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This book discussed the role of the contents of black seed, especially iron, vitamin B2, vitamin B6 and vitamin B3 in tryptophan metabolism, and links between the disturbance in these elements and the etiologies of several pathological and physiological states, and introduced new definitions for physiology, pathology, medicine and pharmacology based on the tryptophan metabolism.
Also, this book offers a new practical definition for the most important medical sciences. Furthermore it enables physicians to monitor disease prognosis and to avoid the occurrence of many fatal diseases.



Mosab Nouraldein Mohammed Hamad - research and development scientist.

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# Black cumin Provides a new Definitions for , Physiology and Pathology

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**List of content**

**Dedication**

**To the soul of my father**

**To my great mother**

**Acknowledgement**

To The great Prophet Muhammad bin Abdullah(SWAS) for his honest message , then to my teacher of physiology , Mr. Adel Bilal and to my teacher of immunology and Parasitology, Dr. Ahmed Mohammed Abdelhalim , for their motivating words , which inspired me to collect this scientific material. Also, I am thankful to my friend Dr. Yassin Bakri Salih , Dr. Mohammed Abd elgafoor and Dr. Mohammed Omer for their encouragement and continuous support.

## Introduction

### Brain storming

Human Immunodeficiency Virus infects a type of white blood cell in the body's immune system called a T-helper cell (also called a CD4 cell). These vital cells keep us healthy by fighting off infections and diseases.

It cannot reproduce on its own. Instead, the virus attaches itself to a T-helper cell and fuses with it (joins together). It then takes control of the cell's DNA, makes copies of itself inside the cell, and finally releases more HIV into the blood. HIV will continue to multiply and spread throughout the body – a process called the HIV lifecycle. In this way, HIV weakens the body's natural defences and over time severely damages the immune system [1].

Viral proteins, termed "virotoxins," are released from the infected glial cells that initiate a cascade of positive feedback loops by activating uninfected microglial cells and astrocytes. These activated cells release a variety of toxic substances that result in neuronal dysfunction and cell loss[2].



Virotoxins are toxic peptides singularly found in Amanita virosa mushrooms. After purification and resolution by high-pressure liquid chromatography, the main component, viroisin, was selectively cleaved and submitted to Edman degradation. The structure could be completely elucidated and was in part found to be the same as in phallotoxins. Differing from the phallotoxins, however, virotoxins are monocyclic peptides and contain D-serine instead of L-cysteine. In addition, two amino acids were detected in virotoxins which thus far have not been found in nature: 2,3-trans-3,4-dihydroxy-L-proline and 2'-(methylsulfonyl)-L-tryptophan [3].

The metabolism of tryptophan is intimately associated with the differential regulation of diverse physiological processes. including the activation of the aryl hydrocarbon receptor (AhR), thereby altering the nature of immune responses. AhR activation dysregulates the initial pro-inflammatory cytokines production driven by neutrophils, macrophages, and mast cells, whilst AhR activation suppresses the endogenous antiviral responses of natural killer cells and CD8+ T cells [4],Some of the tryptophan catabolites such as 3-hydroxyanthranilic and quinolinic acid have been shown to selectively drive Th1 cells (but not Th2 cells) into apoptosis [5]

Proline (Pro) is a key amino acid involved in protein synthesis and an important regulator of metabolism , immunity, and together with its metabolite, hydroxyproline, play an important role in collagen synthesis and tissue repair. Proline metabolism plays an essential part in innate immune response. Dietary Proline supplementation has been shown to improve the antioxidant and immune activities [6].

Plasma amino acid concentrations were lower in HIV-infected youth compared to healthy controls, regardless of immune status, while glutamate concentrations were elevated [7]. Synthesis of proline begins with the conversion of glutamine to glutamate by the enzyme glutaminase (GLS) [8].

In addition to influencing excitatory neurotransmission by directly acting on glutamate receptors, QUIN and KYNA also modulate glutamate function indirectly. On the other hand, even modest elevations in KYNA rapidly *reduce* the extracellular concentration of glutamate. KYNA concentrations in the midnanomolar range consistently—and reversibly—decrease glutamate levels by 30–40% in every brain region studied so far.

Redox phenomena also play a role in the neuroactive properties of kynurenines and appear to participate in their effects on glutamatergic mechanisms in the brain. Thus, QUIN generates reactive oxygen species, and this effect increases the excitotoxic potency of the metabolite. In contrast, KYNA can function as a free radical scavenger and antioxidant [9].

Kynurenic acid (KYNA) is a tryptophan metabolite and represents the only known endogenous compound acting as an antagonist to excitatory amino acid receptors in the mammalian CNS. Blocking of these receptors in CNS by KYNA affects cardiac function [10]. Diseases of the myocardium in patients with HIV/AIDS include cardiomyopathy, myocarditis, cardiac tumors and drug toxicity. Left ventricular dysfunction associated with HIV/AIDS patients is most often clinically silent, and can progress to symptomatic left heart failure [11].



Study done by Dylla SJ et al [12]showed that proline-rich tyrosine kinase 2 gene products mediate integrin-induced signals that regulate myelopoiesis . Study done by Beinke S et al[13] showed that PYK2 deficiency results in a specific loss of short-lived effector CD8 T cells but does not affect memory-precursor CD8 T-cell development.

The relocation of kinases in T lymphocytes during their cognate interaction with APCs is essential for lymphocyte activation. We found that the proline-rich tyrosine kinase-2 (Pyk2) is rapidly translocated to the T cell-APC contact area upon T cell-specific recognition of superantigen-pulsed APCs. Stimulation with anti-CD3-coated latex microspheres was sufficient for Pyk2 reorientation, and the coengagement of CD28 boosted Pyk2 redistribution [14].

Study done by Van Buul JD et al [15] showed that the inhibition of Pyk2 activity in endothelial cells by the expression of CRNK (CADTK/CAKβ-related non-kinase), an N-terminal deletion mutant that acts in a dominant negative fashion, not only abolishes the increase in β-catenin tyrosine phosphorylation but also prevents the loss of endothelial cell-cell contact.

Study done by Henderson LJ and Al-Harthi L [16] showed that Suppressing β-catenin signaling in infected cells increases HIV replication, suggesting that the endogenous level of β-catenin suppresses HIV replication and without it the level of HIV in this

system would be much higher. Conversely, activating β-catenin signaling potently inhibits HIV replication.

Study done by Di Cioccio V et al [17] showed that Inhibition of Pyk2 activation by PP1, a Src PTK inhibitor, is paralleled by the inhibition of CXCL8-mediated neutrophil chemotaxis.

Study done by Heit B et al[18] showed that impairment in the in vivo recruitment of leukocytes; specifically integrin-dependent neutrophil adhesion and emigration induced by bacterial products among HIV patients.

Study done by Canino J et al[19] showed that Pyk2 acts in the early phases of integrin-mediated adhesion of neutrophils to fibrinogen and regulates a signaling cascade involving PI3K and MAP kinases to sustain neutrophil adhesion and promote ROS generation.

Study done by Madden E et al [20] showed that Median fibrinogen levels (mg/dL) were 8% higher in HIV-infected men (345, 95% CI: 337 to 356) compared with control men, despite the lower levels of subcutaneous adipose tissue and visceral adipose tissue that we found in HIV compared to control men.

Study done by Ryu JK et al [21] showed that Fibrinogen stimulates a unique transcriptional signature in CD11b$^{+}$ antigen-presenting cells inducing the recruitment and local CNS activation of myelin antigen-specific Th1 cells. Fibrinogen depletion reduces Th1 cells in the multiple sclerosis model, experimental autoimmune encephalomyelitis. Major histocompatibility complex (MHC) II-dependent antigen presentation, CXCL10- and CCL2-mediated recruitment of T cells and macrophages, respectively, are required for fibrinogen-induced encephalomyelitis. Inhibition of the fibrinogen receptor CD11b/CD18 protects from all immune and neuropathologic effects.



Study done by Kuniholm MH et al [22] showed that CD11b+ expression on classical monocytes is positively associated with FEV1/FVC ratio in people living with HIV including in those with CD4 T-cell recovery.

Study done by Zhen A et al [23] identified a role for the CD4 molecule in triggering the activation and development of a monocyte into a macrophage following its ligation. Activation of the monocyte through the CD4 molecule in this manner increases the ability of monocytes to bind to and become infected with HIV.

Study done by Cong L et al [24] showed that the HIV-1 accessory protein viral protein U (Vpu) downregulates cell surface levels of CD47, a host protein that interacts with the inhibitory receptor signal regulatory protein-alpha (SIRPα), to deliver a "don't-eat-me" signal to macrophages. This allows for enhanced capture and phagocytosis of infected T cells by macrophages, ultimately leading to their productive infection even with transmitted/founder (T/F) virus.

Study done by Dagda RK et al [25] showed that an increased chronic exposure of humans to PD toxins along with interactions with certain genes and aging can increase the risk of developing PD.

Impaired protein homeostasis and accumulation of damaged or abnormally modified protein are common disease mechanisms in many neurodegenerative disorders, including Parkinson's disease (PD). As one of the major degradation pathways, autophagy plays a pivotal role in maintaining effective turnover of proteins and damaged organelles in cells.

Several decades of research efforts led to insights into the potential contribution of impaired autophagy machinery to α-synuclein accumulation and the degeneration of dopaminergic neurons, two major features of PD pathology [26].

Study done by Santerre M et al [27] showed that among older $HIV^+$ adults, the frequency of cases with SNCA/α-synuclein staining is higher than in older healthy persons and may predict an increased risk of developing a neurodegenerative disease. The accumulation of SNCA aggregates known as Lewy Bodies is widely described to be directly linked to motor dysfunction.

Parkin (PRKN) is a ubiquitin E3 ligase that catalyzes the ubiquitination of several proteins. Mutations in the human Parkin gene, PRKN, leads to degeneration of dopaminergic (DA) neurons, resulting in autosomal recessive early-onset parkinsonism and the loss of PRKN function is linked to sporadic Parkinson's disease (PD).



Study done by González-Barbosa E et al [28]Prkn was identified as a novel target gene of the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor and member of the bHLH/PAS (basic helix-loop-helix/Per-Arnt-Sim) superfamily. AhR binds and transactivates the Prkn gene promoter. Also demonstrated that AhR is expressed in DA neurons and that its activation upregulates Prkn mRNA and protein levels in the mouse ventral midbrain. Additionally, the AhR-dependent increase in PRKN levels is associated with a decrease in the protein levels of its target substrate, α-synuclein, in an AhR-dependent manner, because this effect is not observed in Ahr-null mice.

As many as 5% of patients with HIV meet U.K. criteria for Parkinson's disease, according to the literature, and an additional 10% exhibit parkinsonian features.

Typically, parkinsonism is seen in HIV patients with the most severe immunosuppression—with CD4 cell counts less than 40 [29].

Study done by Okada T et al[30]showed that α-Syn(A53T) inhibited PDGF-induced Rac1 activation, whereas Cdc42 activation remained unaffected, resulting in unbalanced actin filament remodeling. Study done by Angeles-Floriano T et al[31] showed that the expression of CDC42 might be regulated by AHR.

Study done by Ospina Stella A et al [32] showed that the evidence obtained so far suggests that interplay with the actin cytoskeleton occurs at nearly all stages of the viral life cycle. However, targeted manipulation of actin regulators and pathways is particularly important for promoting viral entry, inbound intracellular transport, and highly efficient viral spread via direct cell-cell contacts.

The dysfunction of tryptophan (Trp) metabolism has been observed clinically in association with accelerated HIV-1 pathogenesis.

Study done by Zhou YH et al[33] demonstrated that the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, is activated by Trp metabolites to promote HIV-1 infection and reactivation. AHR directly binds to the HIV-1 5′ long terminal repeat (5′-LTR) at the molecular level to activate viral transcription and infection, and AHR activation by Trp metabolites increases its nuclear translocation and association with the HIV 5′-LTR; moreover, the binding of AHR with HIV-1 Tat facilitates the recruitment of positive transcription factors to viral promoters.

Study done by Katz IR [34] showed that Glutamine significantly inhibits synaptosomal tryptophan hydroxylase activity; it has less marked effects on tyrosine hydroxylase and DOPA decarboxylase activities. Thus, interaction between glutamine and tryptophan transport into nerve terminals may be one of the factors regulating the rate of serotonin synthesis in vivo. Tryptophan hydroxylase (TPH) is an enzyme crucial to the synthesis of the neurotransmitter serotonin [35].

Study done by Benton T et al [36] suggested a role for serotonin in the regulation of immunity in HIV infection, and suggests that serotonin reuptake inhibition may increase extracellular concentrations of serotonin and thereby suppress HIV infectivity and replication, possibly through the secretion of HIV suppressive factors as well as HIV receptor and co-receptor down-regulation. Study done by Keegan MR et al [37] observed a trend toward lower kynurenine (KYN)/Tryptophan (TRP) ratios in aviremic HIV+ patients with CI and MDD.



Study done by Dagenais-Lussier X et al [38] showed that a kynurenine-dependent mechanism through IL-2 signaling for reduced CD4 T-cell survival. Study done by et al [39]showed that the higher KYNA production, contributed to dysfunctional efector CD4+T-cell response.

IL-2 has an immunoregulatory role; it promotes the growth and development of peripheral immune cells in the initiation of the (defensive) immune response, and keeps them alive as effector cells [40].

Kynurenine is a tryptophan metabolite and produced by both IDO-1 and tryptophan-2,3-dioxygenase-2 (TDO-2). It binds, among other endogenous molecules, to the aryl hydrocarbon receptor (AHR) in multiple immune cell types, leading to immune suppression [41]. Absence of aryl hydrocarbon receptors increases endogenous kynurenic acid levels [42].

The kynurenine pathway (KP) is the main route of Trp metabolism. The enzymes of the pathway generate numerous metabolites, some of which are pro-inflammatory and/or generate free radicals, while others are known to be anti-inflammatory and/or scavenge free-radicals. Strong links between KP function and the immune system are demonstrated by extensive amounts of data on changes in the levels of KP metabolites and enzyme activities in diseases accompanied by alterations in immune function [43].

Study done by Bipath P et al[44] showed that Higher levels of inflammatory activity in this low income sub-Saharan HIV/AIDS population than in patients from developed countries lead to greater tryptophan depletion and greater accumulation of metabolites downstream from tryptophan with quinolinic acid levels often reaching levels associated with the development of HIV/AIDS-associated neurocognitive dysfunction.

The association of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing [45].

Study done by Wan M et al [46] provide circumstantial evidence for an essential role of 5-hydroxytryptamine ( serotonin, 5-HT), especially the regulation of 5-HT on immune cells in the pathogenesis of autoimmune diseases.

In humans acute tryptophan depletion inhibits serotonin synthesis and also lowers cerebrospinal fluid concentrations of tryptophan and 5-hydroxyindoleacetic acid (5-HIAA), the major serotonin metabolite [47]. HIV-1-infected patients have low circulating tryptophan concentrations despite evidence of adequate dietary intake of this essential amino acid [48]. Dietary tryptophan is metabolized by the gut microbiota into AHR agonists that have an effect on astrocytes to limit CNS inflammation [49].



The scientists from the Vector research institute in southwestern Siberia say they have identified three types of mushroom found in that region that can be developed into antiviral medicines , which kill HIV[50].

Reishi mushroom (*Ganoderma lucidum*) may help boost the immune system. High doses of reishi may increase the risk of bleeding, especially if you also take blood thinners such as warfarin (Coumadin), clopidogrel (Plavix), or aspirin. Reishi may also lower blood pressure. If you take drugs to treat high blood pressure, taking reishi could cause your blood pressure to be too low [51].

Study done by Yao C et al[52] showed that Ganoderma lucidum promotes sleep through a gut microbiota-dependent and serotonin-associated pathway in mice.

Study done by Park EJ et al [53] showed that Tryptophan enhanced accumulation of phenolic compounds via chorismate mutase activation in the *Ganoderma neo-japonicum* mycelia.

Study done by Ding S et al[54] showed that polyphenols promote immunity to foreign pathogens via various pathways. Different immune cells express multiple types of polyphenol receptors that recognise and allow cellular uptake of polyphenols, which subsequently activate signalling pathways to initiate immune responses.

Phenolic compounds found in black cumin are carvacrol, gallic acid and vanillic acid , and sesamol and sesamin in sesame [55].

Carvacrol (CV) is a phenolic monoterpenoid found in essential oils of oregano (Origanum vulgare), thyme (Thymus vulgaris), pepperwort (Lepidium flavum), wild

bergamot (Citrus aurantium bergamia), and other plants. Carvacrol possesses a wide range of bioactivities putatively useful for clinical applications such antimicrobial, antioxidant, and anticancer activities. Carvacrol antimicrobial activity is higher than that of other volatile compounds present in essential oils due to the presence of the free hydroxyl group, hydrophobicity, and the phenol moiety.

It has high antioxidant activity and has been successfully used, mainly associated with thymol, as dietary phytoadditive to improve animal antioxidant status. The anticancer properties of CV have been reported in preclinical models of breast, liver, and lung carcinomas, acting on proapoptotic processes. Besides the interesting properties of CV and the toxicological profile becoming definite, to date, human trials on CV are still lacking, and this largely impedes any conclusions of clinical relevance[56].

Oregano oil was found to specifically inhibit lentiviruses, such as human and simian immunodeficiency viruses (HIV and SIV), irrespective of virus tropism. Oregano oil's most abundant components, carvacrol and its isomer, thymol, were shown to block virus-target cell fusion while not perturbing other stages of the virus life cycle .

Study done by Mediouni S et al[57] suggested that cholesterol depletion from the HIV-1 envelope membrane reduces virus entry. Furthermore, infection was rescued by adding exogenous cholesterol. The evolution of viral resistance to carvacrol supported this mechanism of action with the identification of mutations in the viral gp41 fusion protein that counteracted cholesterol depletion.

Gallic acid is a natural phenolic compound found in several fruits and medicinal plants. Several beneficial effects are reported for gallic acid, including antioxidant, anti-inflammatory, and antineoplastic properties. This compound has been reported to have therapeutic activities in gastrointestinal, neuropsychological, metabolic, and cardiovascular disorders [58].

Recent studies have shown that GA and its derivatives not only enhance gut microbiome (GM) activities, but also modulate immune responses. Thus, GA has great potential to facilitate natural defense against microbial infections and modulate the immune response [59].

Study done by Guo L et al[60] showed that GA administration can improve age-associated thymic involution via stimulation of FoxN1 expression, increasing of proliferating cells and reduction of apoptotic cells also reversed the alteration of CD4+ and CD8+ cells.

Study done by Lee H et al [61] suggested that methyl gallate can be used to reverse immune suppression and as a potentially useful adjunct for enhancing the efficacy of immune-based cancer therapy. As it inhibited Treg cell-suppressive effects on effector CD4(+) T cells and Treg migration toward tumor environment.

Study done by Nutan et al[62] showed that Gallic acid showed an inhibition in reverse transcriptase whereas ellagic acid inhibited the HIV-1 protease activity.

Vanillic acid is a phenolic compound, found in various dietary sources and medicinal plants. Apart from its extraction from these biological sources, it is also synthesized

chemically. It is used as flavouring agent in various food products. It possesses anticancer, antiobesity, antidiabetic, antibacterial, anti-inflammatory, and antioxidant effects. Despite possessing good therapeutic potential and safety profile, it has not been well explored as nutraceutical or, therapeutic moiety [63].
Study done by Kim MC et al[64] showed that vanillic acid inhibits LPS-induced production of tumor necrosis factor (TNF)-α and interleukin (IL)-6. During the inflammatory process, the levels of cyclooxygenase (COX)-2 and nitric oxide (NO) increased in mouse peritoneal macrophages, but vanillic acid suppressed both the enhanced levels of COX-2 and the production of prostaglandin $E_2$ and NO. Moreover, vanillic acid suppressed the activation of nuclear factor-kappa B (NF-κB) and caspase-1.
Study done by Thitilertdecha P et al [65] showed that vanillic acid has no effect on immunosuppression but shows more potential on immunostimulation.

Sesamol has many important biological activities and health-promoting benefits such as inducing growth arrest and apoptosis in cancer and cardiovascular cells and enhancing vascular fibrinolytic capacity [66].

Study done by Khorrami S et al [67] showed that sesamol may capable of suppressing the response of cellular immunity with the domination of Th2 responses and also could modulate macrophages and the dendritic cells proinflammatory functions**.**

Study done by Ansari MA et al [68] showed that sesamol is an effectual antifungal agent in immunocompromised patients.

Sesamin, a major lignin isolated from sesame (Sesamum indicum*) seeds* and sesame oil, is known to possess antioxidant and anti-inflammatory properties [69].

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor with important functions in the immune response and cancer. AHR agonists are provided by the environment, the commensal flora and the metabolism [70].

Agonist is a drug or substance that binds to a receptor inside a cell or on its surface and causes the same action as the substance that normally binds to the receptor **[**71].

We hypothesized that disturbance of binding of tryptophan with aryl hydrocarbon receptor leads to the development of diseases.

Tryptophan is an amino acid needed for normal growth in infants and for the production and maintenance of the body's proteins, muscles, enzymes, and neurotransmitters. It is an essential amino acid. This means your body cannot produce it, so you must get it from your diet.
The body uses tryptophan to help make melatonin and serotonin. Melatonin helps regulate the sleep-wake cycle, and serotonin is thought to help regulate appetite, sleep, mood, and pain.

The liver can also use tryptophan to produce niacin (vitamin B3), which is needed for energy metabolism and DNA production. In order for tryptophan in the diet to be changed into niacin, the body needs to have enough:

- Iron
- Riboflavin
- Vitamin B6 [72].

**Selective pathological and physiological states**

1. **Cancer:**

The overall cancer risk was significantly elevated among patients with iron deficiency anemia(IDA). After we excluded patients diagnosed with IDA and cancer within 1 and 5 years, the SIRs remained significantly elevated compared with those of the general population. The increased risk of cancer was not confined to gastrointestinal cancer when the standardized incidence ratios of pancreatic, kidney, liver, and bladder cancers significantly increased after exclusion of patients diagnosed with IDA and cancer within the first 5 years. This finding may be caused by immune activities altered by IDA [73].

Riboflavin supplementation increase cancer cell proliferation, invasion and migration , ultimately increasing tumor survivability, but the inhibition of flavin-containing enzymes also arrested tumor growth [74]. Several studies indicate that riboflavin deficiency inhibits tumor growth in experimental animals and possibly in man [75].

Epidemiologic and laboratory animal studies have suggested that the availability of vitamin B6 modulates cancer risk. The means by which B6 mediates this effect is not known with any surety but it has been reported that high dietary vitamin B6 attenuates and low dietary vitamin B6 increases the risk of cancer [76].



Riboflavin deficiency alters iron metabolism. Although the mechanism is not clear, research in animals suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin (Hb) [77].

Vitamin B6 is considered to be a risk nutrient for elderly people. Conversion of most naturally available vitamin B6 to its functional coenzyme pyridoxal 5'-phosphate (PLP) depends on riboflavin [78].

2. **Blood pressure:**

A protein known to regulate iron levels in the body has an unexpectedly important role in preventing a form of high blood pressure that affects the lungs, and in stabilizing the concentration of red cells in blood, according to a study in mice by researchers at the National Institutes of Health [79].

Study done by Kim MK et al [80] showed that Serum ferritin, but not iron level, was a significant predictor of hypertension in middle-aged Korean men.

Study done by Horigan G et al [81] showed that riboflavin is effective in reducing blood pressure specifically in patients with the MTHFR 677 TT genotype. The findings, if confirmed, may have important implications for the prevention and treatment of hypertension.

Study done by Liu M et al [82] showed that there was an inverse association between riboflavin intake and new-onset hypertension in general Chinese adults.

Study done by Houston MC [83] showed that Low serum vitamin B6 (pyridoxine) levels are associated with hypertension in humans. High-dose vitamin B6 significantly lowered BP by 14/10 mmHg .

Flavin-dependent enzymes that can mobilize iron from ferritin have been shown to be sensitive to riboflavin depletion in animal models [84]. And repleting vitamin B6 caused an increase in ferritin [85].

**3. Diabetes:**

Several lines of evidence suggest that iron play may a role in the pathogenesis of type 2 diabetes. Iron is a strong pro-oxidant and high body iron levels are associated with increased level of oxidative stress that may elevate the risk of type 2 diabetes [86]. Iron plays a direct and causal role in diabetes pathogenesis mediated both by β-cell failure and insulin resistance. The underlying molecular mechanisms mediating these effects are numerous and incompletely understood, but include oxidant stress and modulation of adipokines and intracellular signal transduction pathways [87].

Anaemia can lead to a false diagnosis of diabetes by distorting readings of glycated haemoglobin ($HbA_{1c}$) concentrations [88].

Study done by Braun KV et al [89] showed that those who consumed the highest amounts of vitamin B2(Riboflavin) foods and supplements had a 10% lower risk for type 2 diabetes, while those who consumed the highest amounts of vitamin B6 foods and supplements had an 11% lower risk for type 2 diabetes.



**4. Asthma:**

In US women, higher iron stores were inversely associated with asthma and lower body iron and higher tissue iron need were associated with lower lung function [90]. Iron deficiency anemia may be considered as an indirect risk factor for childhood asthma also iron deficiency anemia may have a negative effect on spirometry of asthmatic children [91]. Therapies directed at asthma demonstrate a capacity to impact iron homeostasis [92].

Study done by Ali MK et al [93] showed that altered levels of iron and iron-related gene expression in the airways of patients with asthma are linked with lung function, with evidence for increased iron accumulation into tissues being detrimental for disease [93].

Vitamin B6 deficiency is common in asthmatics. Supplementing with the vitamin may decrease the frequency and severity of asthma attacks [94]. As we mentioned above that Flavin-dependent enzymes that can mobilize iron from ferritin have been shown to be sensitive to riboflavin depletion in animal models [84].

### 5. Tuberculosis:

Iron deficiency is associated with decreased cellular immunity, which may predispose patients with iron deficiency anemia (IDA) to increased risk of developing tuberculosis (TB) [95].

Mycobacterium tuberculosis strictly depending on endogenously flavin biosynthesis. Therefore, riboflavin biosynthetic enzymes might be potential anti-TB drug targets. Elucidation of the role of these enzymes in the M. tuberculosis survival or virulence might validate its drug target value [96]. Supplementation with vitamin B6 is thought to help prevent isoniazid-induced niacin deficiency (Isoniazid is an antibiotic used to prevent and treat tuberculosis) [97].

### 6. Malaria:

By studying mice and samples from malaria patients, the researchers found that extra iron interferes with ferroportin, a protein that prevents a toxic buildup of iron in red blood cells and helps protect these cells against malaria infection [98].

High doses of riboflavin are used clinically to treat congenital methemoglobinemia without any adverse side effects. This activity, in conjunction with its impressive antimalarial activity, makes riboflavin attractive as a safe and inexpensive drug for treating malaria caused by P. falciparum [99].
The active form of vitamin B6, pyridoxal 5-phosphate, is, besides its antioxidative properties, a cofactor for a variety of essential enzymes present in the malaria parasite which includes the ornithine decarboxylase (ODC, synthesis of polyamines), the aspartate aminotransferase (AspAT, involved in the protein biosynthesis), and the serine hydroxymethyltransferase (SHMT, a key enzyme within the folate metabolism) [100].



### 7. Typhoid fever:

The adhesion and translocation ability of Salmonella could be increased by the presence of iron . So the presence of iron determines their pathogenicity and virulence [101]. The precursor function of riboflavin in the biosynthesis of 5,6-dimethylbenzimidazole in S. Typhimurium [102].

YggS (COG0325) is a pyridoxal 5′-phosphate (PLP)-binding protein proposed to be involved in homeostasis of $B_6$ vitamers. In *Salmonella enterica*, lack of *yggS* resulted in phenotypes that were distinct and others that were similar to those of a *yggS* mutant of *Escherichia coli*. Like other organisms, *yggS* mutants of *S. enterica* accumulate endogenous pyridoxine 5′-phosphate (PNP) [103].

### 8. Hepatitis:

Recent studies have suggested that there is a close link between iron metabolism and viral hepatitis, especially hepatitis C. Some studies seem to indicate that the total quantity of iron present in the liver as well as the lobular and cellular distribution of iron are important determinants of the long-term outcome. And patients with lesser amounts of hepatic iron respond better to antiviral therapy than those with larger amounts of hepatic iron [104].

In well-compensated chronic hepatitis B infection, hepatic iron deposits and elevation of serum iron indices are common, especially in male gender and in patients coinfected with HDV. As HBV/HDV liver disease is generally more rapidly progressive than that caused by HBV monoinfection, we speculate that iron overload may be one of the factors contributing to the severity of liver disease [105].

A case study done by Zou DM et al[106] showed that the importance of monitoring liver iron status, and beginning iron chelation therapy once liver iron overload occurs and before heart iron overload occurs in patients with CHB. Iron chelation therapy can even increase the possibility of seroconversion.

Autoimmune hepatitis is a rare disease, and the diagnosis can be further complicated by a similar presentation of iron overload syndrome. Markedly elevated transferrin saturation can simulate iron overload syndrome, but a liver biopsy can guide physicians to navigate the diagnosis [107].



The riboflavin photochemical method is effective in the inactivation of HBV in plasma, which has relevance for preventive strategies against transfusion-derived infections[108].

Study done by Diehl AM et al[109] suggested that pyridoxal 5′-phosphate(active coenzyme form of vitamin B6) depletion is partially responsible for the low serum alanine to aspartate aminotransferase ratio that is typical of patients with alcoholic hepatitis.

### 9. Systemic Lupus Erythematosus:

Iron deficiency is common in patients with SLE as a result of menorrhagia and increased gastrointestinal blood loss, caused by the use of non-steroidal anti-inflammatory drugs, aspirin, and oral anticoagulants[110]. Higher intake of vitamin B6 and dietary fiber may prevent the occurrence of active disease in SLE [111]. Vitamin B2 (riboflavin) deficiency was detected in 88% of a cohort of Chinese patients with SLE [112].

### 10. AIDS:

Anemia is a common clinical finding in HIV-infected patients and iron deficiency or redistribution may contribute to the development of low hemoglobin levels. Iron overload is associated with a poor prognosis in HIV and Hepatitis C virus infections [113].

Niacin (vitamin B3) could control the excess of tryptophan depletion and represents a potential strategy to improve immune functions and CD4 count recovery in immunological non-responder HIV-infected individuals on antiretroviral therapy (ART) [114].

**11. Anemias:**

Study done by Hussein S et al[115] suggested that serum ferritin reflects reticuloendothelial iron and the high levels in untreated megaloblastic anaemia are due to the shift in iron from Hb to reticuloendothelial stores. Iron deficiency continues to be the top-ranking cause of anemia worldwide [116]

It has also been reported that vitamin B6 deficiency causes ringed sideroblastic anemia as well as microcytic anemia that is not associated with ringed sideroblasts.

Megaloblastic anemia due to folic acid deficiency and ringed sideroblastic anemia have been reported in alcohol abusers [117].

Research has shown that riboflavin deficiency can alter iron absorption and cause anemia, which leads to fatigue. Riboflavin is involved in red blood cell production and transportation of oxygen to the cells [118].

**12. COVID-19:**

In COVID-19 patients, inflammation can lead to an alternation of iron hemostasis and reduced intestinal iron absorption, resulting in the reduced availability of the metal for erythropoiesis and the production of hemoglobin [119].

Study done by et al[120] showed that riboflavin supplementation could be promising for decreasing inflammation in COVID-19 [120].

Study done by et al [121] suggested that vitamin B6 may ameliorate the severity of COVID-19 by exerting its anti-oxidative and anti-inflammatory actions in lung, a primary target organ for COVID-19 virus infection.



**13. Bipolar disorder:**

Iron deficiency can cause mood swings, a key factor in the disease progression of bipolar disorder . A study suggests that bipolar disorder may be more prevalent among female children and adolescents with iron deficiency anemia [122].

B2-deficient patients exhibited a nonsignificant trend toward more unipolar depression (44% vs 14%), but not toward bipolar or schizophrenic disorders. Suggested that B2 (FAD) activity may serve as a sensitive marker of thyroxine status in certain female psychiatric inpatients and that B2 deficiency may play an etiological role in defects of the methylation pathways in a subset of mentally ill individuals [123]. Vitamin B6 may also improve cognitive symptoms in bipolar disorder [124].

**14. Polycystic ovaries syndrome:**

The polycystic ovary syndrome (PCOS) is associated with insulin resistance and abnormal glucose tolerance. Iron overload may lead also to insulin resistance and diabetes. Serum ferritin levels are increased in PCOS, especially when glucose tolerance is abnormal, suggesting mild iron overload. Factors contributing to potential iron overload in PCOS include the iron sparing effect of chronic menstrual dysfunction, insulin resistance, and a decrease in hepcidin leading to increased iron absorption [125].

Women with PCOS are deficient in riboflavin (vitamin B 2 ); furthermore, vitamins (watersoluble) play important roles in the therapy of women with PCOS [126]. Taking vitamin B6 is purported to improve countless areas of PCOS, including mood regulation, PMS, heart health, and blood sugar balance [127].

**15. Epilepsy:**

In some studies, iron deficiency anemia increases the risk of febrile seizures in children, probably because it is one of the essential factors for growth, development, and immunity. In addition, anemia reduces the seizure threshold, resulting in increased seizure activity [128].
The only vitamin deficiency known to cause or worsen seizures is a deficiency of vitamin B6 (pyridoxine) [129].

Study done by Husebye ES et al[130] showed that High antiseizure medication (ASM) concentrations correlated with high concentrations of unmetabolized folic acid and inactive folate metabolites, and with low concentrations of riboflavin and metabolically active pyridoxine. There was no association between ASM and niacin status.

A high-Tryptophan Diet Reduces Seizure-Induced Respiratory Arrest and Alters the Gut Microbiota in experimental animals [131].

**16. Glaucoma**

Importance Evidence suggests that altered iron metabolism may be associated with oxidative damage to several organ systems, including the eye. Supplementary iron consumption is also associated with greater odds of self-reported glaucoma [132].



A world-first clinical trial led by Melbourne researchers suggests vitamin B3 (nicotinamide) could play an important role in protecting against retinal ganglion cell damage that leads to blindness in glaucoma [133].

Treatment with a supplement which includes homotaurine, carnosine, forskolin, vitamins B1, B2, and B6, folic acid, and magnesium has been shown to be able to slow down the rate of progression of functional damage and improve visual function after 2 and 6 months of daily intake [134].

**17. Cataract:**

Hyperferritinemia-cataract syndrome is a disorder characterized by an excess of an iron storage protein called ferritin in the blood (hyperferritinemia) and tissues of the body. A buildup of this protein begins early in life, leading to clouding of the lenses of the eyes (cataracts) [135].

Study done by Skalka HW et al[136] showed that no evidence of an association between riboflavin deficiency and early cataract formation, either idiopathic or secondary. Older cataract patients had more riboflavin deficiency. An absence of riboflavin deficiency was found in our older patients with clear lenses. The degree of

riboflavin deficiency encountered in the general population does not appear to be cataractogenic.
Study done by Christen WG et al [137] conclude that daily supplementation with a combination of folic acid, vitamin B6, and vitamin B12 had no significant effect on cataract, but may have increased the risk of cataract extraction.

**18. Renal failure:**

Anemia is a complication that affects a majority of individuals with advanced CKD. Although relative deficiency of erythropoietin production is the major driver of anemia in CKD, iron deficiency stands out among the mechanisms contributing to the impaired erythropoiesis in the setting of reduced kidney function [138].
Study done by Porrini M et al [139] among patients with chronic renal disease showed that riboflavin status is inadequate even before the beginning of the follow up and worsens with time, while thiamin and pyridoxine( vitamin B6) status becomes inadequate in some patients after a long period on the low-protein diet.

**19. Heart failure:**

Iron deficiency is a major heart failure co-morbidity present in about 50% of patients with stable heart failure [140]. Riboflavin (vitamin B-2) and pyridoxine (vita- min B-6) play critical roles in production of red blood cells and are essential cofactors in cellular energy production. Therefore, deficiency of these vitamins may contribute to depletion of energy reserves observed in the failing heart [141].



**20. Pancytopenia:**

Severe iron deficiency anemia may be associated with pancytopenia and iron replacement may cause a transient decline in megakaryopoiesis and leukopoiesis. Severe iron deficiency should be added to the list of conditions leading to thrombocytopenia [142].

**21. Haemorrhoids:**

Supplements and medications may have gastrointestinal side effects, which in turn could result in your hemorrhoids becoming worse. Iron is important for the body to function optimally, however, taking iron supplements can lead to adverse reactions. Iron supplements are one of the potential triggers for haemorrhoids [143].

**22. Schizophrenia:**

iron-dopamine interaction might therefore conceivably account for symptoms in patients with schizophrenia. Some evidence suggests a role for iron deficiency in chronic and tardive akathisia, which is associated with reduced dopamine activity due to the use of dopamine antagonists [144].
Low riboflavin related to poor diet in schizophrenia may enhance susceptibility to low grade bowel inflammation and poor vitamin absorption. In addition, chronic stress with high cortisol levels has been found to reduce intestinal absorption of riboflavin [145].

Study done by Xu XJ et al [146] suggested that niacin deficiency is a contributory factor in schizophrenia development in some patients and symptom alleviation in these patients will benefit from niacin augmentation

**23. Endometriosis:**

Iron overload could affect a wide range of mechanisms involved in endometriosis development, such as oxidative stress or lesion proliferation. And, excess iron accumulation can result in toxicity and may be one of the factors contributing to the development of endometriosis [147].

Vitamin B6 is found in cauliflower, cabbage, peppers, bananas, squash, broccoli, asparagus, lentils, kidney beans, onions, nuts and seeds. This is an important vitamin in endometriosis which has been shown to relieve menstrual cramps in 70 percent of women within two menstrual cycles [148]. Inflammation-induced catabolism of tryptophan is thought to permit immune tolerance of endometriosis implants [149].

**24. Aging:**

Iron accumulates with aging, and is associated with many age-related diseases; it also shortens the lifespans of several model organisms. Blocking iron absorption through drugs or natural products extends lifespan [150].



Study done by Madigan SM et al[151] showed that a high proportion of healthy elderly people may have suboptimal status for these nutrients despite apparently adequate dietary intakes. Furthermore, we showed that riboflavin supplementation at physiologic doses corrects biochemical abnormalities of not only riboflavin (erythrocyte glutathione reductase activation coefficient; EGRAC), but also plasma B-6 (plasma pyridoxal-5'-phosphate ;PLP), confirming the biochemical interdependency of these vitamins and suggesting that riboflavin is the limiting nutrient.

**25. Diarrhea:**

Iron alone significantly increases risk of diarrhea in children [152]. riboflavin deficiency can be seen with chronic diarrhea [153]. Vitamin B6 has tendency to decrease diarrhea rate [154].

**26. Alzheimer's disease:**

There is an imbalance in iron homeostasis in Alzheimer's disease (AD). Excessive iron contributes to the deposition of β-amyloid and the formation of neurofibrillary tangles, which in turn, promotes the development of AD [155].

Study done by Zhao R et al [156] showed that riboflavin protects the brain from ROS-induced AD damage, most likely due to its potential anti-oxidant property and activation of the Nrf2 pathway.

Epidemiological studies indicate that poor vitamin B6 status is common among older people. Hyperhomocysteinaemia has been suggested as a cause or mechanism in the development Alzheimer's disease and other forms of dementia. Supplementation with B vitamins including vitamin B6 has been shown to reduce blood homocysteine levels [157].

**27. Cirrhosis:**

Iron overload is very common in many types of non-biliary cirrhosis, and, in end stage liver disease, hepatic iron concentrations may reach the ranges of haemochromatosis. Haemosiderosis in these livers seems to be acquired and to occur rapidly once cirrhosis has developed [158].
Riboflavin (vitamin $B_2$) deficiency has been described in patients with either alcoholic or non-alcoholic cirrhosis[43] and has been explained by inadequate intake, increased utilization, deficient absorption and storage, or abnormal metabolism of the vitamin [159].
Vitamin B6, were found to be significantly lower than normal in22 out of 31 patients with decompensated cirrhosis or subacute hepatic necrosis. There was no significant difference in plasma PLP levels between those with liver disease due to alcohol and those with other varieties [160].

**28. Headache:**



Several types of anemia can cause headaches. A deficiency of iron or vitamins can lead to headaches related to low oxygen levels in the brain. IDA has also been shown to play a role in migraine, especially during menstruation [161].
Study done by Boehnke C et al [162] demonstrated that a significant reduction of headache frequency following riboflavin treatment.

Recently, there have been anecdotal reports demonstrating the effectiveness of niacin for aborting acute migraine attacks , and for preventing migraine headaches [163].

**29. Gout:**

Ferritin positively associates with serum urate and an interventional study suggests that iron has a role in triggering gout flares [164]. Riboflavin supplementation significantly decreased plasma total homocysteine and erythrocyte glutathione reductase activation coefficient , but not plasma ferritin, uric acid or C-reactive protein [165]. A previous case-control study in Taiwan showed that high folate intake may protect against gout [166]. One study suggested that high doses of supplemental folate may be beneficial in preventing gout and recurrent attacks [167].

**30. Cholera:**

Vibrio cholerae, the causative agent of the diarrheal disease cholera, requires iron for growth and possesses a variety of iron acquisition systems [168]. Vibrio cholerae is a riboflavin prototroph and it also has the ability to scavenge riboflavin through the RibN riboflavin importer [169]. Diarrhea from an infection called cholera. Taking niacin by mouth seems to control the loss of fluid due to cholera [170].

**31. Anthrax:**

Bacillus anthracis, the causative agent of anthrax disease, represents an excellent model organism to study iron acquisition processes owing to a multifaceted lifecycle consisting of intra- and extracellular phases and a tremendous replicative potential upon infection [171]. Following the addition of vitamin B6 to the nutrient medium containing radioactive sulfur, the growth of the Bacillus anthrax increases [172].

**32. Botulism:**

the micronutrient riboflavin (vitamin B2) showed the ability to photooxidatively inactivate Botulinum neurotoxin (BoNT)in cell-based assays without the need for toxin and riboflavin pre-exposure [173].

**33. Brucellosis:**

Brucella strains require iron, manganese, zinc, and magnesium transporters for wild-type virulence in natural and experimental hosts [174].

**34. Chikungunya virus disease:**

Ferritin could serve as a prognostic marker for development of chronic Chikungunya virus infection [175].

**35. Dengue:**

Iron-deficient blood makes it easier for dengue virus to colonize and multiply in mosquitoes' guts. Summary: Mosquitoes are more likely to acquire the dengue virus when they feed on blood with low levels of iron [176]. Riboflavin used with ultraviolet light to treat dengue fever through inactivation of the dengue virus[177]. And vitamin B6 along with niacin , folic acid and cobalamin play a role in helping to move some of the vital functions of the human body [178].



**36. Ebola virus disease:**

High serum ferritin levels normally correlate with disease severity and haemorrhages, which are characteristic of Ebola [179]. One study showed that ultraviolet light and riboflavin treatment efficiently reduces EBOV titers to below limits of detection in both serum and whole blood [180].

**37. Mental retardation:**

A significantly higher risk of anxiety disorder, ASD, ADHD, delayed development, and mental retardation was noted among children with iron deficiency anemia [181]. A previous study among mentally retarded patients showed that 17% had evidence of riboflavin deficiency [182]. Vitamin B6 deficiency hyperactivates the noradrenergic system, leading to social deficits and cognitive impairment [183].

**38. Schistosomiasis**:

Chronic intestinal schistosomiasis may lead to symptomatic iron-deficiency anaemia. The pathophysiological mechanism of iron-deficiency anaemia with schistosomiasis may include extracorporeal blood loss and/or impaired iron absorption. Iron-deficiency anaemia may present many decades after leaving the endemic region [184].

One study showed that The hepatic levels of thiamine, pantothenic acid and niacin in hamsters infected with S. mansoni were depressed, while the levels of riboflavin and pyridoxine remained unchanged [185].

**39. Helicobacter pylori infection:**

H. pylori infection is associated with anemia by impairing iron absorption as a result of chronic gastritis which causes gastric hypochlorhydria, leading to impair reduction of the dietary iron from the ferric to ferrous form [186]. Riboflavin inhibits growth of H. pylori by inhibiting replication of the bacteria [187].
Scientists have determined that Helicobacter pylori, the bacterium that causes peptic ulcers and some forms of stomach cancer, requires the vitamin B6 to establish and maintain chronic infection [188].

**40. Thalassemia:**

People with thalassemia can get too much iron in their bodies, either from the disease or from frequent blood transfusions. Too much iron can result in damage to your heart, liver and endocrine system, which includes hormone-producing glands that regulate processes throughout your body [189]. The possibility that a low activity of glutathione reductase and a slow metabolism of B6 and riboflavin in the red-cell might play a part in the degree of severity of the thalassaemic disease [190].



**41. Sickle cell anemia:**

This type of anemia is not caused by too little iron in the blood; it's caused by not having enough red blood cells. In fact, taking iron supplements could harm a person with sickle cell disease because the extra iron builds up in the body and can cause damage to the organs [191]. Poor riboflavin status in patients may be restricting availability of pyridoxal phosphate (PLP) due to combined effects of enhanced PLP requirements and effects of poor riboflavin status on the synthesis of PLP by pyridoxine phosphate oxidase (PPO) [192].
Liposomal transport system which transferred Phenylalanine and tryptophan into intact RBCs did not have any adverse effect on RBC metabolism and function, and may have therapeutic implications in the treatment of sickle cell disease [193].

**42. Leukemia:**

Leukemia cells show increased iron uptake and decreased iron efflux, leading to elevated cellular iron levels. The systematic iron pool in patients with leukemia is also increased, which is aggravated by multiple red-blood-cell transfusions [194]. Besides having a pivotal biological function as a component of coenzymes, riboflavin appears a promissing antitumoral agent, but the underlying molecular mechanism remains unclear.

Importantly, induction of apoptosis by irradiated riboflavin was leukaemia cell specific, as normal human lymphocytes did not respond to the compound with cell death. Our data indicate that riboflavin selectively activates Fas cascade and also constitutes a death receptor-engaged drug without harmful side effects in normal cells, bolstering the case for using this compound as a novel avenue for combating cancerous disease [195].
Researchers from CSHL and Memorial Sloan Kettering Cancer Center have discovered how Acute Myeloid Leukemia is addicted to vitamin B6 [196].

**43. Abortion:**

In women with spontaneous abortion, the serum iron concentration was significantly increased by 2.2 times compared with the first trimester normal pregnancy [197]. Having both low folate and vitamin B6 increases the risk of miscarriage four-fold [198].
Vitamin B3 may prevent miscarriages and birth defects, study suggests. Taking Vitamin B3 could prevent miscarriages and birth defects [199].

**44. Autism :**



The current studies confirm that deficiencies of iron and Vitamin D and anemia were higher in autistic compared to control children. The results suggest that serum ferritin levels should be monitored in every case of autism as a part of baseline investigation [200].
Preliminary research suggests that supplementation with vitamin B2, along with vitamin B6, and magnesium reduces the level of dicarboxylic acids (abnormal organic acids) in the urine of autistic children [201].
Autism may be nutritionally related to a possible deficiency of riboflavin or the cognitive vitamins such as thiamine or vitamin D [202].

**45. Schnitzler Syndrome:**

The Schnitzler syndrome is a rare and acquired systemic disease which bears in common many features with a group of inherited diseases referred to as auto-inflammatory syndromes. Its main clinical features include fever, an urticarial rash, muscle, bone and/or joint pain and enlarged lymph nodes. [203]. Characterized by low haemoglobin and low iron [204]. riboflavin inhibits histamine-dependent itch by modulating transient receptor potential vanilloid 1 activity [205]. Vitamin B6 Prevents IL-1β Protein Production by Inhibiting NLRP3 Inflammasome Activation [206].

The most prominent member of NLR family in the study of hereditary autoinflammatory syndromes is NLRP3 [207].

### 46. Goodpasture Syndrome:

Goodpasture's syndrome (GS) is a rare and organ-specific autoimmune disease that is mediated by anti-glomerular basement membrane (anti-GBM) antibodies and has pathology characterized by crescentic glomerulonephritis with linear immunofluorescent staining for IgG on the GBM. It typically presents as acute renal failure caused by a rapidly progressive glomerulonephritis, accompanied by pulmonary hemorrhage that may be life-threatening. It was first described as a distinctive syndrome by Pasture in 1919 [208].

An unusual case of a patient with Goodpasture's disease presenting with hemoptysis, severe iron deficiency anemia and microscopic hematuria and proteinuria is described [209]. Environmental factors such as hydrocarbon chemical exposure, cigarette smoke, or infections such as influenza may play a role in the development of the disorder [210].

### 47. Leukocyte Adhesion Deficiency:

Leukocyte adhesion syndromes are rare, genetic disorders. LAD I is caused by mutations of the ITGB2 gene. LAD II is caused by mutations of the SLC35C1 gene. The genetic defect in LAD III is a mutation in the gene for Kindlin 3, a protein essential for all integrins activation [211]. Riboflavin-based PRT treatment of PCs leads to the enhancement of thrombus formation on collagen, which is related to the activation status of αIIbβ3, which does not bind to fibrinogen but binds to PAC-1. The impact of this finding on the hemostatic or even thrombogenic potential in vivo must await clinical evaluation [212].



### 48. Agammaglobulinemia:

It has been confirmed that tryptophan 563 is sandwiched between residues R562 and A582 in Bruton's agammaglobulinemia tyrosine kinase (Btk) [213].

### 49. Alice In Wonderland Syndrome (AIWS):

Alice in Wonderland syndrome (AIWS) is a rare neurological disorder characterized by distortions of visual perception, the body image, and the experience of time. People may see things smaller than they are, feel their body alter in size or experience any of the syndrome's numerous other symptoms [214].

The trademark symptom of AIWS is migraine. The individual loses a sense of time. For him, time seems passing either at a snail's pace or passing too swiftly. Some people experience strong hallucinations; they may visualize things that are not there and may also get the wrong impression about certain situations and events.

Typical migraine, temporal lobe epilepsy, brain tumours, psychoactive drugs or Epstein-barr-virus infections are causes of AIWS [215].

a. Migraine:
   After stratified analyses by sex and age, we found that dietary iron was negatively associated with migraine in women aged 20–50 years. For women aged over 50 years and men, the relationship between dietary iron intake and migraine was not statistically significant [216].
   In adults, riboflavin at a dose of up to 400 mg daily reduces migraine frequency by more than 50% [217].
   The body uses vitamin B6 to make cells for blood flow and brain function. Vitamin B6 has been used to ease migraine pain and morning sickness in pregnancy [218].
b. Temporal lobe epilepsy:

Studies have shown that inhibition of ferroptosis improves cognitive dysfunction in rats with temporal lobe epilepsy induced by KA [219].
One study demonstrated dysfunction of the serotonergic system, which could include metabolism through the kynurenine pathway in TLE patients with normal hippocampal volumes [220].

c. Brain tumours:
   Brain cancer therapy may be more effective if the expression of an iron-storing protein is decreased to enhance the action of therapeutic drugs on brain cancer cells [221].



In a study published in Science Translational Medicine, the researchers showed that niacin, also known as vitamin B3, can stimulate immune cells that are otherwise compromised by brain tumors. Treating mice with niacin increased the number of immune cells in the tumor, reduced tumor size and extended survival [222].

d. Psychoactive drugs:

Iron is present in high concentrations in the basal ganglia and stimulant drugs may interfere with iron homeostasis [223]. One study suggests that certain psychotropic drugs interfere with riboflavin metabolism at least in part by inhibiting the conversion of riboflavin to its coenzyme derivatives, and that as a consequence of such inhibition, the overall utilization of the vitamin is impaired [224].
Vitamin B6 appears to be effective in reducing symptoms of tardive dyskinesia in patients with schizophrenia [225].

e. Epstein-barr-virus infection:
   One study showed that EBV viremia is associated with cell-mediated immune activation and increased tryptophan degradation, which may partly account for the symptoms found in this disorder [226].

**50. Dehydration:**

Tryptophan, which is an amino acid converts to serotonin. Your body needs to have sufficient water to transmit tryptophan across your

brain. When you are dehydrated, the amount of tryptophan in your brain is limited, which ultimately affects the serotonin level [227].

## Conclusion

Carvacrol and thymol have been demonstrated to undergo phase I metabolism such as hydroxylation reaction [228]. Hydroxylation is important in detoxification since it converts lipophilic compounds into water-soluble (hydrophilic) products that are more readily removed by the kidneys or liver and excreted [229].

Gallic acid, including antioxidant, anti-inflammatory, and antineoplastic properties. This compound has been reported to have therapeutic activities in gastrointestinal, neuropsychological, metabolic, and cardiovascular disorders [230].

Vanillic Acid Inhibits Inflammatory Pain by Inhibiting Neutrophil Recruitment, Oxidative Stress, Cytokine Production, and NFκB Activation in Mice [231].

Furthermore, black seed contains, in addition to the above mentioned phenolic compounds , 8 of the 9 essential amino acids that are combined to make a “whole” protein. Black Seed also has vitamin B1, vitamin B2, vitamin B3, folic acid, calcium, iron, copper, zinc and phosphorous. And we can say that the black seed is the cure of all diseases. And this confirmed , Abu Hurairah narrated that he heard the Messenger of Allah (swas) say: “In black seed there is healing for every disease, except the Sam.” "Sam means death [233].

Lastly , we can define physiology as homeostasis of tryptophan metabolism , pathology as an alteration of tryptophan metabolism, medicine is regulation of tryptophan metabolism and pharmacology is study of the elements that adjust the tryptophan metabolism.

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