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Vitamins, omega-3, magnesium, manganese, and thyme can boost our immunity and protect against COVID-19

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ABSTRACT: A new coronavirus, SARS-CoV-2, has been recognized as a cause of severe acute respiratory syndrome (SARS) and COVID-19 disease. In the absence of stable treatments for COVID-19, the possibility that vitamins: B_1, C, D, and E, omega-3, minerals (magnesium and manganese), and herb thyme may have unspecified effects on infection with COVID-19 would be considered. Various reports have revealed that vitamins B_1, C, D, and E, omega-3, magnesium, manganese, and thyme may affect the human innate system, for example, thiamine may play beneficial roles in human immunodeficiency viruses (HIV), treating megadose ascorbic acid can assist prevent cold and flu symptoms, vitamin D can decrease the risk of developing COVID-19, vitamin E has been evaluated against the influenza virus in mice, and omega-3 fatty acids supplementation has been efficient in reducing the severity and frequency of sickle cell rate. Magnesium may be effective in patients with a mutation in the interleukin-2-inducible T-cell kinase, as well as manganese associates with the metabolism of glucose and fats, vitamin C, and B, accelerating protein synthesis, endocrine regulation, stimulating hematopoiesis, improving innate function, and reducing reactive oxygen species (ROS) generation. Moreover, thyme extract can have beneficial antiviral effects against human papillomavirus (HPV) and influenza A (IAV). The possibility that the vitamins B_1, C, D, E, omega-3, magnesium, manganese, and thyme appear to affect the human innate system warrants further study, especially in light of the recent COVID-19 epidemic.

Keywords: COVID-19; Vitamin B_1; Vitamin C; Vitamin D; Vitamin E; Omega-3; Magnesium; Manganese; Thyme.

Abbreviations:

Acyl-coenzyme A - acyl-CoA; Adenosine triphosphate - ATP; α-Linolenic acid - ALA; α-tocopherol transfer protein - α-TTP; Calcium - Ca; Cholecalciferol - vit. D_3; Disease caused by SARS-CoV-2 - COVID-19; Corticosterone - CORT; Damage-associated molecular patterns - DAMPs; Docosahexaenoic acid - DHA; Dynamin-related protein 1 - DRP1; Eicosapentaenoic acid - EPA; Ergocalciferol - vit. D_2; Fatty acid - FA; Fatty acids - FAs; Glucocorticoid - GC; Glucose-6-phosphate - G6PD; Herpes simplex virus - HSV; Human immunodeficiency virus - HIV; Human papillomavirus - HPV; Hypothalamic-pituitary-adrenal - HPA; Influenza A - IAV; Interferon - IFN; Iron - Fe; L-Ascorbic acid - AsA; Magnesium - Mg; Manganese - Mn; Mitochondrial DNA - mtDNA; Omega-3 - ω-3; Open reading frame-9b - ORF-9b; Pathogen-associated molecular patterns - PAMPs; Pattern-recognition receptors -

PRRs; Phosphorus - P; Polyunsaturated fatty acids - PUFAs; Potassium - K; Reactive oxygen species - ROS; Red blood cells - RBC; Respiratory syndrome coronavirus -SARS-CoV; Selenium - Se; Severe acute respiratory syndrome coronavirus-2 - SARS-CoV-2; Sodium - Na; Thiamine adenosine diphosphate - AThDP; Thiamine adenosine triphosphate - AThTP; Thiamine diphosphate - ThDP; Thiamine monophosphate - ThMP; Thiamine pyrophosphate - TPP; Thiamine triphosphate - ThTP; Thiamine - vit. B$_1$; Vitamin A - vit. A; Vitamin D - vit. D; Vitamin E - vit. E.

1. INTRODUCTION

In humans, the innate system composes of groups of effector systems that are able to destroy pathogenic microbes such as parasites, fungi, bacteria, and viruses [1]. It includes two types of effectors: an adaptive antigen-specific innate effector and a natural innate effector that identifies pathogen-associated molecular patterns (PAMPs) [2]. These PAMPs are determined by pattern-recognition receptors (PRRs), which are mostly expressed in natural innate cells. PRRs can also identify host particles that contain damage-associated molecular patterns (DAMPs), which are mostly freed particles from dead cells damaged by invasive pathogens [3]. The natural innate system consists fundamentally of physical barriers (mucous membranes and skin), chemical barriers and antimicrobial peptides), natural innate cells, and soluble mediators (the complement system, natural antibodies, and associated-cytokines) [4-5]. The main goal of the natural innate system is (1) to prevent pathogens from entering the body by biophysical and biochemical barriers [4]; (2) avoid the prevalence of infection by the supplementary system and other humoral elements; (3) remove pathogens by phagocytosis and cytotoxicity processes [6]; and (4) activation of the adaptive innate system by synthesizing several cytokines and antigen presentation of T and B cells [7].

Various innate cell patterns use distinctive metabolic programs to realize their functions, such as responder T cells prefer aerobic glycolysis at anabolic metabolism to equilibrium the synthesis of macromolecules and create support energy [8]. On the contrary, memory and regulatory T cells prefer to oxidize fatty acids to support energy demand for survival and function [8]. In almost eukaryotic cells, mitochondrion mainly provides metabolic energy [9], and is also associated with various cellular activities, such as maintaining cellular balance, innate immunity, signaling pathways, aging, and cell apoptosis. Moreover, the mitochondrion is a dynamic organelle and can modify its position and morphology within cells through harmonious cycles of fusion and fission to regulate its activity, functioning, and cell metabolism [10]. Local reactive oxygen species (ROS) production is another significant function of mitochondria, which are also important signal molecules for cell activation [11-14]. Mitochondria can coordinate immunity by modifying both physiological and metabolic states in various kinds of innate cells.

Various pathogens have developed ways to target mitochondria to influence their survival within cells or to spread them by mediating cell death caused by mitochondria, or by avoiding host immunity [15]. Mitochondria are a suitable target for infectious microbes, such as viruses, as they act as a force in the cell and have different important functions [16]. The mitochondrion is the objectives of ROS, which are generated within the cell when viral infections are present, and that mitochondrial DNA (mtDNA) is a primary objective of these ROS [17]. Mitochondrial adenosine triphosphate (ATP) production needs proteins from the mitochondrial and nuclear genomes. ROS deactivates the oxidative ATP generation needed for ordinary cellular function as mtDNA damage deactivates the normal biosynthesis of proteins required for mitochondrial functioning and makes them appropriate objectives for attack by ROS during viruses and infections of other microorganisms, although ROS also have other cellular objectives [16]. Influenza A's PB1-F2 protein, which targets the mitochondria leads to mitochondrial fragmentation, and causes the mitochondrial membrane potential to be lost [18]. The virulence factor open reading frame-9b (ORF-9b) of

the severe acute respiratory syndrome coronavirus (SARS-CoV) causes proteasomal dissolution of dynamin-related protein 1 (DRP1) that leads to the fusion mitochondrial that ultimately reduce interferon (IFN) host cell reactions against the virus [19]. These and other studies [20] appeared the function of mitochondria and their interaction with antiviral immunity when infected with viruses.

In December 2019, the coronavirus disease (COVID-19) raised by the SARS-CoV-2, novel appeared in China and is now spreading almost all over the world. The cause of COVID-19 is SARS-CoV-2, a new type of encapsulated RNA coronavirus that can be transmitted from person to person through air and contact [21]. It is described by slight upper respiratory infection with cough, fever, and typical variations in radiation, while lower respiratory infections including non-life-threatening pneumonia, and life-threatening pneumonia with acute respiratory distress syndrome [22]. Generally, SARS-CoV-2 infection is vulnerable to all age groups, involving the elderly and newborns [21]. SARS-CoV-2 infection is a widespread challenge for the innate system, as there is as yet no efficient targeted treat for the virus, and persistent infection may include stages of silent and productive host-cellular infection [23].

There is a controversy that both macronutrient and micronutrient deficiencies cause impaired innate functions that can be inverted by depleting nutrients. While it is accepted that deficiency or under-nutrition requires it to be correct to ensure the innate system is functioning properly, increasing evidence indicates that for some nutrients, increasing absorption above the currently recommended standards may help improve innate function involving enhancing defense function and therefore impedance to infection whilst maintaining tolerance [24]. Many vitamins, minerals, and herbs have been exhibited to have a beneficial effect on mitochondrial function and thus the innate system. The most important effects of vitamins: B_1, C, D, E, omega-3, minerals: magnesium and manganese, herbs: thyme on the innate system under the virus infection, especially the COVID-19 virus that received special attention to the newest discoveries and their interactions with the innate system in this review

2. VITAMIN B_1

Vitamin B_1 (thiamine) is recognized as thiamin and anurine and also the first type of vitamin B that has been identified. Thiamine participates in glycolysis, the tricarboxylic acid cycle, branched-chain amino acids, and nucleotide metabolism [25]. It includes a thiazole ring attached with a methylene bridge with a pyrimidine ring and is named a 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium [26]. It is a water-soluble vitamin that mammalian cells cannot synthesize, but only plants and microorganisms can synthesize it [27]. It is found in various forms: free, monophosphate (ThMP), diphosphate (ThDP), or also recognized as pyrophosphate (TPP), triphosphate (ThTP), adenosine diphosphate (AThDP), and adenosine triphosphate (AThTP) [28]. Free and ThMP account for about 5-15% of total thiamine and have no known function yet, understanding the first stage of thiamine phosphorylation. ThTP, AThDP, and AThTP account for less than 1% of total thiamine in normal circumstances, but they appear to be likely to perform specific roles such as intracellular messengers or metabolic regulators [28-29]. ThDP accounts for about 80-90% of total thiamine and performs as a catalyst for many enzymes and thus plays important roles in all cells [30].

Thiamine shortage is more common than before and underlies acute cases in serious seriously sick patients [31]. Although B_1 deficiency is uncommon in evolved societies, its deficiency may additionally show up in cases of alcohol, diet, some illnesses, and excessive use of certain medications [32-35]. Moreover, the hazard of B_1 deficiency in advanced societies includes the elderly, after significant surgery, breastfeeding women and pregnant, diabetes, smokers, and young adults prefer high carbohydrates diets [36]. Also,

Anderson [37] stated that niacin and thiamine may become deficient during viral disease even if the patient has these vitamins at normal levels before the disease, because of the increased B_1 vitamins, which are used due to metabolic requirements during the disease.

However, at the present time in some developing countries, thiamine shortage and activity are not easily diagnosed, which is useful for diagnosis. Thiamine deficiency reduces oxygen consumption in different tissues by reducing the pyruvate dehydrogenase activity that converts the pyruvate into the acetyl-CoA, which enters the tricarboxylic acid cycle to provide ATP using oxygen. Thiamine deficiency has sub-deadly health effects such as reduced eating, metabolism changes in carbohydrates, proteins and fats, immunosuppression and blood-brain barrier damage, nerve and memory disorders, and ultimately it is lethal [38-41].

In HIV patients, it is essential to test the extent of thiamine, as it can play beneficial roles in these cases [42]. When Wallace and Weeks [43] examined three sufferers with chronic active hepatitis B and treated them with thiamine, they reported that thiamine treatment reduced the levels of aminotransferase to ordinary levels, while those levels increased when thiamine treatment was withdrawn. Lévy et al. [44] suggested that cirrhosis patients must be given thiamine regardless of its causes. They compared the thiamine shortage prevalence in 40 cases with alcoholic-cirrhosis (group A), 48 cases with hepatitis C virus-related cirrhosis (group B), and 59 cases with chronic-hepatitis-C without cirrhosis (group C) and concluded that thiamine shortage was similar in group A and group B. Not any of the group C (chronic hepatitis) cases had a thiamine shortage. Moreover, they added that thiamine shortage is not related to the activity or severity of liver diseases. Although recently reported that vitamins B_1 and C with corticosteroids are active in stopping progressive organ dysfunction, an additional study is wanted to affirm this initial finding [45].

3. VITAMIN C

L-ascorbic acid (vitamin C, AsA) is a water-soluble vitamin and necessary for many biological roles [46]. It is hexuronic acid with an enediol group combined in a five-membered heterocyclic lactone ring with the formula $C_6H_8O_6$, (5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one). Plants and generality of animals can synthesize AsA, while humans and other primates cannot synthesize it [46]. In most organisms, AsA performs major roles in metabolism. In humans, AsA mainly acts as antioxidants and cofactors for mono- and di-oxygenases [47]. It renews other metabolites, such as α-tocopherols, from oxidative stresses and protects some enzymes from oxidation, which may be induced by active oxygen in cells [48]. Also, AsA can be utilized as substrates or cofactors for some enzymes in many biological reactions [49-50]. Plants, fungi, protozoa, and animals synthesize AsA through many biosynthetic pathways [51-54]. Due to the deprivation of the enzyme that stimulates the last stage of AsA biosynthesis, human has lost the capability to biosynthesize it [55-56].

The physiological roles of ascorbate are mainly dependent on oxidation-reducing properties. Ascorbate acts as a cofactor for mono-oxygen and hydroxyl enzymes associated with the biosynthesis of carnitine, neurotransmitters, and collagen [57-58]. Ascorbate plays an important function in conservation collagen that is the major proteins in the skin, cardiovascular valves, teeth, tendons, ligaments, bones, intervertebral discs, cartilage, eye lens, and corneal [58].

Ascorbate is required for the biosynthesis of the β-hydroxybutyric acid (muscle carnitine) needful to transfer fatty acids into mitochondria for energy production [59]. It is essential for the biosynthesis of catecholamines, as it is a catalyst for the dopamine-β-hydroxylase enzyme that stimulates the neurotransmitter dopamine to norepinephrine [58]. Ascorbate stimulates the reactions of the hormonal activity of oxytocin, cholecystokinin, vasopressin, and α-melanotripin [60]. Moreover, its significant role is an antioxidant, which

helps prevent certain ailments such as cardiovascular ailments, age-related muscle declination, cataracts, cancer, and colds [61]. Additionally, this antioxidant may act roles in pathogens such as inhibiting the formation of carcinogenic nitrous compounds that predominate in the lumen of the gastrointestinal tract [62].

Naturally, inadequate AsA causes serious injuries to various organs, especially the brain and heart, as both are highly aerobic organs that produce more free oxygen species. On average, daily, about 3% of the AsA is lost from the man-body, which is the daily loss parallel to the first degree of AsA disposal assuming it is not ingested [63]. The half-life of AsA is about 16 days [64], and under the non-ingestion of AsA, a deficiency in blood is detected after about 35-40 days [65] and 12 weeks later Harvard felt tired in trying with a non-ascorbate diet [66]. Therefore, the symptom of ascorbate deficiency develops very slowly. Besides the paradoxical consequences of the medical use of ascorbate for a broad variety of ailments [67], the shortage of AsA was a great health problem. Actually, the content of AsA can reduce by 20-40% under normal cooking of fruits and vegetables [68]. Furthermore, Carr and Maggini [69] stated that smokers, alcoholics, and drug users who do not use nutritional supplements have a high hazard of ascorbate deficiency. Air pollution can result in a deterioration of the respiratory system and increased hazard of respiratory diseases, especially in individuals at risk of weakened immunity and deficiency of AsA [70-71].

The antihistamine impact of ascorbate is related to improved chemotaxis [72]. AsA appears to have a considerable function in the maturity, development, and distinction of immature T-cells [73-74]. Some literature has indicated that incubating AsA with human fibroblasts and viruses has strengthened the output of antiviral interferon (IFN) [75-77]. The widespread complications of AsA deficiency (scurvy) and the main causing of death are the observed susceptibilities to viruses, especially pneumonia [78]. Cases of pneumonia have exhibited speedy clearance of chest X-rays following the giving of intravenous ascorbate [79-80]. Moreover, treatments for individuals with a deficiency of AsA reduced the occurrence of colds [81]. Gorton and Jarvis [82] stated that treating megadose AsA can help in preventing and therapeutical treatment cold and flu symptoms. Also, Cai et al. [83] found that the protective influences of AsA on pneumonia induced by the influenza virus may be linked with inhibition of corticosterone (CORT) biosynthesis, which lowers susceptibility to influenza virucidal in experimental restraint-stressed mice. CORT may modify the inflammatory reaction, but it may catalyze the infection [84].

4. VITAMIN D

Vitamin D (vit. D) is one of the fat-soluble vitamins and secosteroids group responsible for elevated intestinal absorption, calcium and magnesium, and diverse other biological roles [85]. Vit. D is a cholesterol derivative and is linked with steroid hormones. Generally, cholecalciferol (vit. D_3) and ergocalciferol (vit.D2) are the central groups of vit. D, in humans [86]. Vit. D is synthesized under skin epidermis by a photochemical reaction from pro-vitamin to cholecalciferol based on ultraviolet radiation (exposure to sunlight), vit. D_3 and vit. D_2 can be absorbed from the diet and nutritional supplements too [87-88]. Little foods are vit. D dietary sources such as fish, eggs, dairy, meat (animal-based), yeast, mushrooms, planktonic microalgae, and Solanaceae family, plant-based after UVB-exposure [89-90]. Although there is evidence that vit. D_5 was discovered in the *Arabidopsis thaliana* plants, it has not been discovered whether vit. D_5 or its derivatives show a biological function in plant growth similar to that in vit. D_3 in humans [91].

Hypovitaminosis D is increasing in the global and is related to many ailments caused by calcium stabilization disorder [92]. This deficiency is related to autoimmune ailments [92], cardiovascular diseases [93], and respiratory diseases [94]. Zosky et al. [95] clarified that a vit. D caused lung volume to decrease in mice without significantly affecting somatic growth. Vit. D organizes ROS levels through anti-inflammatory

actions and mitochondrial-based expression of antioxidants *via* cell signaling pathways [96-97]. Ricca et al. [98] appeared that the mitochondrial impacts of vit. D receptors not only control respiratory activity, however, also maintain oxidative damage and protect the safety of mitochondria and the survival of healthy and also cancerous cells. Soe et al. [99] stated that vit. D deficiency is prevalent in patients of sickle cells at any season or age. Moreover, Mocayar Marón et al. [100] stated that the chronic deficiency of vit. D and melatonin certainly causes pathophysiological consequences.

Various studies have disclosed that vit.D plays important parts of the signals through adaptive and innate responses to bacterial and viral infections, such as influenza, *in vitro* respiratory syncytial virus, and tuberculosis [101-108]. Katz et al. [109] stated that aging is also related to raising the hazard of death from pneumonia and that persons up 65 years of age account for more than 90% of influenza-related deaths. Several observations reinforced that susceptibility to acute influenza related to the gradual accumulation of vitamin A (vit. A) with age [110-111], and vit. A absorption also increases in elderly humans [112-113]. Mawson [114] reviewed that a new pattern of influenza infection indicates that host resistance and sensitivity depend heavily on the ratio of vit. D to vit. A activity and vit.A at optimal concentration limits may prevent influenza disease while high concentration (i.e., very low vit. D: vit. A ratios) raise the hazard of acute influenza complications. Zhou et al. [115] studied infant (400 infants) therapies (3-12 months) with vit. D against influenza A infection, the study included viral loads, the period of fever, wheezing, and coughing. The researchers reported that the group treated with a high dose of vit. D (1200 IU/d) showed a rapid decrease in temperature compared to another group treated with a low dose of vit. D (400 IU/d). Gruber-Bzura [116] has shown that vit. D is definitely an aspect of the complex factors that influence innate responses, and therefore it is essential to maintain vit. D at optimal levels in children and all elderly adults to improve action against diseases.

Goncalves-Mendes et al. [117] advised that nutrition vit. D supplementation in old aged persons isn't always an effective manner to enhance their antibody reaction to the influenza vaccine. Newly, Grant et al. [118] exhibited the action of vit. D in reducing the hazard of evolving of COVID-19, as the number of COVID-19 cases is less in late summer (Southern Hemisphere) than others cases living in winter (Northern Hemisphere); and that the death rate increases with chronic ailments and age, both attached to a vit. D deficiency. Further, diverse studies have established the correlation between vit. D deficiency and venous thromboembolism in the lower extremities, patients with pulmonary venous thrombosis and ischemic stroke [119-121].

5. VITAMIN E

Vitamin E (Vit. E) is a class of amphiphilic soluble molecules, tocotrienols, and tocopherols, which are the head of a chromanol and side chain of a prenyl and biosynthesized by non-photosynthetic/photosynthetic organisms [122-123]. The difference between tocopherols and tocotrienols is the degree of saturation of the prenyl side chain, and four α-β-γ-δ-forms differ from tocotrienols and tocopherols in the position and number of methyl particles attached to the particle of chromanol.

Vitamin E is an active antioxidant for the removal of lipophilic radicals, and tocopherols are the active form in human cells [124]. α-tocopherol can perform as a molecule in gene modulating and regulation signal pathways through membrane-linked integrated proteins [125]. It maintains red blood cells (RBC) from oxidation, as it saves polyunsaturated fatty acids (PUFAs) from oxidation [126]. Further, it modifies the activity of inflammatory cytokines and innate cells and prevents the proliferation of smooth muscle cells [127-128]. Vitamin E was reported to curb sarcopenia and muscle weakness in preclinical models [129]. An

integration of vit. E with omega-3 fatty acids increased the expression of sirtuin-1 genes from peripheral mononuclear cells in patients of coronary artery [130]. Tocopherols are antioxidants that have been assessed against the influenza virus in mice [131] due to their activity versus oxidative damage through their activity in the scavenging of ROS [132]. Various studies, in humans, have revealed the immune impacts of vit. E, which gives resistance to many infections [133]. Dworski et al. [134] stated that vit. E protects against allergies and asthmas.

Tocotrienols have the potential to inhibit the mevalonate pathway, accountable for the biosynthesis of cholesterol, bone remodeling, and carcinogenesis [135-136]. Deficiency of vit. E is common in hereditary anemia, including anemia induced by a deficiency of glucose-6-phosphate (G6PD), a mutation in the gene for α-tocopherol transfer protein (α-TTP), and alcohol-induced ailments [126, 137-139]. In children with vit. E deficiency with cystic fibrosis, anemia is noticed in a short life span of red blood cells [140]. Vitamin E deficiency leads to progressive neurological disorders, spinal cerebellar ataxia, and death [141].

6. OMEGA-3

Omega-3 (ω-3) is a main human fatty acid (FA), long-chain PUFAs, belonging to a family of fats that the body can't biosynthesize and absorb through diet [142-144]. The name Omega is associated with the location of the double bond in relation to the methyl group present in a molecule of FAs. α-Linolenic Acid (ALA) is a short-chain ω-3 FA that polymerizes into long-chain ω-3 FAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which is a very weak step in the body [145]. Plant source is rich in ω-3 FA, especially ALA that can be an inexpensive, sustainable, renewable, and suitable source for vegetarians, compared to fatty fish acids [146].

In humans, there is strong evidence that adequate ω-3 are essential in maintaining health and can minimize the risks of inflammatory and chronic ailments [147]. In a 20-year study of 80,000 volunteers, women, increased consumption of PUFA was linked with a lower hazard of coronary heart ailment when replacing carbohydrates [148-149]. Moreover, ω-3 and docosahexaenoic acid are needed for healthy growth, improving children's brain and eye development, and continuing ordinary brain function for adults [150]. The literature also revealed the advantages of ω-3 in protecting and treating digestive, rheumatic, respiratory and bone disorders [151-152]. Also, ω-3 is related to enhance vascular endothelial function, decreased triglycerides, levels of residual lipoprotein, risk of thrombosis, blood pressure, and unequal heartbeat [153]. The literature revealed the benefits of ω-3 in reducing the hazard of breast, prostate, and lung cancer [154-155]. Daak et al. [156] reported that ω-3 supplementation for homozygous sickle cells (SCD) patients was active in reducing the severity and frequency of vascular blockages, blood transfusion rate, and severe anemia. Moreover, there are several studies that indicate defects in membranous fatty acids, red blood cells flow defects, inflammation, and hemolysis in SCD cases are improved with ω-3 treatments [157-159]. Daak et al. [160] reported that SCD studies did not confirm the critical role of anomalies in the blood cell membrane lipids in causing disease, and the therapeutic potential of ω-3 FAs proven in pioneering and randomized studies [161-164]. In contrast, Schwerbrock et al. [165] reported that PUFA consumption, in mice, has the possibility to raise the risk of influenza virus infection and possibly other viral diseases as well.

Torrinhas et al. [166] reported that ω-3 FAs are precursors of quite potent specialized pro-resolution mediators (SPMs), including resolvins, protecting, and maresins, which are related to a less attacker inflammatory inception, after competing together with ω-6 FAs for eicosanoid biosynthesis, thus, it is used for the clinical management of COVID-19 patients. They added that the resolvins, protectins and maresins of ω-3 FAs can inactivate polymorphonuclear leukocyte and stimulate the mobilization of non-inflammatory

leukocytes, which eliminates programmed cell death (efferocytosis). These SPMs also contribute to the pro-inflammatory cytokine "carry off" and remove other residues (such as invasive microorganisms) that provide restoration of the natural structure and tissue stabilization [167-171]. With its role in preventing pro-inflammatory mediators, it has appeared that SPMs reduce the extent and duration of inflammation, improve reepithelization, tissue regeneration, and wound healing in experimental models [172]. Moreover, Souza et al. [173] demonstrated that ω-3 leads to increased rapid regulation of SPM contents in peripheral blood and reprogramming of peripheral blood cell responses to sterile and infectious stimulants, adjustments that were managed to continuo after SPM contents returned to normal.

7. MAGNESIUM

Magnesium (Mg) is an important cation of crops, humans, and animals, and its deficiency decreases the sustainability of agrarian output and development and has long-term period negative consequences on animal and human health [174-175]. It is significant to keep the Mg content in agrarian products within an appropriate range because these products are the main source of Mg for animals and humans [176].

In humans, Mg plays several roles, stimulating many enzymes, and regulating basic roles such as neuromuscular conduction, muscle contraction, myocardial contraction, blood sugar control, and blood pressure [177-178]. Furthermore, Mg has a significant function in energy metabolism, bone development, and transfer of ions across membranes [178], and consequently, Mg deficiency is related to many diseases [179]. Regulating the intracellular Mg is key to maintaining tissue integrity and cellular functions, as Mg plays a significant role in immunity and metabolism [180-185].

Hypomagnesemia is unknown because its levels are not often evaluated as in which deficiency or surplus may occur, and data in developed countries reveal that about 10-30% inhabitance suffers from subclinical Mg deficiency [186-187]. Many diseases are related to Mg deficiency such as metabolic diseases, cardiovascular diseases, respiratory diseases, neurological abnormalities, and skeletal disorders [188]. Usually, hypomagnesemia is caused by decreasing consumption or insufficient absorption and/or excessive excretion and it is not easy to diagnose clinical, as symptoms related to it are not specific and generally confusing, due to down consuming other nutrients [188]. Hypomagnesemia was observed in patients treated with a proton pump inhibitor [189-190], thiazide diuretics, elevated doses of vit.D, and alcoholism [191]. Various studies have manifested that Mg deficiency is common in clinical cases, in particular in patients admitted to the comprehensive care unit as it has been observed to be related to increased hospital stay and deaths [192-194]. Magnesium deficiency may lead to reduced lung function, in particular in asthma cases [195]. Traviesa [196] confirmed that hypomagnesemia leads to thiamine deficiency, which sometimes appears in cases with Wernicke-Korsakoff encephalopathy. Magnesium is necessary to uptake thiamine [197], phosphorylation of thiamine phosphate [198], and action of enzymes that depend on thiamine in the cell [199-200]. Uwitonze and Razzaque [201] also added that Mg is needed for vit.D because all metabolic vit.D enzymes require Mg that represents as a stimulus for reactions in the liver and kidneys. In adults, hypomagnesemia leads to unspecified clinical type with relevant central and peripheral neuromuscular markers, such as chronic fatigue syndrome, idiopathic Barlow's ailments, spasmophilia, hypoventilation syndrome, neurocirculatory asthenia [202]. Cross et al. [203] stated that $MgSO_4$ may be useful in preventing fetal membranes inflammation produced by polymicrobial viral-bacterial infection. It is known that Mg is related to many protein kinases and additional Mg may indirectly stimulate T-cell receptor signals [204]. Howe et al. [205] added that oral Mg may also be efficient in patients with a mutation in the Interleukin-2-inducible T cell kinase.

The function of Mg in the lung can be interpreted at three standards: Mg has an acute vasodilator and bronchodilator impact; Mg controls the liberation of acetylcholine and histamine; magnesium represents as an anti-inflammatory [175]. Studies on X-linked immunodeficiency with Mg deficiency disease (XMEN) have shown that deficiency of Mg leads to a poor immune reaction that can lead to increased viral load by Epstein - Barr (EBV) [206]. Lately, it was found that 93% of acute and seriously ill patients with COVID-19 have hypokalemia [207], where hypokalemia is a widespread outcome in cases with hypomagnesemia [208].

8. MANGANESE

Manganese (Mn) is a fundamental element in almost all organisms as it acts as an enzymatic catalyst and as a catalyst in the activities of biological groups [209]. Manganese is significant for plant growth because it participates in photosynthesis, respiration, defense of pathogens, hormone signals and ROS scavenger [210]. In plants, it has been noticed that only the evolution of O_2 in photosynthesis, oxalate oxidase, and Mn superoxide dismutase (MnSOD) exclusively require Mn. MnSODs are located in mitochondria and peroxisomes and give protection against ROS that cause oxidative stress [211-212]. The oxalate oxidase is located in the oblast and stimulates the breakdown of oxalate into CO_2 and H_2O_2, where it participates in defense by generating H_2O_2, which involves the biosynthesis of lignin that appears as an impediment against pathogens [213].

In humans, Mn is an essential microelement, distributed throughout the body, and high concentrations are found in mitochondrial-rich organs such as the thyroid, pituitary, liver, pancreas, bones, and kidneys [214-215]. Mn catalyzes many enzymes, inclusive MnSOD, glutamine synthetase, arginase, and pyruvate carboxylase. It activates and synthesizes many enzymes participated with the metabolism of glucose and fats, ascorbate and thiamine, accelerate protein synthesis, endocrine regulation, stimulate hematopoiesis, improve innate function, and reduce ROS [216-217]. Interestingly, research points out that levels of Mn in the blood depend on sex and age, for example, the level is lower in adulthood than in childhood, and men have somewhat lower levels than women [218]. Moreover, Mn levels in non-pregnant women are lower compared to pregnant women [219], and individuals with high blood Mn levels have lower levels of iron (Fe) [220-222].

Compared to other essential micronutrients, Mn deficiency is rare, while Mn toxicity may occur more frequently when overexposed to Mn that causes polycythemia, dystonia, liver cirrhosis, and signs similar to Parkinson's ailment [217]. Accumulation and excessive exposure to Mn cause harm to the central nervous system that favors Mn absorption, while prolonged exposure to low Mn levels leads to Parkinson's disease [223]. However, the *in vivo* experiments in Mn-deficient mice increase the question of whether Mn depletion in humans is able to reduce response versus DNA viruses, resulting in reduced antiviral defense in people with Mn deficiency [224]. Haase [224] pointed out that THP1 cells, a cell line derived from peripheral blood, acquired antiviral activity while Mn averaged 2 mM, and Mn concentrations required to stimulate innate immunity.

Both Fe and Mn are transitional minerals and have opposite effects, which may alter the absorption of Mn, excretion, or distribution of tissues/cells, and thus change Mn standards in the blood [225]. Common causes of high Fe concentrations, which can harm a number of different organs, especially the liver, in humans are alcohol addiction, cytolysis, inflammation, and metabolic syndrome [226]. Fernandez-Real et al. [227] reviewed that excess Fe in the blood is related to the development of type two diabetes. Various researches have also reported that the hazard of developing diabetes-related to high Fe intake is not considered by hemochromatosis or inflammation, but is fully linked to excessive Fe diet [228-229]. Bowers et al. [230] and Qiu et al. [231] noticed that the risk of gestational diabetes is especially associated with heme-

Fe, which is absorbed more efficiently than Fe-heme-Fe. Moreover, Cunningham et al. [232] and Memişoğulları and Bakan [233] reported that greater ceruloplasmin levels and lower transferrin [233] noticed in type two diabetic cases could lead to increased free copper (Cu) and Fe levels, respectively.

Furthermore, it was found that Mn was heavily involved and wanted for the host's defense versus DNA viruses in mice [234]. As Mn accumulation stimulates the prominent innate immunity, which leads to the production and secretion of cytokines [234]. However, excessive accumulation or exposure to Mn damages the central nervous system as a result of preferential absorption of magnesium through brains and spinal cords. It is found that Manganism appears in response to sever manganese exposures, whereas Parkinsonism may outcome from long-time exposure into low concentrations of Mn [223]. Moreover, colloidal Mn salt (MnJ) showed significant adjunctive effects for all of the antigens tested including recombinant proteins, peptides, and inactivated viruses either by intramuscular or nasal immunization, which these results may have participations for the development of robust and safe Mn vaccines [235]. Manganese also participates with tumor immunology, as it is represented in dendritic cells to stimulate an anti-tumor reaction by cytotoxic T cells [236]. More studies are needed to clarify the relationship between influenza viruses and Mn.

9. THYME

Thyme is a prevalent semi-evergreen or evergreen shrub originated from the Mediterranean area and characterized by different species that differ in flavors [237]. The species are commonly used as ornamental, flavoring agents in culinary, and medicinal. It belongs to the Lamiaceae, the mint family has been used in traditional medicines to treat many diseases with many therapeutic effects related to volatile compounds and essential oils that have been used as anti-bacterial, anti-fungal, and anti-inflammatory properties [238-240]. The thyme plant contains many proteins, fats, fiber, flavonoids, and phenolic antioxidants, which are the highest levels of antioxidants among herbs, such as lutein, luteolin, naringenin, pigenin, zeaxanthin, thymonin, and vitamins such as A, B, C, and is considered the richest source of minerals such as K, Fe, Ca, Mn, Mg and Se, Na, and P [241-243].

Thyme phytochemical ingredients contain terpenoids, phenolic compounds, and usually, thymol, saponins, eugenol [244], and the essential oil appeared a high level of oxygenated monoterpenes (56.53%), monoterpene hydrocarbons (28.69%), sesquiterpene hydrocarbons (5.04%), and oxygenated sesquiterpenes (1.84%) [245]. The spicy aroma of thyme is an essential oil, as the dried plant contains about 1-2.5% of the essential oil [246]. The dominant essential oil is thymol (γ-terbene; 51.34%) while other essential oil components are less than 19% [245]. Most essential thyme oil belongs to monoterpene: linalol, myrcene, camphor, borneol, β-pinene, β-caryophyllene, *p*-cymene, carvacrol, thymol, γ-terpinene, thymyl methyl ether, limonene, α-terpinol, γ-terpinol, carvacryl methyl ether, and sabinene hydrate [245]. Also, thyme has triterpenes oleanolic acid (0.37%) and ursolic acid (0.94%) [247]. Thyme phenolic compounds are rosmarinic acid, *p*-hydroxybenzoic acid, caffeic acid, ferulic acid, syringic acid, gentisic acid, and *p*-coumaric acid [245, 248-249]. Thyme flavonoids are about 25 among them flavones: apigenin, luteolin, 6-hydroxyluteolin; and methylflavones: cirsilineol, 8-methoxycirsilineol, cirsimaritin, 5-desmethylnobiletin, 5-desmethylsinensetin, gardenin B, genkwanin, 7-methoxyluteolin, salvigenin, sideritoflavone, thymonin, thymusin, and xanthomicrol [245, 250-251].

The essential oil of thyme is characterized by its ability to scavenging free radicals, and therefore it is a natural antioxidant factor [252]. Thyme extracts appeared to fix the impacts on behavioral and memory disorders generated by scopolamine in mice, suggesting their beneficial effect in treating Alzheimer's ailment [253]. Thyme contains anti-inflammatory activities, where thymol, a major component of thyme, has been

notified to show anti-inflammatory impacts in the laboratory and *in vivo* [254]. Thyme extracts have been stated for their anti-inflammatory activities, as they reduce the inflammatory mediators: alpha tumor necrosis factor, beta-interleukin-1, and interleukin-6, and increase the expression of the anti-inflammatory cytokine, interleukin-10 [255]. Moreover, Vigo et al. [256] illustrated that thyme has anti-inflammatory activity by significantly inhibiting the expression of nitric oxide synthase mRNA. The antimicrobial mechanisms of carvacrol and thymol rely on their potentiality to degrade the outer membrane of Gram-negative bacteria, increase the permeability of the cytoplasmic membrane to ATP and release lipopolysaccharides [257]. Essential oils of *Thymus vulgaris* and *T. zygis*, which contain an elevated content of carvacrol and thymol, exhibited anti-fungal activities against seven Candida app. strains [258]. Thyme essential oil was a powerful antifungal against *Aspergillus flavus*, *A. parasiticus*, *A. ochraceus*, and *Fusarium moniliforme* [259]. It also has antioxidant action and has a protecting effect versus aflatoxin toxicity [260].

Regular and mostly critical bronchitis is induced by viral diseases, which are commonly treated by self-medication without a prescription, and herbal medicines, such as thyme extraction, with known efficiency and safety [261-264]. Thymus extracts (80% ethanol) have been stated for their antiviral activities against the Newcastle ailment virus, decreasing the potency of the virus more than 56-fold [265], and against herpes simplex virus (HSV) 1 and 2, and against HSV strains 1 Acyclovir Resistance [266]. Recently, Lenz et al. [267] reported that the tested standard thyme extract can have beneficial antiviral effects against HPV, leading to common cold ailments and possibly against flu A virus, leading to respiratory complications. The broad antimicrobial activity can be associated with phenol and its derivatives have antimicrobial effects by denaturation proteins, and thymol is 30-fold more active compared to phenol [267-268].

10. CONCLUSION

The multiple roles of vitamin B_1, vitamin C, vitamin D, vitamin E, omega-3, Mg, Mn, and thyme in humans provide these compounds with essential functions in defense against pathogens. While several open queries continue, there is an agreement that these compounds can be employed for medicinal advantage. It will be significant to assess the net impacts of these agents, as these factors seem to have a function in enhancing innate responses. The result of this review will visualize potential strategies that may benefit the host's innate system and improve the human defense.

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