($:H^-$)	• The enzyme NAD+ kinase phosphorylates NAD to NADPH, both acting as coenzymes for many dehydrogenases which participate in hydrogen transfer processes. • NAD is a significant contributor to the catabolism of fat, carbohydrate, protein, and alcohol, • NADP mostly occurs in anabolistic reactions such as fatty acid and cholesterol synthesis.

				• NAD is required for cell signalling and DNA repair
Vitamin B5 (Pantothenic Acid)	Coenzyme A (CoA)	Acetyl CoA carboxylase	Acyl groups	• Acyl group carrier to form acetyl-CoA and other related compounds; • Energy metabolism for pyruvate to enter TCA as acetyl-CoA, • Ketoglutarate to be transformed to succinyl-CoA in the cycle. • Biosynthesis of fatty acids, cholesterol, and acetylcholine. • Formation of acyl carrier protein, • Acylation and Acetylation involved in signal transduction and enzyme activation and deactivation, respectively.
Vitamin B6 (Pyridoxine)	Pyridoxal Phosphate	Glycogen phosporylase	Amino groups	• Cofactor in the biosynthesis of serotonin, dopamine, epinephrine, norepinephrine, gamma-amino butyric acid • Synthesis of histamine. • Co-factor for amino acid breakdown and moving amine groups from one amino acid to another. • Aids serine racemase to synthesize serine (a neuromodulator) • Helps transform methionine into cysteine. • Helps transform selenomethionine to selenium. • Releases selenium from selenohomocysteine to produce hydrogen selenide, which can then be used to incorporate selenium into selenoproteins. • Conversion of tryptophan to niacin.
Vitamin B7 (Biotin) (Vitamin H)	Biocytin	Pyruvate carboxylase	CO_2	• Acetyl-CoA carboxylase alpha • Acetyl-CoA carboxylase beta • Methylcrotonyl-CoA carboxylase • Propionyl-CoA carboxylase • Pyruvate carboxylase • Gluconeogenesis, fatty acid synthesis, amino acid catabolism
Vitamin B9 (Folic Acid)	Tetrahydrofolate	Thymidylate synthase	one carbon groups	• (THF) and other folate derivatives important in a series of single carbon transfer reactions. • Important in methylation along with B12 and B6 for recycling homocysteine into methionine.

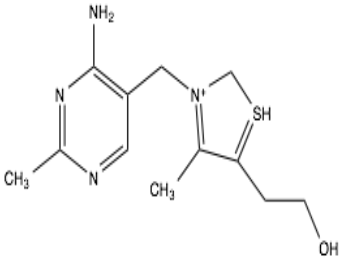
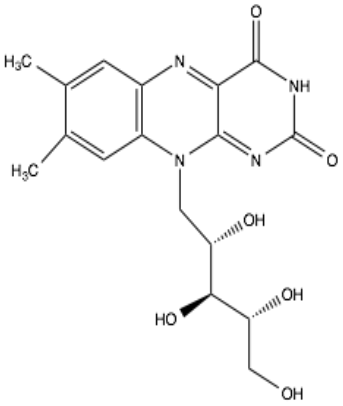
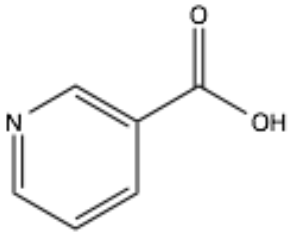
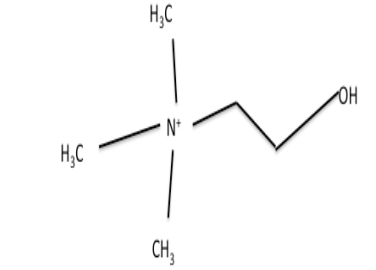
				• Synthesis of DNA and the process of cell division. • Folate in the form of 5-MTHF helps to regulate neurotransmission of monoamines. • DNA methylation. • NO2 synthesis.
Vitamin B12 (Cobalamin)	Methylcobalamin Cyanocobalamin	Methylmalonyl mutase (MUT) Methionine Synthase (MTR)	H atoms and alkyl groups	• Metabolism of carbohydrates, protein and fat. • Co-factor for fatty acid elongation • Participates in Isomerase and Methyltransferase reactions. • MUT converts L-methylmalonyl Co-A to Succinyl Co-A before it enters the citric acid cycle. • MTR uses B12 as a cofactor to transfer a methyl group from 5-MTHFR to homocysteine to generate THF and methionine used in the methylation cycle.

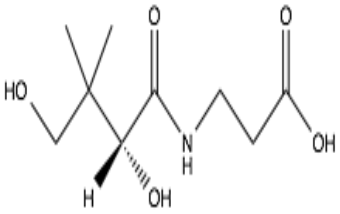
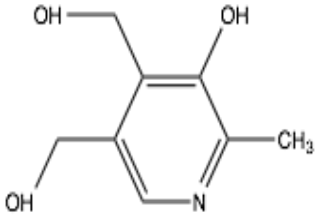
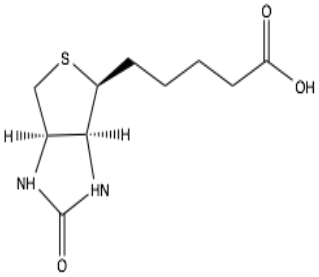
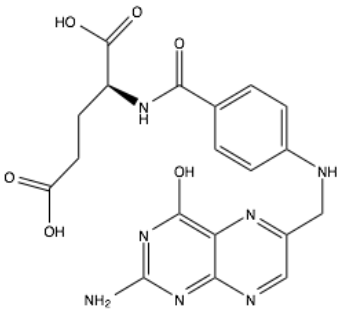
Table 2. B Vitamins: Function, Deficiency, Sources

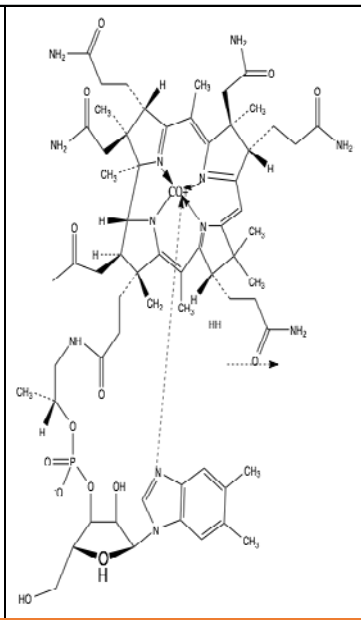
B Vitamin	Function	Deficiency Symptoms	Deficiency Diseases	Sources
Vitamin B1 Thiamin	-Generation of nerve impulses -Synthesis of neurotransmitters, nucleic acids, fatty acids, steroids Complex CHO	-Cardiomegaly, -Cardiac failure -muscular weakness -apathy -poor short term memory -confusion - irritability -anorexia, weight loss. -Depressive symptoms	-Wet or Dry Beriberi, -Wernicke Korskakoff syndrome.	Whole grain fortified or enriched grain products. pork, contained in moderate amounts in most nutritious food
Vitamin B2 Riboflavin	-Co-Enzyme in many reactions. -Energy Metabolism in the forms- flavin mononucleotide flavin adeninedinucleotide	-inflammation of membranes of mouth, skin, eyes and gastrointestinal tract. -Poor cognitive outcomes	Ariboflavinosis	Milk products, wholegrain fortified or enriched grain products, liver
Vitamin B3 Niacin Nicotinamide Niacinamide	Part of co-enzyme NAD. Can be made by tryptophan	Diarrhoea, Dermatitis, Dementia, Death. - abdominal pain, vomiting, inflamed swollen smooth bright red tongue, (glossitis), -depression, apathy, fatigue, memory loss headache, bilateral symmetrical rash on areas exposed to sunlight. -Depressive symptoms	Pellagra	Milk, eggs, meat, poultry, fish, wholegrain, fortified and enriched grain products, nuts and all protein containing foods.
Choline	Synthesizes acetylcholine and lecithin	Liver damage cognitive deficits		Milk, liver. eggs. Peanuts, wheat germ. Also synthesized endogenously by renal medullar cells
Vitamin B5 Pantothenic Acid	-Part of chemical structure of coenzyme A. -Important for TCA (Krebs) cycle in energy metabolism, fat synthesis, amino acid metabolism, glycogen synthesis. synthesis of steroid hormones, melatonin and acetylcholine.	Vomiting, nausea, stomach cramps, insomnia, fatigue, depression, irritability, restlessness, apathy hypoglycemia, increased sensitivity to insulin, numbness, muscle cramps, inability to walk. Depressive symptoms	-Loss of myelin sheath and peripheral nerve damage	Chicken, beef, potatoes, oats, tomatoes, liver, egg yolk, broccoli, wholegrain
Vitamin B6	-Energy metabolism as	Fatigue, Gastrointestinal		Meats, fish, poultry, potatoes and

B Vitamin	Function	Deficiency Symptoms	Deficiency Diseases	Sources
Pyridoxine Pyridoxal, pyridoxamine (all forms can be converted to co-enzyme pyridoxal phosphate – PLP)	coenzyme A -Cognitive performance -Immune function, - Steroid hormone activity - Aids conversion of tryptophan to niacin or serotonin. -Synthesis of GABA, dopamine, norepinephrine and serotonin	distress, -Neurological disturbances (irritability, depression, confusion and seizures) -Depressive symptoms		other starchy vegetables, legumes, non citrus fruits, fortified cereals, liver, soy products
Vitamin B7 Biotin Vitamin H	Energy metabolism Carries activated CO_2 which in TCA (Krebs) cycle turns pyruvate into oxaloacetate and combines with Acetyl CoA. Gluconeogenesis and fatty acid synthesis and breakdown. Biotin is the isomer of B2 complex	Lethargy, hallucinations, numb or tingling sensation in the arms and legs, red scaly rash around the eyes nose and mouth, hair loss		Liver, egg yolks, soy beans, fish, whole grains, also produced by gut flora
Vitamin B9 Folate Folic acid Folacin	DNA synthesis and new cell formation. Tetrahydrofolate in its primary co enzyme form facilitates transfer of one carbon compounds during metabolism. Aids conversion of B12 to a conenzyme form. synthesis of norepinephrine, dopamine, and serotonin. Breakdown of norepinephrine and dopamine	Smooth red tongue, mental confusion, weakness, fatigue, irritability, headache, shortness of breath, elevated homocysteine. Depressive symptoms	Anaemia. Neural tube Defect in foetus.	Fortified grains, leafy green vegetables, legumes, seeds, liver
Vitamin B12 (Cobalamine)	Synthesis of new cells, nerve cell maintenance, reforms folate coenxyme, helps break down fatty acids and amino acids. A close relationship exists between folate and B12 each depends on the other for activation. B12 removes a methyl group and activates folate coenzyme. The removal of the methyl group from B12 activates cB12 co-enzyme	Anaemia (large cell type), fatigue, degeneration of peripheral nerves progressing to paralysis, sore tongue, loss of appetite, constipation. Depressive symptoms	Pernicious Anemia can lead to magablastic anaemia if untreated. Atrophic gastritis. Megaloblastic madness (delusions, anand hallucinations)	Foods of animal origin, meat, fish, poultry, shellfish, milk, cheese, eggs, fortified cereals

Table 3. B Vitamins: Structure, binding, absorption, metabolism and excretion.

B Vitamin	Chemical Structure	Binding	Absorption	Metabolism of vitamin	Excretion
Vitamin B1 (Thiamin)		Serum proteins mainly albumin	Low concentrations by passive transport in upper small intestine. Low concentrations by active transport mostly in jejunum and ileum	~ 80 % is phosphorylated and most is bound to proteins	Urine as thiamin and acid metabolites (2-methyl-4-amino-5-pyrimidine carboxylic acid, 4-methyl-thiazole-5-acetic acid, and thiamine acetic acid)
Vitamin B2 (Riboflavin)		Free B2 binds to albumin and certain immunoglobulin's	Upper part of small intestine best absorbed when taken with food (60% versus 15% with no food)	In tissues mostly enzyme bound. Intracellular phosphorylisation . Free riboflavin is diffused from cells and excreted	Excreted in urine as riboflavin or other metabolites
Vitamin B3 (Niacin)		Binds to Nicotinate D-ribonucleotide phyrophsopate, phosphoribosyltransferase, Nicotinic acid phosphoribosyltransferase, Nicotinate N-methyltransferase and Niacin receptor	stomach and small intestine stored in liver	Absorbed niacin is synthesized to NAD Tryptophan also synthesizes NAD via kynurenine pathway	In urine as *N*1-methyl-nicotinamide and its 2-pyridone derivative (*N*1-methyl-2-pyridone-5-carboxamide)
Choline		Capable of forming phosphoester bonds (Phosphocholines.) Acetyl group from Acetyl CoA binds to choline to create Acetylcholine. This process is catalyzed by acetyltransferase	By Small intestine by carrier mediated process. Unabsorbed choline acted on by bacteria producing trimethylamine and dimethyl amine. Once absorbed enters portal system and taken up by liver	Three systems for uptake. Facilitated transport in red blood cells. Na+ dependent active transport in neuronal tissue. Low affinity high capacity active transport in cells. Oxidized in mitochondria to betaine	Reabsorbed by renal tubules when levels are normal. When levels are above normal choline is actively excreted by renal tubules

B Vitamin	Chemical Structure	Binding	Absorption	Metabolism of vitamin	Excretion
Vitamin B5 (Pantothenic Acid)		Bound to proteins as acyl carrier protein	Absorbed in small intestine by active transport at low concentrations passive transport at high concentrations	Found in food as CoA or acyl carrier protein must be covered to free pantothenic acid before absorption can take place in intestinal cells	Excreted intact in the urine
Vitamin B6 (Pyridoxine)		Pyridoxal, pyridoxine and Pyridoxamine are converted to metabolically active form of pyridoxal phosphate. This conversion is catalyzed by pyridoxal kinase and requires zinc for full activation	Absorbed in jejunum and ileum by passive diffusion	Dephosphorylation of pyridoxal phosphate and pyridoxamine phosphate catalyzed by an alkaline phosphatase	Excreted in urine mostly as 4-pyridoxic acid when vitamin B6 levels are high pyridoxal, pyridoxamine, pyridoxine and their phosphates are also excreted. A small amount of B6 is excreted in the faeces
Vitamin B7 (Biotin) (Vitamin H)		Dietary biotin binds to dietary avdin and prevents its absorption			
Vitamin B9 (Folic Acid)		Pteridine ring linked to benzoic acid	Epithelial cells of intestine into blood stream this is done after removal of glutamate from folate	Reduced within cells to tetrahydrofolate by dihydrofolate reductase and NADPH requiring enzyme	Excreted in urine

B Vitamin	Chemical Structure	Binding	Absorption	Metabolism of vitamin	Excretion
Vitamin B12 (Cobalamin)		Bound to protein in food. Released by HCL and gastric proteases	B12 combines with intrinsic factor and is absorbed in ileum. Absorption reliant on the capacity of intrinsic factor. In healthy people only 1mcg of a 500mcg oral supplement is actually absorbed	Once inside the cell lysosomal activity degrades transcobalamin II-B12 complex and the free B12 is released into the cytoplasm	Main source of excretion via bile but most of this is reabsorbed via enterohepatic circulation and stored in liver with only a small amount entereing faeces. Higher amounts are excreted in the urine