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VMP35, a Novel Bioflavonoids and Phytonutrient-Fortified Formulation Demonstrated to Boost Metabolic Competence and Athletic Performance

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ABSTRACT

Metabolic competence in conjunction with well-balanced nutritional support is extremely important for normal biochemical and physiological functions, as well as for enhanced athletic performance. Research-affirmed nutraceuticals enriched in structurally diverse phytonutrients including bioflavonoids may help to boost athletic, functional, and bio-physiological competence. Earlier clinical studies in our laboratories using VMP35 have been demonstrated to boost aerobic competence and provide protection against diverse chronic degenerative diseases. It has been well demonstrated that occurrence of chronic degenerative disorders is associated with an increase in anaerobic events viz, the inability to effectively use oxygen and water, and inability to use nutrients, for cellular energy production, management, metabolic homeostasis, and waste removal. Anaerobic pathologies generate a significant increase in oxidative stress. Proper bioflavonoid-enriched VMP35 also supplies an abundant reservoir of buffers to restore aerobic metabolic events, minimizing oxidative stress, and provide additional antioxidants to boost the redox potential and immune competence. We demonstrated the molecular mechanisms in conjunction with validation from a clinical investigation, case studies, and concept validation pilot studies. The clinical evidence demonstrates that the iron-free liquid VMP35 dietary supplement restores aerobic metabolism by restoring iron-dependent hemoglobin to RBCs, bolstering neutrophils in the blood (immune support), and significantly improving performance output in a diverse range of different types of extreme athletes.

Keywords: VMP35; Bioflavonoids; Phenolic Saccharides; Prodosome®; Aerobic Metabolism; Anemia; Sports Nutrition; Athletic Performance

INTRODUCTION

Oxidative damage is a universal antecedent to inflammatory sequela. Oxygen deprivation, as opposed to oxygen deficiency, is a major contributor to reactive oxygen species generation (ROS), oxidative damage, cytokine production, and inflammation. When our cells are unable to efficiently and effectively utilize the oxygen we are breathing to facilitate aerobic glycolysis and other cellular metabolic events, the oxygen instead oxidizes cell membranes, lipids, cross-links proteins, and damages DNA among other consequences [1]. These anaerobic events are hallmarks of chronic degenerative diseases and an indication that the body's own antioxidant defense systems, i.e. SOD, GSH, etc., are overburdened. Dietary sources of antioxidants become even more important to augment and assist in reduction of oxidative stress, damage, and inflammatory sequela.

The authors report on the compositional properties, mechanistic effects, and clinical results of a patent-pending VMP35 Multinutrient Complex (MNC) ('Prodovite®'). Aside from correctly appearing as a Multinutrient formula, the VMP35 MNC is primarily a botanical formulation designed to provide a variety and abundance of phytonutrients, including bioflavonoids, polyphenols, stilbenes, nutritionally valuable saccharides (and phenolic glycosides), etc., for antioxidant protection, immune support, and to ensure the structural strength and integrity of various molecular species.

A diverse range of water-extracted nano-emulsified VMP35 phytonutrient ingredients fortified with vitamins and minerals, are encapsulated in a complex concentric configuration of proprietary SK713 SLP multi-lamellar phospholipid envelopes (Prodosomes®) to engineer a highly stable and rapidly bioavailable technology. This patent-pending iron-free formulation was shown to be absorbed into the blood within five minutes, rapidly restoring iron-dependent hemoglobin and its oxygen-carrying capabilities [2]. Product ingredients were

meticulously researched to achieve a formulation that provided a broad spectrum of synergistic system-biological benefits to improve cellular functionality, immunity, and overall metabolic health. The 1:1 water extraction process is not intended to target a specific bioactive compound or molecule (i.e., a reductionist premise). While water extracting is a slower and longer process, the 1:1 water-extracted botanicals contain no chemical solvent residues, are more potent than extract to water ratios of 1:3, 1:4, and other more highly diluted extracts (i.e., up to 1:50), also exhibiting a more representative profile of naturally occurring beneficial bio-active ingredients. Following is a summarized overview of ingredient properties and benefits.

Astragalus membranaceus (family Fabaceae) Root Extract

This novel water-extracted medicinal plant is being used as an 'adaptogen' in Traditional Medicine in China, Japan, Korea, and Southeast Asia for centuries for diverse degenerative diseases, especially inflammatory disorders, cancers, and diverse dysfunctions [3]. It also functions as an antioxidant and an immune modulator.

It is well established that Astragalus membranaceus (AM) acts as an adaptogen and interacts with 'stress response mediators' to effectively regulate metabolic homeostasis and energy metabolism. It also appropriately synchronizes the neuroendocrine system as well as promotes superior immune competence and stress adaptation. Other important research [4] demonstrated that AM strengthened immunological function, promoted the discharge of pus, and the growth and regeneration of new tissue.

This novel medicinal plant is comprised of flavonoids, saponins, phytosaccharides, amino acids, and isoflavan glycosides [3,5], and Ono et al. reported [6] that demonstrate potent anti-viral and immunostimulatory properties and inhibits murine retroviral reverse transcriptase and human DNA polymerase activities.

Astragalus-based treatments have demonstrated significant amelioration of toxicity induced by other concurrently administered immunosuppressants and cancer chemotherapeutics [7]. Furthermore, Auyeung et al. (2016) elaborated its antitumorigenic mechanisms in ameliorating various gastrointestinal cancers and disorders. These researchers demonstrated the potent immunomodulating activities against diverse cancer signaling pathways and the interaction with specific transcription molecules during protection against gastrointestinal inflammation and cancers. Overall, Astragalus membranaceus exhibits an array of potent health benefits.

Water-extract of Polygonum multiflorum (family Asparagaceae), commonly known as Fo-Ti, Root Extract

Ho et al. (2019) reported [8] that Polygonum multiflorum is rich in naturally occurring flavonoids, stilbenes, alkaloids, and quinones, and is a natural hepato- and nephron-protectant, immunomodulator, as well as exhibits diverse anti-aging/longevity promoting benefits including anti-alopecia, anti-cancer, antioxidant, anti-bacterial, anti-hyperlipidemia and anti-atherosclerosis activities [8,9]. Furthermore, Fo-Ti promotes rejuvenating effects on the nerves, brain cells and endocrine glands [10]. It supports and promotes competent adrenal function and helps detoxify the body [11]. It is also reported to boost immune function and increase sexual vigor [12]; be a blood toner and improve cellular energetics; and to fortify muscles, tendons, and bones [13].

Water-Extract of Camellia sinensis (family Theaceae) (well-known as Green Tea) Leaf [GTE]

Green tea has powerful antioxidant properties owing to its potent content of polyphenols, especially epigallocatachingallate (EGCG) [14-16]. These polyphenols are beneficial bioflavonoids that also help increase the strength of the body's connective tissues. This helps to reduce tissue fragility, providing increased protection against the initiation of inflammatory events [14,17,18]. The decaffeinated form of a standardized green tea extract removes the genetically adversarial stimulatory effects of caffeine.

Matricaria chamomilla (family Asteraceae) (well-known as Chamomile) Flower Water Extract

Matricaria chamomilla (MC) contains a significant number of therapeutically active compounds including flavonoids, sesquiterpenes, coumarins, and polyacetylenes. Several coumarins including herniarin, umbelliferone, and (Z)- and (E)-2-β-d-glucopyranosyloxy-4-methoxycinnamic acid, the glucoside precursor of herniarin, as well as chlorogenic acid and caffeic acid (phenylpropanoids), apigenin, apigenin-7-O-glucoside, luteolin and luteolin-7-O-glucoside (flavones), quercetin and rutin, and naringenin were identified in chamomile [19]. This novel medicinal plant has been demonstrated to improve muscle tone and reduce the potential for spasms. It also improves connective tissue strength, reducing the need to initiate inflammatory events, especially those related to the digestive system; it supports a calming and stress relieving effect; and supports restful restorative sleep [20,21].

Water extract of Rosa canina (family Rosaceae) (a novel, natural source of citrus bioflavonoids from Rose Hips) Extract

The phytochemical constituents in Rosa canina include (RC) citrus bioflavonoids, triterpenoids, and phytosterols, and therapeutically target, through multiple signaling pathways, biomolecules including NF-κB, and potentially inhibit pro-inflammatory enzymes including matrix metalloproteinases and cyclooxygenase-2. RC lowers the abundance of inflammatory cytokines and chemokines including TNF-α, IL-1β, IL-6, CCL5 [chemokine (C-C motif) ligand 5], and reduces oxidative stress, which in turn inhibits inflammatory sequela [22-24]. Originally, citrus bioflavonoids were termed 'Vitamin P', supposedly because they improved membrane health and 'permeability' through multiple mechanistic pathways. A significant number of

preclinical and clinical investigations have exhibited that Rosa canina exerts potent analgesic, anti-arthritic, anti-inflammatory, anti-oxidative, and bone-preserving activities [25]. These citrus bioflavonoids exhibit repair, re-structuring, regenerative, re-vitalizing, and rebuilding of tissues, as well as strengthening connective tissues [26-28]. Rosa canina reduces the fragility and susceptibility of connective tissues to injury from airborne, topical contact, and orally ingested allergens [29,30].

Water extract of Eleutherococcus senticosus (family Araliaceae) (known as Eleuthero) Root Extract

Eleutherococcus senticosus (ES), a novel functional food from ancient times, revitalizes hepatic and kidney tissues, replenishes vitality, supports energy and stamina, boosts immune system function, strengthens bones, stimulates appetite, helps reduce fatigue and enhance endurance, as well as improves brain and memory functions. Its chemical constituents mainly include glycosides and flavonoids [31]. ES is widely used in China, Korea, Japan, and Russia. ES has positive pharmacological effects on the cardiovascular, central nervous, and immune systems. Representative pathways stimulated by eleuthero root extract are related to neuroactive ligand-receptor interactions, cancer inhibition, and phosphatidylinositol-3-kinase/protein kinase B signaling. Importantly, eleuthero root extract is safe and exerts no significant adverse effects at normal doses [32,33].

Water-Extract of Crataegus oxyacantha (family Rosaceae) Berry (known as Hawthorn Berry) Extract

Hawthorn berry (HB) is a beneficial source of flavonoids, especially epicatechin and oligomeric proanthocyanidins, particularly procyanidin and procyanidin B-2, as well as tannins, flavonoids such as vitexin, rutin, quercetin, and hyperoside, flavone-C, triterpene acids including ursolic acid, oleanolic acid, and crataegolic acid, and phenolic acids such as caffeic acid, chlorogenic acid, and related phenolcarboxylic acids [34,35]. Hawthorne berry supports digestion and cardiovascular function [36]. HB helps improve fatigue; normal heartbeat rhythms; exercise performance, tolerance, and breathing; and the strength with which the left ventricle of the heart ejects blood into the arteries, technically referred to as ‘Ejection Fraction’ [34,37].

Water-Extract of Centella asiatica (family Apiaceae) (known as Gotu Kola) Whole Herb Extract

Centella asiatica, a triterpene-rich medicinal plant, has been extensively used in both traditional Ayurvedic medicine and in Chinese medicine for centuries. It is considered a vital herb for revitalizing the nerves and brain cells, and is referred to as “food for the brain” [38] as well as diverse neurological, dermatological, and metabolic dysfunctions [39]. Centella asiatica contains structurally diverse chemical constituents including polyacetylenes, triterpenoids, glycosides, asiaticosides, asiatic acid, madecassic acid, madecassoside, centellin, asiaticin, and centellicin, as well as a unique source for vitamin K, magnesium, calcium, and sodium. It is important to mention that Asiatiocides are potent, natural antileprotic agents, while asiatic acid, asiaticoside, madecassic acid, and madecassoside have potent cardioprotective properties [38]. Overall, Centella asiatica exerts potent cardioprotective, anti-atherosclerotic, antihypertensive, antihyperlipidemic, antidiabetic, antioxidant, reduces fatigue, and induces anti-inflammatory activities, as well as promotes tranquility, stress relief, and intelligence, improving mental functions such as focus, concentration, and memory. It is believed to fortify the immune system, both cleansing and feeding it, and to strengthen the adrenals. In Ayurveda, Centella asiatica is reported to exert a calming effect and thus helps support restful sleep. It is widely used in yoga and meditative practices [40].

Water-Extract of Zingiber officinale (family Zingiberaceae) (well known as Ginger) Root

The rhizomes (i.e. ‘roots’) of ginger exhibit a myriad of health benefits including for arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, hypertension, dementia, fever, headaches, infectious diseases, catarrh, nervous diseases, gingivitis, toothache, asthma, stroke and diabetes, as well as in treating various gastric ailments like constipation, dyspepsia, belching, bloating, gastritis, epigastric discomfort, gastric ulcerations, indigestion, nausea, and vomiting. Scientific studies have validated the ethnomedicinal uses. Ginger promotes anti-inflammatory events by strengthening connective tissues, reducing fragility and susceptibility. It is ideal for boosting blood circulation, immune function, stabilizing blood pressure, and maintaining the rheology of the blood. Ginger exhibits gastroprotection against diverse NSAID-induced gastric ulcers, as well as reserpine-, ethanol-, stress-, acetic acid- and Helicobacter pylori-induced gastric ulcerations. Ginger root promotes digestive comfort and reduces various types of discomfort after eating [41-43].

Ginger contains numerous bioactive compounds including phenolic and terpene compounds, but has a predominant presence of gingerols, shogaols, and paradols, which account for its diverse bioactivities [44]. Ginger also supports controlled and voluntary muscle strength and stability, as well as boosts sports performance [45,46].

Water extract of Sambucus nigra (family Adoxaceae) (well known as Elderberry) Berry

Elderberry contains significant amounts of bioflavonoids, known as Vitamin P for its 'permeability factor'. Elderberry promotes tissue strength, integrity, and permeability of all connective tissues and thereby reduces tissue fragility and susceptibility to damage from diverse types of insults, including antigens/allergens and trauma [47,48].

Elderberry promotes cellular integrity and overall health by mitigating inflammatory events, boosting immune function, reducing the need for water retention and congestion [49]. The bioflavonoids and anthocyanins in Elderberry provide antioxidant benefits and help support the body's fight against viruses. Elderberry also helps support respiratory health. Laboratory studies have shown that elderberry helps maintain

the healthy structure and function of the sinus membranes and reduces excessive sinus mucus secretion [48].

Lignaloe is a proprietary combination of a novel water-extracted Aloe vera and a patented water extracted pinecone extract.

Standardized DSR0114 Aloe barbardensis (family Asphodelaceae) [proprietary Organic BiAloe® DSR0114] Aloe Vera (Inner Leaf) water-extracted freeze-dried gel powder

Aloe vera, a well renowned ancient plant well recognized for its healing properties, has fleshly leaves which are purported to be filled with a gel containing at least 75 nutrients, 20 minerals, 12 vitamins, 18 amino acids, an array of nutritional sugars, and 200 active enzymes [50,51]. Egyptians used to call Aloe vera a "Plant of Immortality", while Aristotle persuaded King Alexander to conquer the Isle of Socotra to get uninterrupted supply of Aloe. Old Chinese doctors referred to aloe as a "harmonic remedy". Researchers demonstrated the outstanding pharmacological activity of the aloe gel polysaccharides, which are often referred to as acemannan [-(1,4)-acetylated polymannan] [50,51].

Chemical constituents of Aloe vera are categorized into the following main areas (a) amino acids, (b) anthraquinones, (c) enzymes, (d) lignins, (e) minerals, (f) mono- and polysaccharides, (g) salicylic acid, (h) saponins, (i) sterols, and (j) vitamins. A unique water extraction technique was adopted to preserve and protect the maximum synergistic benefits of all the natural components in the leaf gel.

A unique planting, harvesting, and proprietary freeze-dried processing technique of BiAloe® resulted in a 15% total acemannan [acetylated mannans, mostly monoacetyl mannose polymers with -(1,4)-D-linkage] content, exhibiting a novel, bioavailable, and significant immunomodulatory activity. It is important to emphasize that acemannan is a sub-group of polymannosides, which is a sub-group of polysaccharides. Approximately 87% of the acemannan in BiAloe® ranges from 5 KDa to 400 KDa (kilodaltons), providing a complete range of acemannans and the optimal immunomodulatory benefits with enhanced bioavailability and bioactivity. Furthermore, Folgeman et al. (1992) demonstrated the broad-spectrum safety of acemannan in mice, rats, and dogs [53].

Lewis et al. conducted an open-labelled investigation in 34 subjects (male = 6, female 28, age = 60-98 years, mean = 79.9 years) suffering from moderate to severe Alzheimer's disease to assess the efficacy of BiAloe® over a period of 12 months [52]. BiAloe® significantly improved cognitive functions, as well as improved inflammatory and immune functioning profile.

Standardized LPC108 Pinus sylvestris (family Pinaceae) [known as Proligna® Freeze Dried LPC108 Scotch Pine Cone Extract (freeze dried)] Powder

Patented water-extracted Proligna® exhibited potent antibacterial, antiviral, and antitumor properties, and is supported by 14 patents and 30 peer-reviewed publications [54-57]. An unpublished toxicological investigation in rats demonstrated that Proligna® exhibited no toxicity when orally supplemented at a range of doses 5 mg/kg to 405 mg/kg over a period of 30 consecutive days. A report demonstrated that more than a million doses of pinecone extract has been distributed, which have exhibited no side effects.

Proligna® contains a complex of poly-phenylpropanoid polysaccharides and demonstrated to exhibit potent biological and immunological activities and demonstrated potent antimicrobial effects [55,58-64]. Proligna exhibited anti-parasitic activities [55], and anti-viral activities [65-67], potent anti-cancer, cytotoxic/mitogenic effects [68 -70], and immunomodulating activities [71-80].

Proligna® rapidly increased immune cell development as demonstrated by Bradley et al. (2014) in cultured human peripheral blood mononuclear cells to produce mature dendritic cells, the primary hallmark for the development of immune responses against bacterial- and viral-infected cells, as well as against cancer cells and vaccine antigens [81]. Proligna® inhibited HIV-induced effects on cultured cells, while in vivo protection was observed against a lethal dose of E coli treatment [82]. Another investigation by Dr. Mark Jaroszeski demonstrated the beneficial effect of Proligna® in the treatment of tumors when used in conjunction with electrochemotherapy. It was demonstrated that Proligna® applies electrical impulses to living cells, which induce rapid appearance and disappearance of tiny holes in the cell membranes and facilitates the entry of the chemotherapeutic drugs into the cells. This technology has been explored in several research institutions [83]. These researchers demonstrated that at the end of 50 days of treatment, complete absence of tumors was observed in 50-64% of animals who were simultaneously treated with Proligna® plus electrochemotherapy, while treatment with electrochemotherapy alone cured only 31% of animals, ~doubling the efficacy of the treatment.

Standardized Botanicals	Chemical Constituents	Physiological Performance and Metabolic Function
Astragalus membranaceus (family Fabaceae)	Flavonoids, saponins, phytosaccharides, amino acids and isoflavan glycosides	• An adaptogen
		• An antioxidant and immunomodulator
		• Regulate metabolic homeostasis and energy metabolism
		• Potent enhancement of immunity and immunostimulatory properties
		• Regeneration and revitalization of tissue
Polygonum multiflorum (family Asparagaceae)	Flavonoids, stilbenes, alkaloids, and quinones	• Antioxidant, anti-ageing, inhibits anaerobic events and organisms, helps protect DNA and prevent cell mutations, supports proper blood lipid levels and protects the structure of cells in

		the endothelium, reducing scarring.
Known as Fo-Ti		• Enhance brain function
		• Rejuvenate nerve, brain cells and endocrine and adrenal glands
		• Fortify muscles
		• Enhance detoxification
Camellia sinensis (family Theaceae)	Structurally diverse polyphenols and catechins especially (-)-Epigallocatechin gallate (EGCG)	• Antioxidant, reduces the need for inducing inflammatory events, anti-photoaging and autophagy
		• Neuroprotectant
		• Enhances brain function, cognition and mood alleviator
		• Stress resistance
		• Reduces tissue fragility and promotes connective tissue repair
Matricaria chamomilla (family Asteraceae)	Flavonoids, sesquiterpenes, coumarins, and polyacetylenes including herniarin, umbelliferone, chlorogenic acid, apigenin, luteolin, quercetin, rutin, and naringenin	• Improves muscle tone
		• Reduces the potential for spasms
		• Improves connective tissue strength
		• Reduces the need for inducing inflammatory events
		• Calming and stress relieving
		• Promotes restful restorative sleep
Rosa canina (family Rosaceae)	Citrus bioflavonoids, triterpenoids, and phytosterols	• Antioxidant
		• Reduces the need for inducing inflammatory events
		• Promotes joint health & function
		• Promotes tissue strength and integrity, increasing tissue resistance to allergenic insults
		• Promotes connective tissue repair
		• Repair, re-structure, regenerate, re-vitalize and re-build tissues

Eleutherococcus senticosus (family Araliaceae)	Flavonoids, glycosides	• An adaptogen
		• Strengthens immune function
		• Enhances endurance
		• Boosts stamina and energy
		• Strengthens bones
		• Reduces fatigue
Crataegus oxyacantha (family Rosaceae)	Flavonoids (vitexin, rutin, quercetin, and hyperoside, flavone-C, epicatechin), oligomeric proanthocyanidins (procyanidin B-2), triterpene acids (ursolic-, oleanolic-, crataegolic acids), and phenolic acids (caffeic acid), chlorogenic acid	• Promotes cardiovascular functions
		• Supports digestion
		• Reduces fatigue
		• Promotes improvements in exercise performance, tolerance, and breathing
Centella asiatica (family Apiaceae)	Triterpenoides, glycosides (asiaticosides, asiatic acid, madecassic acid, madecassoside, centellin, asiaticin and centellicin), polyacetylenes, vitamin K, magnesium, calcium, sodium and potassium	• Antioxidant, reducing the need for inducing inflammatory events
		• Cardioprotectant
		• Boosts immune functions
		• Boosts metabolic homeostasis
		• Promotes healthy aerobic metabolism
		• Supports proper blood lipid levels, and protects the structure of cells in the endothelium, reducing scarring.
		• Promotes proper blood sugar utilization,
		• Promotes the health of cardiovascular tissues, improves cellular energy output.
		• Promotes tranquility
		• Relieves stress
		• Promotes improved intelligence
		• Improves mental functions focus, concentration, and memory
		• Strengthen adrenals
		• Exerts calming effect and support restful sleep

Zingiber officinale (family Zingiberaceae)	Phenolic acids and terpenoids, gingerols, shogaols, and paradols	• Antioxidant; reduces the need for inducing inflammatory events
		• Boosts immune functions and blood circulation
		• Promotes digestive health
		• Boosts muscle performance, muscle strength, and overall sports performance
		• Reduces muscle damage and delayed onset to muscle soreness
Sambucus nigra (family Adoxaceae)	Bioflavonoids	• Antioxidant and reduces the need for inducing inflammatory events.
		• Promotes improved tissue structural strength and functional competence, protecting against viral insult, allergic vulnerability and damage from trauma
		• Supports respiratory health
Standardized DSR0114 Aloe barbardensis (Inner Leaf water extracted freeze-dried gel powder) [Organic BiAloe® DSR0114]	Acemannan [acetylated mannans, monoacetyl mannose polymers with □-(1,4)-D-linkage]	• Immunomodulatory activities
Standardized LPC108 Pinus sylvestris Proligna® Freeze Dried LPC108 Scotch Pine Cone freeze dried powder	Poly-phenylpropanoid polysaccharide complex	• Promotes improved tissue structural strength and functional competence, protecting against viral insult
		• Helps diminish the extent of damage from trauma
		• Restore aerobic cellular metabolism creating an adverse environment for anaerobes, i.e. yeasts, parasites, etc.
		• Promote an aerobic cellular environment to protect DNA and promote normal cell structure and function, preventing cell mutations.

Table 1. Phytonutrients in VMP35

VITAMINS

Vitamin B Complex

Vitamin B complex consists of eight B vitamins including vitamin B1 (thiamin hydrochloride), vitamin B2 (riboflavin), vitamin B3 (niacin & niacinamide), vitamin B5 (pantothenic acid as d-calcium pantothenate), vitamin B6 (pyridoxine hydrochloride), vitamin B7 (biotin), vitamin B9 (Orgen-FA®, food-form Folate from organic orange peel) and vitamin B12 (cyanocobalamin). These essential vitamins immensely contribute to cellular integrity, cell metabolism, growth and viability of red blood cells, cardiovascular functions, ocular health, neuronal function, healthy appetite and digestive health, hormones and normal cholesterol production, energy levels, muscle tone, exercise performance, and diverse biophysiological functions. B-vitamins are especially vital for pregnant women for fetal brain development, as well as during breastfeeding, and reduce the risk of birth defects [84-86]. Selected studies demonstrated that B-vitamins boosts testosterone levels, exercise performance, strength, and stamina in men, which declines with age. In pregnant women, B-vitamins also boosts energy levels, ameliorates nausea, and reduces the risk of developing preeclampsia [86,87].

OTHER VITAMINS

Vitamin A

Vitamin A and Provitamin A carotenoids such as alpha-carotene, beta-carotene, and beta-cryptoxanthin, also known as retinol, retinal, and retinoic acid, are fat soluble vitamins and extremely vital for the maintenance of healthy vision also protecting against night blindness (known as nyctalopia) and advancing age-induced decline in vision. Vitamin A is an integral component of the pigment rhodopsin, which is extremely vital for night vision [88,89]. Age-related macular degeneration occurs due to oxidative stress-induced cellular injury to the retina, while vitamin A supplementation may have ability to (i) reduce or protect against cellular injury in the retina; (ii) cellular growth and integrity; (iii) protect DNA and cell structure and function against aberrant mutations. [Note: A paucity of studies have indicated that beta-carotene supplementation may cause an increased risk of lung cancer in smokers. Importantly, in that research, vitamin A was the only supplement taken, which is a reductionist paradigm (vitamin A is not a drug). That perspective is inconsistent with the 'systems biology' paradigm of healthy nutrition. Metaphorically, 'there are no solos in the orchestra of nutrition.' The synergies of nutritional ingredient interactions are implicit by natural design. Results of research on single nutritional ingredients cannot be interpreted the same way, nor offer the same expectations for outcomes as when those single ingredients are included within the context of a complete and comprehensive nutritional/nutraceutical complex]; (iv) boosts immune health and protects the mucosal barriers in your eyes, lungs, gut, and genitals from infections; (v) boosts the production and functions of immune system white blood cells; (vi) promotes neonatal health; (vii) nourishes the skin,

promoting dermal health and immunity, strengthening dermal structural integrity and reducing the potential for acne and the need for other chronic inflammatory skin issues; (viii) supports and maintains bone health. Dietary intake of vitamin A exhibits a 6% reduced risk of fractures; (ix) promotes healthy reproductive health and ensures normal growth and development of embryos during pregnancy, however, an overdose can cause harmful effects; and (x) beneficial for wound healing [88-91].

The daily recommended dose for adult males is 900 mcg and adult females is 700 mcg, while children and adolescents should consider taking 300-600 mcg [90,91].

Vitamin C

Vitamin C is extensively available in diverse vegetables and fruits, including bell pepper, tomato, cantaloupe, cabbage, cauliflower, potato, spinach, green peas, orange, grapefruit, kiwi, broccoli, strawberry, and Brussels sprouts. The South American fruit Myrciaria dubia is especially rich in vitamin C, all of which is bound to nitric oxide [92-94]. Vitamin C is a well-established antioxidant, a potent free radical scavenger with remarkable immune enhancing properties and prevents cellular oxidative damage [93-95]. Vitamin C is intricately associated with multiple vital metabolic pathways including (a) the synthesis of collagen, a vital protein, essential for the formation of connective tissue, skin, cartilage, bone, and tendons; (b) formation of elastin and connective tissues; and (c) it is synergistic with carnitine, which mediates the transportation of fats for its metabolism. In fact, vitamin C is utilized by both collagen and carnitine for diverse biochemical functions and health benefits. Furthermore, it is important to reemphasize that in human physiology, collagen, connective tissues, elastin, and carnitine offer multiple biodynamics including strength, elasticity, flexibility, resilience, and stability [94-96]. Administration of vitamin C over a period of 30 days was shown to significantly reduce total cholesterol, low density lipoprotein, and very low-density lipoprotein. However, no effects were observed on high-density lipoprotein and triglyceride levels, while moderate to high doses of vitamin C may protect against hypertension and atherosclerosis. Excessive intake of vitamin C (i.e., mega dosing) can cause digestive problems (i.e., diarrhea) and kidney stones. Thomas et al. and dietary guidelines allow a daily dose 90 mg for adult males and 75 mg for adult females, while cigarette smokers need an additional daily dose of 35 mg [95-97].

Vitamin D

Approximately 75% people in the USA have low levels of vitamin D [98], especially darker skinned people. Vitamin D has exhibited diverse health benefits including (i) promotes bone growth, integrity, and strength by improving gut calcium absorption through synchronizing serum calcium and phosphate homeostasis, by cell proliferation, differentiation, and regulation of the innate and adaptative immune systems, as well as by organizing and restructuring the action of osteoblast and osteoclast cells, (ii) overall longevity and muscle strength, (iii) healthy blood pressure and arteries, (iv) boosts energy, mood, and mental clarity, (v) promotes healthy glucose, and (vi) promotes proper vision, protecting against macular degeneration [98-100] . In fact, vitamin D is a classic regulator of plasma calcium concentration and skeleton mineralization. Several studies have demonstrated that immune enhancing properties associated with vitamin D along with vitamin D receptor expression in the sexual organs may significantly contribute to the prevention in the pathogenesis of endometriosis, as well as maintenance of healthy breasts during pregnancies [98-100].

Vitamin D (as vitamin D3) boosts immune regulation, antimicrobial defense, is anti-inflammatory, confers cardioprotective functions, has antiaging effects, anticancer effects, and xenobiotic detoxification. Dr. Holick summarized that vitamin D deficiency is associated with a myriad of acute and chronic diseases including preeclampsia, childhood dental caries, periodontitis, autoimmune disorders, infectious diseases, high cholesterol, and cardiovascular disease, cancers, type 2 diabetes, and neurodegenerative diseases. In a clinical investigation, Okereke and Singh exhibited the efficacy of vitamin D in improving mood and lowering depression risk in older adults [99-101].

Vitamin E

It is another lipophilic chain-breaking powerful antioxidant, well-known to protect against free-radical mediated cellular injury, consisting of four tocopherols and four tocotrienols termed as alpha-, beta-, gamma-, and delta-, which is well documented to prevent the cyclic propagation of lipid peroxidation. However, vitamin E requirements in humans are limited to alpha-tocopherol because other forms are poorly recognized by the hepatic alpha-tocopherol transfer protein (TTP) [102,103]. Moreover, other forms may have beneficial effects of their own, that are not converted to alpha-tocopherol in humans. Several mechanisms are involved, which include (a) the preferential role of TTP in secreting alpha-tocopherol into the blood stream, particularly in the plasma; (b) biliary excretion of vitamin E is regulated by ATP-binding cassette proteins; and (c) phase I and phase II metabolic pathways of vitamin E [102-105].

Vitamin E has been demonstrated to protect against (a) neurodegeneration, (b) diverse inflammatory pathologies, (c) high blood pressure, (d) cardiovascular diseases and dysfunctions, (e) hardening of arteries, (f) cancer, (g) diverse environmental stressors including UV radiation, cigarette smoke and environmental pollutants, and furthermore, vitamin E boosts immune health [103-107].

Sources of Vitamin E include dry roasted sunflower seeds, peanuts, almonds, and hazelnuts; and vegetables, oils, and fruits, including spinach, wheat germ oil, broccoli, tomato, kiwifruit, and mango respectively. Recommended dietary allowance of natural Vit E is 22.4 IU, and synthetic Vit E is 33.3 IUs [108-110].

Vitamins	Constituents	Physiological Performance and Metabolic Function

Vitamin B Complex, a combination of eight water soluble vitamins	Composed of eight B-vitamins including vitamin B1 (thiamine),	1. Cellular health and integrity
	B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine),	2. Growth of red blood cells
	B7 (biotin), B9 (folic acid), and B12 (cyanocobalamin)	3. Boosts energy level
	Note: Methylcobalamin is unstable in a liquid (rapidly deconjugating) and therefore inappropriate for use in the VMP35.	4. Promotes cardiovascular health
		5. Boosts ocular health and neuronal functions
		6. Boosts digestion and healthy appetite
		7. Optimizes hormones and cholesterol synthesis
		8. Strengthens muscular integrity and muscle tone
		9. Fetal brain development and reduces of birth defects
Vitamin A, a fat soluble vitamin	Retinol, Retinyl esters and provitamin A carotenoids	1. Promotes ocular and bone health
		2. Boosts immune competence
		3. Protects against night blindness and age-induced decline
		4. Promotes healthy growth and reproductive health
		5. Reduces the risk of acne
Vitamin C, a water soluble vitamin	Ascorbic acid; Ascorbates	1. A potent antioxidant
		2. Boosts immune competence
		3. Promotes ocular and cardiovascular health
		4. Maintains healthy blood pressure
		5. Ameliorate iron deficiency
Vitamin D	Also, known as Calciferol, Cholecalciferol, and 1,25-Dihydroxycholecalciferol.	1. Maintains healthy bones and teeth.
(Classified as a prohormone, or precursor of a hormone)		2. Supports Immune and Neuronal Health.
		3. Boosts Pulmonary and Cardiovascular Functions
		4. Insulin Sensitizer
		5. Modulates genes involved in cancer development
Vitamin E	Alpha-tocopherol	1. Promotes healthy skin and eye
		2. Boosts cardiovascular health
		3. Promotes insulin sensitivity

Table 2: Vitamins in VMP35

MACRONUTRIENTS AND MICRONUTRIENTS

Calcium (as Calcium lactate)

Calcium bound to a ligand (as lactate in this instance) exists in a neutral state. However, on dissolution/ionization in the blood it carries a positive charge (Ca2+). Calcium plays integral roles in the (i) formation of strong bones and teeth; (ii) mobilization of skeletal muscle; (iii) stabilization of blood pressure; and (iv) as a pH buffer in the ion pool [111,112], the last two being the most dynamic and homeostatically active. A physiological condition of hypocalcemia or hypercalcemia occurs due an imbalance in calcium. A shortage of calcium availability in the blood stream causes hypocalcemia, which in turn causes hypoparathyroidism, kidney problems, pancreatitis, and prostate cancer, as well as malabsorption [113,114]. Hypercalcemia, an excessive amount of blood calcium, is associated with diverse diseases and dysfunctions ultimately leading to tuberculosis, lung and breast cancers, hyperparathyroidism, kidney diseases, and sarcoidosis. Too much use of calcium plus vitamin D supplements, antacids, theophylline, lithium-based medications, or selected water pills cause hypercalcemia [112-113].

Iodine (as Potassium iodide)

Iodine, an essential mineral, has been demonstrated to regulate hormones, fetal development, and several vital functions. It is a widely used method for brain disinfection. As a routine practice, 2% of liquid iodine tincture is added to water, while iodine tablets are also used. Iodine helps treat and prevent infections. Use of a tincture of iodine is well documented, which has been demonstrated to kill bacteria in and around mild cuts and scrapes. However, it shouldn't be used for deep cuts, animal bites, or burns [115,116].

Iodine plays an important role in thyroid health, cognitive performance, and hormone production, which regulates metabolism, cardiovascular and immune health [116]. It has been well demonstrated that an underactive (i.e., exhausted) thyroid gland can lead to hypothyroidism, so, appropriate iodine

supplementation is vital, while excessive iodine can impose a negative effect. Enlargement of the thyroid gland (due to excessive metabolic challenges), a condition termed as goiter, may result from either hypothyroidism or hyperthyroidism, an overactive thyroid gland. Enlargement of the thyroid gland may lead to non-cancerous thyroid nodules. Iodine-rich foods and supplements can reverse iodine-induced goiters. Radioiodine is a therapeutically used to treat thyroid cancer and hyperthyroid treatment [115,117].

Iodine is essential for neuronal development during pregnancy. The literature reveals iodine intake during pregnancy is intricately associated with birth weight and brain development in the fetuses, and iodine deficiency is linked to lower IQs. Iodine is recommended at a daily dose of 220 mcg during pregnancy, while 150 mcg/day is recommended for non-pregnant adults. During nursing, a daily amount of 290 mcg is recommended, which is very vital for infants till the babies reach 6 months of age [116,117].

Iodine supplementation is important for fibrocystic breast disease, which cause painful breast lumps. While megadoses of potassium iodide are associated with gastrointestinal upset, inflammation, and allergic reactions, the CDC recommends using iodine during nuclear emergencies. Potassium iodide is the recommended form to protect the thyroid gland from radiation injuries and radio waves from electro-magnetic fields (EMFs), so ubiquitously abundant in our modern society [115-117].

Selenium (as Sodium selenite)

It is an essential trace element, well demonstrated to scavenge reactive oxygen species, reduce DNA damage, and prevent cellular injury. It also performs diverse thyroid and metabolic functions, and boosts immunity. Low serum levels of selenium are associated with an increased risk of autoimmune thyroiditis and hypothyroidism [118]. Moreover, selenium supplementation helps the production of thyroid hormones. Also, selenium provides antioxidant protection mediated through selenoproteins, mainly through glutathione peroxidase and thioredoxin reductase. A deficiency in selenium is linked to diverse diseases, including cardiovascular disease and coronary artery disease, osteoarthritis, and cancer. Studies have demonstrated a high blood level of selenium is linked with reduced side effects in people undergoing radiation therapy, inflammatory responses, as well as a lower risk of certain types of cancer, including breast, lung, colon, cervical, uterine, and prostate cancers [118-121]. Studies have demonstrated that selenium supplementation reduces inflammatory marker C-reactive proteins (CRP), and increases the levels of glutathione peroxidase. Selenium may lower the risk of cardiovascular disease by reducing inflammation and oxidative stress. A 50% increase in blood selenium levels is associated with a 24% reduction in the risk of cardiovascular disease [120,121]. Oxidative stress and inflammation are intricately linked to atherosclerosis and buildup of arterial plaques leading to strokes, myocardial infarction, and diverse cardiovascular diseases. Several neurological diseases including Parkinson's, multiple sclerosis, and Alzheimer's diseases are associated lower blood levels of selenium. Selenium supplementation prevents mental decline and helps reverse memory loss in people suffering from Alzheimer's disease [121-123].

Copper (as Copper gluconate)

Copper, a vital micronutrient extensively available in all body tissues for proper organ function, is intricately associated in producing red blood cells and for the maintenance of neuronal cells, neurotransmitter function, in the formation of collagen, boosting immune health, and energy production, as well as in the formation of pigments and connective tissue [124]. It participates in diverse metabolic processes such as hemoglobin synthesis, absorption, and oxidation of iron, cellular respiration, peptide amination, antioxidant defense, and in the formation of pigments and connective tissues [125]. Metallothionine binds to copper to facilitate absorption across the GI mucosal border. Cellular uptake of dietary copper takes place via the Ctr1 transporter into the intestinal cells, while the excretion of copper occurs from the enterocytes via the Cu-ATPase and ATP7A into the blood [126].

A greater portion of copper is found in the hepatic, cardiovascular, and neuronal tissues, as well as in the kidneys and skeletal muscle. However, too much or too little copper affects the neuronal system, and is intricately associated with Menkes, Wilson's, and Alzheimer's diseases. Copper deficiency is mainly linked to cardiovascular dysfunctions [127]. Heredity (i.e. genetics) and nutritional deficiencies are the primary contributors to copper deficiencies. Copper deficiency is assessed by measuring serum copper, serum ceruloplasmin, and 24-hour urinary excretion of copper levels. Copper deficiency afflicts diverse physiological pathologies including bone marrow hematopoiesis, optic nerve function, and the nervous system [128]. Copper-deficient anemia is mitigated either by oral or intravenous copper supplementation in the form of copper gluconate, copper sulfate, or copper chloride [127,129]. Generally, hematological deficiencies are reversible following supplantation of dietary copper over a period of 4- to 12-weeks. However, copper supplementation can only partially reverse neurological disorders.

Magnesium (as magnesium lactate)

It plays an integral role in diverse metabolic activities including as a pH buffer in the blood [130], muscle performance, skeletal muscle contraction, and functioning and relaxation of selected smooth muscles; specifically the muscles surrounding the bronchial tubes in the pulmonary tissues as well as the excitation of neuronal cells [130-133]. In a physiological system, more than 300 enzymes require magnesium for diverse biochemical and catalytic actions. Furthermore, magnesium is a vital element for strengthening and structuring teeth and bones. In fact, teeth and bone contains 50% of the body's total magnesium. In a physiological state, magnesium bound to a ligand (i.e. protein or organic acid) is electrically neutral, and remains reserved in the teeth and bones, as well as bound to protein molecules. However, following its dissolution and/or ionization in body fluids and blood, magnesium carries a positive electrical charge [133-135]. Magnesium is absorbed from a human diet via a feedback mechanism that primarily depends

on the status and availability of magnesium in a human body. Food intake, as well as the quality and quantity, determines the blood content of magnesium, which, in turn, is metabolized and excreted in the urine and feces. Moreover, magnesium is greatly involved with the metabolism of calcium, sodium, and potassium, and is regulated by the kidney. Interestingly, feedback in homeostatic regulation finds that a little magnesium intake stimulates increased absorption from the intestine, while a large increase in magnesium intake decreases absorption [134].

Absorption, distribution, metabolism, and excretion of magnesium in a human body are largely associated with other electrolytes. Magnesium content in the blood stream largely depends on the physiological conditions (i) extremely high concentration of magnesium is known as hypermagnesia, which leads to diverse pathological conditions including diabetic ketoacidosis, adrenal insufficiency, and hyperparathyroidism. Hypermagnesemia can also be associated with hypocalcemia and hyperkalemia. (ii) Exceptionally low magnesium concentration is termed hypomagnesia. In fact, excretion of magnesium is subdued in kidney dysfunction of patients [130-133]. Overdose of dietary magnesium- or magnesium-based supplements induces an elevated magnesium level. Conversely, a reduced intake of dietary magnesium, as well as certain diseases or dysfunctions, and certain medications significantly decrease the ability of the intestine to absorb magnesium or increase the excretion of magnesium. It has been reported that hypomagnesia is greatly associated with diverse symptoms including cramps, nausea, vomiting, muscle weakness, breathing difficulties, confusion, arrhythmias, hallucinations, and seizures [133-134]. Hypomagnesia is also caused by an overdose of alcohol intake and associated malnutrition, chronic diarrhea, dehydration, and intake of diuretic medicines to control high blood pressure. It has been reported that about 50% of ICU patients have a greater possibility of becoming magnesium deficient [131-135].

Chromium (as Chromium (III) chloride)

Chromium (III) chloride is soluble and bioavailable in an aqueous Prodosomed solution, such as the VMP35 MNC. Chromium (III), an “essential trace element”, is essential for glucose and lipid metabolism and is required for normal protein, fat, and carbohydrate metabolism; as well as in lowering blood pressure and plasma cholesterols; enhancing insulin sensitivity, energy production, facilitating weight loss, increasing lean body mass; and reducing metabolic syndrome-associated risk factors [136,137]. Chromium (III) deficiency has been demonstrated to be associated with diabetes, high cholesterol, polycystic ovary syndrome, and many other conditions. A broad spectrum of investigations demonstrated that chromium (III) supplementation is effective in attenuating insulin resistance, improving insulin sensitization, and lowering plasma cholesterol levels [138]. Insulin resistance has been demonstrated to significantly contribute to metabolic syndrome, which consists of an array of metabolic aberrations including obesity, dyslipidemia, hypertension, and hyperglycemia. Furthermore, insulin resistance has been associated with the occurrence of cardiovascular disease, type 2 diabetes, and even exacerbates type 1 diabetes. As obesity and diabetes have become predominantly alarming in recent years, the scientific literature reveals that dietary interventions and regular exercise may improve body mass index and lipid profiles, as well as alleviate insulin resistance. In addition, insulin sensitizers may be beneficial in the prevention and treatment of obesity and type 2 diabetes [139]. Dr. Vincent highlighted that the transition of chromium (III) in the body, particularly in response to changes in insulin concentration, indicates that chromium (III) could act as a secondary messenger, amplifying insulin signaling [140].

One of our authors, et al., assessed the efficacy of the physiological benefits of niacin-bound chromium (III) supplementation on the transcriptome of subcutaneous fat of male obese diabetic Leprdb mice by high-throughput whole mouse genome expression utilizing microarrays in an unbiased genome-wide interrogation of the transcriptome [141]. Niacin-bound chromium (III) supplementation consistently altered the expression of a small subset (approximately 0.61%) of the 41,101 probe sets in the adipose tissues of the obese diabetic mice. Niacin-bound chromium (III) rendered a positive influence on the transcriptome of fat tissues with more up-regulated genes. Approximately 161 genes were up-regulated, and only 91 genes were suppressed by Niacin-bound chromium (III). Thus, a pronounced effect of chromium-gene regulation was observed by niacin-bound chromium (III) rather than a random, genome-wide perturbation caused by the supplement. Significant fold changes of the selected candidate genes were observed in the microarray screening, which were subsequently verified by RT-PCR analysis. Interestingly, niacin-bound chromium (III) supplementation upregulated muscle-specific genes including those involved in glycolysis, muscle contraction, muscle metabolism, and muscle cell development in the fat tissue. The literature demonstrates that adipose tissues are quite competent of differentiating into myocytes if appropriately triggered by myogenic signals. In these obese diabetic mice, following treatment with niacin-bound chromium (III), Enolase 3 (ENO3) was the most sensitive gene upregulated in the fat tissues of the obese diabetic mice. Incidentally, ENO3 encodes for the b-enolase subunit which accounts for more than 90% of the enolase activity in adult human muscle. In a clinical investigation, it was observed that a patient with mutation in the ENO3 gene, exerts reduced level of b-enolase enzyme in the muscle, exhibited exercise intolerance and myalgia. Glucose phosphate isomerase 1 (GPI1) gene, known to be involved in glycolysis, was up-regulated in the adipose tissue of the niacin-bound chromium (III)-supplemented obese diabetic mice. It is important to emphasize that glycolytic genes such as ENO3 and GPI have been found to be down-regulated in the visceral adipose tissues of morbidly obese individuals. Overall, this study established that niacin-bound chromium (III) supplementation facilitates the homeostasis of glycolysis mediated via up-regulation of ENO3 and GPI1 in these mice. Additionally, glucose transportation and metabolism to glucose-6-phosphate are essential for insulin regulation of calcium homeostasis in vascular smooth-muscle cells through a glucose-6-phosphate-dependent carbohydrate-responsive element in the calcium-ATPase gene. Niacin-bound chromium (III) is intricately associated with the enhancement of vascular smooth-muscle

cells calcium transport by stimulating plasmalemmal calcium-ATPase mRNA and protein expression. Niacin-bound chromium (III) induced calsequestrin expression, which is the most abundant calcium-binding protein responsible for calcium storage in the sarcoplasmic reticulum and that elevated intracellular free calcium level has been observed in adipocytes, it is plausible to speculate that niacin-bound chromium (III) supplementation decreases the free intracellular calcium level by increasing the levels of calsequestrins. Niacin-bound chromium (III) upregulated the expression of tropomyosin-1 (TPM1), which facilitates muscle contraction. Expression of these upregulated niacin-bound chromium (III)-specific myogenic genes in adipocytes has exhibited to reduce these fat cells [141].

Niacin-bound chromium (III) suppressed genes including cell-death-induced DNA fragmentation factor (CIDEA), thermogenic uncoupled protein 1 (UCP1), and tocopherol transfer protein (TTP). Incidentally, CIDEA is expressed at high levels in brown adipose tissue (BAT), which is the major site of adaptive thermogenesis. Incidentally, mice deficient in CIDEA are lean and resistant to diet induced obesity and diabetes. These CIDEA-knockout mice exhibit higher metabolic rate and lipolysis in BAT suggesting a functional role for CIDEA in modulating energy balance and adiposity. UPC1 is another niacin-bound chromium (III)-suppressed gene that is otherwise highly expressed in BAT. Indeed, ultrastructural analysis indicates that brown adipocytes contain numerous large mitochondria packed with UCP1. UPC1 has been found to mediate the thermogenic activity of BAT and impaired BAT activity has been proposed to play an important role in the development of obesity. TTP is involved in the transport of ?-tocopherol (vitamin E) from hepatocytes to peripheral tissues including adipose tissues which serve as the major a-tocopherol storage. Vitamin E readily interconverts and equilibrates between lipoproteins and TTP and is likely to be responsible for the incorporation of α-tocopherol into LDLs such that TTP facilitates the preferential enrichment of LDL with a-tocopherol. Down-regulation of TTP by niacin-bound chromium (III) supplementation is expected to reduce the level of LDL in the adipose tissues [141]. Interestingly, the lipid profile analysis revealed that LDL levels in the plasma of niacin-bound chromium (III)-treated obese diabetic mice were significantly reduced. Since α-tocopherol serves as potent antioxidant, down-regulation of TTP may decrease the lipid-phase antioxidant defense in the adipose tissue thereby facilitating adipose tissue breakdown. Overall, these data suggest that niacin-bound chromium (III) demonstrates its beneficial effects through regulation of specific genes in the fat cells of obese diabetic mice.

Potassium (as Potassium citrate)

Potassium is a very vital electrolyte and a nutrient. The recommended dietary allowance of potassium is approximately 3X that of calcium. It participates in various important biochemical and pathophysiological functions such as metabolizing sugar to glycogen to provide energy for regular activities including the relation of nerve impulses, muscle contractions, fluid and nutrient homeostasis and movement in and out of the cells, as well as regulation of blood pressure [142,143]. Blood potassium level is maintained in the normal range by the kidneys, but patients suffering from kidney diseases have a diminished capability to critically regulate and/or dispose of redundant potassium [143].

Potassium and sodium balance is important for performing diverse physiological functions. Accordingly, in a diet, the optimal ratio of potassium: sodium is very vital than the concentration of either micronutrient. In cellular system, the exchange between potassium and sodium takes place via transmembrane sodium-potassium pump mediated through ATPase enzyme [142,143].. It has been well exhibited that one ATP molecule is required for exporting three sodium ions and importing two potassium ions. Accordingly, the blood potassium level must therefore maintain in a ratio between 3.5 to 5 mmol/L [143].

A disruption in sodium and potassium equilibrium can lead to diverse disease conditions by either permitting as excess accumulation of sodium in the intracellular compartment and/or a shortage of intracellular potassium levels, leading to aggravation and exaggeration of the severity of disease pathologies.

Hypokalemia, a physiological condition of low potassium level, causes diverse adverse effects [149]. Although no signs and symptoms are observed in mild hypokalemia, however, moderate hypokalemia causes muscle weakness, fatigue and cardiovascular arrythmias, while fatal heart attack can result from extreme hypokalemia. It has been reported that several blood pressure and cardiovascular medications including enalapril, captopril and lisinopril, irbesartan, valsartan, and angiotensin receptor blockers, can significantly raise the blood potassium level. Increased level of potassium overload causes a significant inhibitory effect on intracellular pH buffering capabilities and ATP production [142-145].

Zinc (as Zinc sulfate)

Zinc, the second most abundant transition or post-transition metal, acts as an essential multipurpose trace element and nutrient, connected tissue repair, and essential constituent for cell growth and replication, which immensely contributes to human health. Basically, zinc regulates three vital biological roles, (i) as catalyst(s), (ii) maintain structural integrity, and (iii) as a regulatory ion. Zinc potentiates antioxidant functions, boosts immune health, ameliorating chronic diseases, acts as a membrane stabilizer, catalytic activation, and plays a vital role in the activity of a host of zinc metalloenzymes [146-148]. Zinc-binding motifs have been demonstrated to be abundant in several proteins encoded by the human genome physiologically, while free zinc is mainly regulated at the single-cell level [148,149].

It has been demonstrated that transportation of zinc occurs through proteins including macroglobulin, transferrin, and albumin, and stored in metallothionein and ultimately bound to proteins [147-150]. Zinc mainly binds to carboxylate-containing residues, histidines and cysteines, and is essential for the synthesis and functioning of DNA, RNA, collagen, antioxidant enzymes and proteins, as well as for the replication of cells and

gene expression [149]. More than twenty different DNA and RNA polymerases are known, which are integral for the maintenance of genetic integrity [149-151]. Zinc plays a vital role in the activation and functioning of a host of zinc metalloenzymes, and an integral constituent of the hormone insulin. More than 100 structurally diverse enzymes including alkaline phosphatase, aldol dehydrogenase, glutamic dehydrogenase, lactic dehydrogenase, carbonic anhydrase, carboxypeptidase, arginase, enolase, histidine deaminase, peptidases, and nucleic acid polymerases, are involved which are intricately connected with primary metabolic pathways [149].

This novel micronutrient constituent is essential for normal growth, skin and connective tissue repair, metabolism and reconstruction, and wound healing; for sexual development, to fight and combat infections, for night vision, sense of taste, construction of healthy epithelial tissue, and other vital functions. In fact, zinc deficiency can lead to an array of adverse genetic effects [150,151]. It has been well demonstrated that schizophrenia and allied dysfunctions may arise due to elevated levels of copper and decreased levels of zinc and manganese in the physiological system, while requisite corrections of these imbalances provide clinical improvements [146,149].

Overall, zinc acts as a unique trace element and plays a vital biological role in homeostasis, proliferation, and apoptosis, as well as ameliorating diverse degenerative diseases including cancer, diabetes, depression, Wilson's disease, Alzheimer's disease, and other advancing age associated distress and dysfunctions [148-151].

Micronutrients and Macronutrients	Constituents	Physiological Performance and Metabolic Function
Calcium	Calcium lactate	1. Strong bones and teeth
		2. Mobilizes skeletal muscle
		3. Stabilizes blood pressure
		4. Acts as a pH buffer in the ion pool
Iodine	Potassium iodide	1. Promotes disinfections in brain and other tissues
		2. Promotes cardiovascular, immune, and thyroid health
		3. Boosts metabolism
		4. Neuronal development during pregnancy
Selenium	Sodium selenite	1. Scavenges oxygen free radicals
		2. Reduces DNA damage
		3. Prevents cellular injury
		4. Boosts immune competence
		5. Promotes cardiovascular health
		6. Reduces inflammatory response
		7. Protects against neurological injuries
Copper	Copper gluconate	1. Promotes cellular respiration and antioxidant defense
		2. Enhances production of red blood cells
		3. Maintains neuronal health and neurotransmitter functions
		4. Boosts immune health
		5. Helps synthesize collagen
		6. Promotes energy homeostasis
		7. Builds and repairs connective tissues
Magnesium	Magnesium lactate	1. Boosts muscle performance including muscle contraction, functioning and relaxation
		2. Promotes bone and dental health
		3. Enhances neuronal functions
Chromium (III), an essential trace element	Chromium chloride	1. Boosts glucose and lipid metabolism
		2. Enhances insulin sensitivity
		3. Promotes lean body mass
		4. Boosts metabolism
		5. Essential for lipid, fat and carbohydrate metabolism
		6. Lowers blood cholesterol
Potassium	Potassium citrate	1. Boosts energy level and diverse physiological functions
		2. Metabolizes sugar
		3. Enhances energy production

		4. Potentiates muscular integrity and functions
		5. Promotes cardiovascular health
Zinc	Zinc Sulfate	1. Maintains structural integrity
		2. Acts as a membrane stabilizer
		3. Enhances cellular growth, metabolism, and replication
		4. Boosts immune competence
		5. Boost sexual competence and reproductive health
		6. Essential for neurological well-being and integrity
		7. Promotes wound healing

Table 3: Macronutrients and Micronutrients

MANUFACTURING TECHNOLOGY: NOVEL VMP35 MNC VITAMIN MICRONUTRIENT PHYTONUTRIENT PHOSPHOLIPID ENCAPSULATED NUTRACEUTICAL FORMULATION

This unique liquid formulation was manufactured by incorporating a novel proprietary SK713 SLP multi-lamellar clustoidal non-GMO phospholipid Prodosome nutrient absorption/delivery technology, a bio-degradable and biocompatible technology, in a multistep cGMP and NSF-certified manufacturing facility. In this multi-step process, the first step involves in the manufacturing of

SK713 SLP, which was performed using a minimum of 85% non-GMO phosphatidylcholine, and subsequently impregnated and saturated using solar-dried electrolytes to confirm the enhanced availability of free ions, which will amplify the ionic properties of the multi-lamellar clustoidal phospholipid spheres. The second step consists of thorough blending a combination of research-affirmed structurally diverse natural polyphenolic antioxidants, multivitamins, micro- and macronutrients, and standardized phytonutrients utilizing an advanced mixing/wet milling technology to create a nano-emulsion. The final step consists of a combination of specific blending, impregnation, and encapsulation technologies to obtain a novel multi-lamellar energetically fortified clustoidal 'Prodosomal' liposome-type encapsulated supplement (VMP35 Prodovite®).

Concept Validation Study

A concept validation open-label pilot study was conducted using VMP35 in conjunction with L-Lysine in a small population of volunteers infected with various herpetic infections. This investigation exhibited promising and favorable efficacy, which motivated us to conduct further research studies in human volunteers.

A RANDOMIZED CONTROLLED ONE-WAY CROSSOVER CLINICAL INVESTIGATION

A randomized controlled one-way crossover study was performed in a total of 38 male and female subjects (age: 22-82 years) to assess the clinical efficacy of an iron-free VMP35 MNC (1 oz dose swished in the mouth for 30 seconds and then swallowed) on blood oxygenation and hydration in the treatment group as compared to the water-control subjects at baseline (0 min), 5-min, and 30-min post-treatment, respectively. Necessary institutional review board (IRB) approval was obtained.

This study evaluated the absorption rate of the iron-free VMP35 and its effects on live human blood by assessing the changes in peripheral blood smears (PBS) from baseline (0 min) incorporating live blood cell imaging (LBCI) using phase contrast microscopy [Olympus BX-30 light microscope equipped with a phase contrast condenser (Tokyo, Japan) in conjunction with a 150-W lightbox and fiber-optic cable assembly] at 5-min post-control intake and 30-min post-VMP35 intake, respectively. It is important to indicate that the lens configuration was adjusted using a 10X eyepiece and 100X-oil immersion objective magnification to approximately ascertain a 1000-X magnification. Specifically, the lighting generated a superior level of cell definition, brightness, clear morphology, and can clearly and distinctly features of the cell membranes.

Significant efficacy of the iron-free VMP35 was observed on hemoglobinization, blood oxygenation, hydration, and neutrophil morphology at 5- and 30-min following a baseline evaluation, respectively. In fact, VMP35 instantly enhanced the morphological, hematological, and rheological properties of live human blood, and it can be concluded that the iron-free VMP35 produced adequate nutritional benefits to restore intracellular iron-dependent RBC hemoglobin within 5 min of intake, which was further sustained for an extended period. In addition, neutrophil white blood cells demonstrated dramatic improvement in numbers and morphology. No adverse events were observed.

An additional athletic case study and two concept validation Pilot Studies have been conducted in a diverse population of well-trained athletes to assess and confirm the effects of the World Anti-Doping Association ('WADA') compliant iron-free VMP35 on athletic performance.

ATHLETIC CASE STUDY

A well-trained athlete specializing in power lifting, certified in sports nutrition and personal training (AAAI/ISMA). He has used a very extensive supplement regimen to support his intense power lifting workouts over the previous 12 months of serious strength training. His personal best in squat weightlifting was 395 lbs. He was attempting to achieve a new personal record of

405 lbs. Prior to supplementing with the VMP35 MNC, to ensure his system was totally clean from any supplement influence, he did a 6-week washout and stopped taking the 20 other supplements his research indicated he should be using up to that time. Shortly before starting an intense Powerlifting workout session, he took 1-ounce of iron-free liquid VMP35, swishing it in his mouth 30 seconds before swallowing. He also added 1-ounce of VMP35 to his regular workout beverage and sipped on it between his sets of squats, swishing it each time briefly before swallowing. He ended his first workout session by achieving a squat lift of 515 lbs! (Contrary to peer warnings, the following day he had no muscle pain). In the following 2 weeks, he continued to experience strength increases in squat training exercises ranging from 545 lbs to 575 lbs (a 180 lb increase over the 395 lb personal best at baseline).

CONCEPT VALIDATION PILOT STUDIES

To confirm the veracity of the previous athletic case study, we conducted a 15-day concept validation pilot clinical investigation in three healthy young male athletes (age: 32-36 years), on the effects of WADA compliant iron-free liquid VMP35 in well trained athletes. Duly signed Informed Consent Forms were obtained from the study participants. Regulatory approvals were obtained and adverse events were critically monitored. The daily dose was 1-ounce consumed BID and swished in mouth for 30 seconds before swallowing. The first dose was about 20 to 30 minutes before engaging in an extremely rigorous exercise regimen. The second dose was consumed later that day. Over the course of the 15-day study, the most significant improvements were experienced within the first two days.

Subject #1

Before VMP35 supplementation, the first subject (male 36 years old) was struggling with 270 lbs. for 4 reps on the Hack Squat. After VMP35 supplementation, subject achieved 270 lbs. for 10 reps; rested, then the very next set increased to 320 lbs. for 10 reps. The 3rd and final set of that exercise, he increased the weight again to 360 lbs. for 8 reps.

Furthermore, another increase in strength was experienced in banded hammer strength incline press. Pre-PV, Subject was doing 180 lbs. for 10 reps, which was increased to 230 lbs. for 10 reps. Moreover, following VMP35 supplementation, respiratory capacity significantly increased.

Subject #2

On the banded reverse hack squat, Subject #2 (male, 32 years old) experienced a significant increase in strength. Pre-VMP35, he achieved a weight of 160 lbs. for one set of 8 reps. Post-VMP35 intake he increased to 180 lbs. for 2 sets of 10 reps.

On the Hammer Strength banded incline chest press, Pre-VMP35, subject's working weight sets were 160 lbs. Post-VMP35, his sets increased to 180 lbs. On side lateral dumbbell raises, Subject's working weight increased from 20 lbs. Pre-VMP35 to 25 lbs. Post-VMP35.

Subject #3

Pre-VMP35 Supplementation, the basic squat result for Subject #3 (male, 36 years old) was 405 lbs. for 10 Reps. Post VMP35, his squat weight increased significantly to 455 for 6 reps. He experienced an increase in muscle mass after VMP35 supplementation; a shorter recovery time between sets and after workout. Over the course of the 15 day study, Subject #3 also reported enhanced sleep quality, increased appetite, and consistently increased overall energy levels.

We also did a Pilot study evaluating the effects of the WADA compliant iron-free liquid VMP35 supplement in trained cyclists to confirm the beneficial effects across a range of athletic endeavors.

ATHLETIC CYCLISTS CASE STUDY

A 47-year old male cyclist consumed 1 oz bid of VMP35 for 2-consecutive weeks. His power output (W) improved from 317 to 325.5 (a 2.7% increase), and his heart rate increased by only 1%.

In another 52-year old male cyclist, who consumed 1 oz bid of VMP35 for 2-consecutive weeks his power output (W) improved from 225 to 241.5 (a 7.3% increase), while the heart rate reduced by 0.3%.

In another 39-year old male cyclist, who consumed 1 oz bid of VMP35 for 2-consecutive weeks his power output (W) improved from 262 to 286.5 (a 9.4% increase), while the heart rate reduced by 1.02%.

Subjects reported that their enthusiasm levels increased significantly. No adverse events were reported by these well-trained athletic cyclists.

Individual Case Study Reports

All case study reports obtained necessary permission from both the patients and supervised physicians.

Case Study #1 (An anemic stroke patient)

A 56-year old Caucasian male stroke patient (Norwich, NY) suffering from cerebral ischemia and anemia with an extremely low hemoglobin (Hb) level of 2.8 gm/dL consumed (????Oz of VMP35/day) over a period of six consecutive months. Following VMP35 supplementation over a period of six consecutive months Hb levels increased to 15.6 g/dL, while significant increases were observed in other parameters including RBCs to 5.01, Hematocrit to 45.9, Platelet Count to 202, and RDW to 12.9. An evaluation of brain MRI exhibited no signs of brain infarction, and a magnetic resonance angiogram (MRA) showed no signs of occlusion or hemodynamically significant stenosis of major intercranial arteries. These results strengthen that VMP35 can significantly enhance hematological characteristics.

Case Study #2 (A motorcycle accident victim)

A 33-year-old male subject (Lederach, PA) encountered a motorcycle accident on Oct 10, 2018, and admitted to Jefferson Hospital with serious life-threatening injuries such as profuse

bleeding between lungs and chest wall, collapsed lung, flail chest, fracture in the left acetabulum, and weakness. Clear signs of blood loss-induced anemia were evident from the hematological counts including hematocrit, and hemoglobin levels, and platelet, RBC, and white blood cell counts. Subject received 5-pint plasma infusion within a short span of the accident and undergone extensive surgical procedures. Subject started consuming 6 ounces of VMP35 per day from Oct 13 until Oct 25, and on the same day the subject was released from hospital and continued taking 4 ounces of VMP35 per day until Jan 31, 2019, and later continued taking a maintenance dose of 2 ounces/day. Along with physical therapy continued although the recovery process was extremely slow and walking only with assistance. It was predicted that the subject will not be able to move appropriately until the late of Spring of 2019.

However, VMP35 significantly accelerated recovery far beyond medical predictions for regaining vitality and optimal functional capabilities. Moreover, both hematocrit and hemoglobin levels remarkably improved including extensive repair of damaged blood vessels and injured tissues. Furthermore, platelet count was normalized.

CONCLUSION

Both people with serious health problems and extreme athletes have in common a need for increased nutritional support to provide nourishment for greater than routine health maintenance. Food sources for the masses include those provided by conventional agribusiness practices (i.e. using chemical fertilizers, pesticides, herbicides, fungicides, growth enhancers, GMO, gassing, irradiation, coloring agents, etc.), food processing (including blanching, preservatives, flavor enhancers, functional food additives, food colorings, etc.), food distributors, snack food products, and fast food outlets. Food stuffs from these sources are not only generally inadequate to meet the special and increased metabolic needs of these populations but are to some extent implicated as a cause of nutritional inadequacies and chemical/toxic insults underlying the shortfalls in both health and enhanced physical performance needs. Dietary supplementation is becoming increasingly commonplace to augment the aforementioned dietary practices and meet nutrition requirements in order to achieve even the minimal functional competence of human biology. It is practically mandatory that both people with chronic disorders and people who engage in more advanced and/or extreme athletic activities increase their nutritional resources through consuming various dietary supplements. The primary etiological factor underlying chronic degenerative diseases (CDD) is the increase in anaerobic events and pathologies; i.e. the inability to effectively use oxygen and water, and therefore nutrients, for cellular energy production, management, and waste removal. Anaerobic pathologies are the consequence of an overburdened pH buffering capability and generate a significant increase in reactive oxygen species (ROS). Given this, in addition to making healthier food choices, supplementation should include ingredients/products that restore aerobic metabolic events, minimizing free radical generation, and provide additional antioxidants to neutralize ROS as well. Clinical research, case studies, and concept validation pilot studies have demonstrated that a WADA compliant iron-free liquid VMP35 dietary supplement supplies an abundant reservoir of buffers to restore aerobic metabolism by restoring iron-dependent hemoglobin to RBCs, bolstering neutrophils in the blood (immune support), and significantly improving performance output in a diverse range of extreme athletes. The VMP35 provides a highly bioavailable source of vitamins, macro and trace minerals, ions, phospholipids, botanicals containing a wide range of evidence-based flavonoids, stilbenes, alkaloids, quinones, phytosaccharides, glycosides, sesquiterpenes, coumarins, polyacetylenes, carotenoids, etc.

Overall, these data strengthen the antioxidant and physiological benefits of structurally-diverse phytonutrients in the bioflavonoid-enriched VMP35 to achieve overall health maintenance for metabolic competence and athletic performance.

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