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Nutrition *Review Article*

Design of a Novel Bioflavonoid and Phytonutrient Enriched Formulation in Boosting Immune Competence and Sports Performance: A product Development Investigation

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ABSTRACT

An increase in anaerobic (oxygen-deprived) pathogenesis significantly increases the generation of reactive oxygen species (ROS) inflicting damage on cell membranes and intracellular constituents. Generation of ROS and concomitant inflammatory response is the two hallmarks of cellular damage caused by cellular injury or invasion by pathogens. Oxygen deprivation, as opposed to oxygen deficiency, is a major contributor to oxidative stress and damage, cytokine production, and inflammation. When our cells are unable to efficiently and effectively utilize the oxygen to facilitate aerobic glycolysis and other cellular metabolic events, the oxygen instead oxidizes cell membranes, lipids, neurons, cross-links proteins, damages DNA, and initiates inflammation among other consequences. These anaerobic events are hallmarks of chronic degenerative diseases (CDD). Excessive demands to curtail oxidative damage can overburden endogenous antioxidative capabilities. A key treatment strategy to tackle the adverse effects of inflammation involves the augmentation of the structural integrity and functional competence of cellular materials, reducing the impact and consequences of tissue insult; the generation of ROS; and the cascade of subsequent pathological disorders. Moreover, restoration of cellular aerobic metabolic events, such as aerobic glycolysis and oxidative respiration, is an equally important collateral goal. A healthy diet and supplementation, providing an abundance of exogenous sources of antioxidants and a host of phytochemical dietary components, becomes even more important to restore aerobic metabolism; augment and assist in improving cellular structural integrity, and thereby reducing oxidative stress, damage, and inflammatory sequela. VMP35 MNC, a research-affirmed Prodosomed nutraceutical technology-based phytonutrient formulation, enriched in structurally diverse bioflavonoids, polyphenols, and phenolic saccharides, etc., have been shown to boost cellular structural integrity and physiological functions, and restore aerobic metabolic competence including for athletic performance as well as for general well-being. This review provides a strategic approach for the design of a novel Prodosomed VMP35 Multinutrient/phytoceutical complex and to evaluate its ability to reverse anaerobic pathologies, including inflammation, and restore healthy cellular aerobic glycolysis.

Keywords: VMP35, Bioflavonoids, Phenolic saccharides, Prodosome®, Aerobic metabolism, Anemia, Sports nutrition, Athletic performance

INTRODUCTION

Oxidative damage is a universal antecedent to inflammatory sequel.[1,2] Oxygen deprivation, as opposed to oxygen deficiency, is a major contributor to reactive oxygen species generation (ROS), oxidative damage, cytokine production, and inflammation.[1,2] 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, neurons, cross-links proteins, and damages DNA among other consequences.[1] These anaerobic events are hallmarks of CDD and an indication that the body's own antioxidant defense systems, that is, superoxide dismutase (SOD), and GSH are overburdened. Dietary sources of antioxidants become even more important to augment and assist in reduction of oxidative stress, damage, and inflammatory sequel.[1,2]

MECHANISMS OF INFLAMMATION

Inflammation is a response of the immune system that is induced either because of an increase in anaerobic sequela, cellular/tissue damage, and/or through infection by a pathogen.[1-5] Inflammation occurs only when the insult is greater than the strength of cellular structures in tissues. This causes a cascade of events including redness, heat, pain around tissues and joints, swelling, capillary dilatation, leukocytic infiltration, and serves as a mechanism initiating the elimination of noxious stimuli and repair/healing/remodeling/restructuring of damaged cells or tissues.[1,3-6] Taken together, inflammation basically induces a sequela of defense mechanisms that are vital for human health.

KEY MEDIATORS OF INFLAMMATION

Role of cytokines

Cytokines are small chemical messengers released by immune cells that play important roles in mediating the innate immune response and as antecedents that catalyze inflammatory sequel.[1,4,5] Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself through a complex network of interactions. However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimate death.[3,5,6] An understanding of the regulation of cytokine pathways will allow for more accurate identification of agent-mediated inflammation and the treatment of inflammatory diseases.[1-5] Pro-inflammatory cytokines, such as interleukin-1beta (IL-1β), IL-6, IL-12, and IL-18, tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ), and granulocyte-macrophage colony stimulating factor (CSF), are signaling molecules that are secreted from immune cells such as helper T cells (T_h), macrophages, and certain other cell types that promote inflammation.[4-6] Major anti-inflammatory cytokines include IL-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13.[7] Interestingly, cytokine dysregulation has been linked to depression and other neurological disorders.[8] Maintaining pro-inflammatory and anti-inflammatory cytokine equilibrium is important to maintain optimal health.[3,4] Aging and exercise are also significant factors that increase the release of pro-inflammatory cytokines and promote inflammation.[1,4-6,9]

Chemokines, a specialized type of cytokine, are chemoattractant molecules that induce cell migration (chemotaxis) through the microcirculatory capillaries (i.e. "venules") from the blood into tissues and back out into the blood again. In addition, chemokines have a function in the nervous system as neuromodulators and also regulate lymphoid organ ontogeny and T-cell differentiation. They are also involved in tumor cell metastasis.[10] Chemokine messages are decoded by specific receptors that initiate signal transduction events leading to a multitude of cellular responses, leukocyte chemotaxis, and adhesion in particular.[11]

Role of adhesion molecules

The process of adhesion of leukocytes to the vascular endothelium is a key step in the inflammatory process. An array of cell adhesion molecules, members of a subgroup of an immunoglobulin (Ig) superfamily, including intercellular adhesion molecules (ICAM-1 and ICAM-2), vascular cell adhesion molecule 1 (VCAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), selectins (E-, P- and L-selectins), receptors of the Ig superfamily as well as integrins, are all intricately involved in diverse inflammatory responses.[11-14] It is important to emphasize that, especially selectins, the lectin-like adhesion glycoproteins initiate leukocyte rolling, which, in turn, dramatically reduce the velocity and rolling of leukocytes along the endothelial cell line to ensure firm adhesion. Moreover, E-selectin is expressed by the endothelial cells, while P-selectins can be expressed by both endothelial cells and platelets.[12,13] Following activation, endothelial cells upregulate the expression of multiple cell adhesion molecules and initiate the interaction of these cells with leukocytes. In conjunction, selectins, integrins, and the Ig gene superfamily adhesion receptors, mediate the different steps of the migration of leucocytes from the blood stream towards the inflammatory foci. Selectins, on the other hand, are associated with the initial interactions (tethering/rolling) of leukocytes with the activated endothelium, whereas integrins and Ig superfamily cell adhesion molecules mediate the firm adhesion of these cells and their subsequent extravasation.[14,15] During rolling, leukocytes are activated through the intracellular signals generated by cell adhesion molecules and chemokine receptors. Inhibition of the

expression of cell adhesion molecules has emerged as a new therapeutic target in inflammatory diseases.[12,13] The extent of endothelial fragility determines the magnitude of cell damage and the need for inflammatory and immunological responsively and repair. An array of nutraceuticals including flavonoids and phytochemicals protect against cell adhesion pathogenesis.

INFLAMMATION TYPES: ACUTE AND CHRONIC

Depending on the pathophysiological symptoms and the consequences involved therein, an inflammatory response can be categorized as either acute or chronic response. Acute inflammation causes warm, reddened, swollen tissues, and pain around tissues and joints, which occurs in response to an injury or toxic insult, while the immune system releases white blood cells to surround and protect the area.[16-18] Table 1 exhibits typical examples of acute inflammation. Acute inflammation helps the human body fight against diverse infections as well as assists in enhancing the healing process. On the other hand, when the propensity of inflammatory responses shoots up too high and/or lingers for a longer period, and the immune system continues to pump out white blood cells and chemical messengers that prolong the process, that pathology is referred to as chronic inflammation.[17,18] These pathological circumstances are the result of the immune system continuing the inflammatory fight indefinitely. During chronic inflammation, these vital roles can be switched to adaptive immune responses, which can lead to ongoing and excessive activation of innate immune cells. During chronic pathology, white blood cells may end up attacking nearby healthy tissues and organs.[17,18] Importantly, there are more visceral fat cells in obese and overweight individuals. The consequence of this is that the immune system recognizes those cells as a threat and attacks them with white blood cells. Thus, overweight, and obese individuals will be in a state of what will manifest as chronic inflammation. Studies have demonstrated that chronic inflammation is involved in diverse cardiovascular diseases and dysfunctions, diabetes, arthritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, and various cancers.[16-18]

Table 1: Acute versus chronic inflammation.

S. No.	Acute inflammation	Chronic inflammation
1.	Burns	Cardiovascular diseases
2.	Cuts, laceration, shooting, stabbing, etc.	Rheumatoid arthritis
3.	Infection	Autism
4.	Noxious chemical irritants	Depression
5.	Frostbite	Autoimmune diseases
6.	Allergic reaction	Neurological disorders
7.	Blunt force trauma	Alzheimer's diseases
8.	DNA damage	Cancer, Diabetes, etc.

A synchronized activation of diverse signaling pathways is involved in the regulation of inflammatory response in diverse human cells and tissues, while inflammatory cells are recruited from the blood.[19] As stated earlier, inflammatory response is involved in diverse chronic diseases and dysfunctions, which is mediated basically through the following discrete stages including (a) recognition of diverse detrimental stimuli by cell surface pattern receptors; (b) activation of inflammatory pathways; (c) recruitment of inflammatory cells; and (d) release of inflammatory markers.[19,20]

The inflammatory response is triggered by pathogen-associated molecular patterns via activation of germline-encoded pattern-recognition receptors (PRRs) expressed in both immune and non-immune cells, while selected PRRs capture various endogenous signals activated during tissue or cell damage, which are known as damage-associated molecular patterns (DAMPs)[21,22] [Figure 1]. DAMPs are host biomolecules that can launch and conserve a noninfectious inflammatory response. The different classes of PRR families include Toll-like receptors (TLRs), C-type lectin receptors, retinoic acid-inducible gene-I-like receptors, and nucleotide oligomerization domain-like receptors.[22,23] It is important to emphasize that in the absence of pathogens, innate inflammatory cells can also be recruited by disrupted cells by releasing DAMPs. Myeloid differentiation factor-88 (MyD88) in conjunction with TLRs activates an intracellular signaling cascade, which leads to nuclear translocation of transcription factors including activator protein-1 (AP-1), and nuclear factor-κB, (NF-κB) and interferon (IFN) regulatory factor 3 (IRF3)[21-23] [Figure 1].

Several intracellular signaling pathways such as mitogen-activated protein kinase (MAPK), NF-κB, and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathologies are involved.[24,25] in initiation of the inflammatory response along with a host of transcription factors such as NF-Kβ, AP-1, and IRF-3 [Figures 1 and 2]. These events turn on the expression of a variety of inflammatory genes, such as IL-1, TNF-α, IL-6, CSF, IFNs, transforming growth factor (TGF), and chemokines. A dysregulation in NF-κB, MAPK, or JAK-STAT activity is involved with diverse inflammatory, autoimmune, diverse metabolic diseases, cancer, and other degenerative diseases.[5,24-26] Several inflammatory proteins including C-reactive protein (CRP), haptoglobin, serum amyloid A, fibrinogen, and alpha 1-acid glycoprotein, help restore homeostasis and reduce microbial growth independently of antibodies during trauma, stress, or infection. Abnormal activation of certain enzymes such as high-mobility group box 1, SOD, glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase

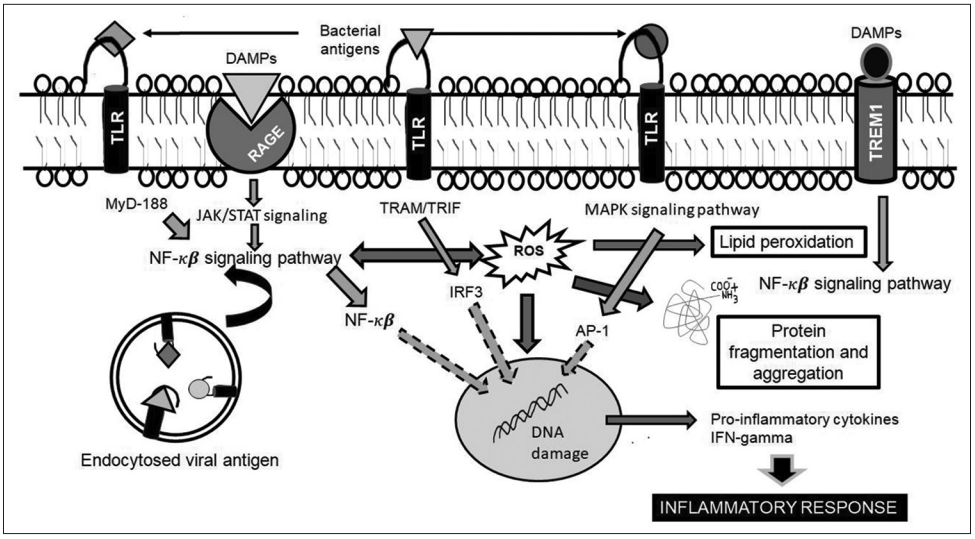

Figure 1: Cellular Inflammatory Response Pathway in response to damage and pathogen intrusion. TLR: Toll Like Receptor; DAMP: Damage Associated Molecular Pattern; RAGE: Receptor for Advanced Glycation End Product; TREM-1: Triggering Receptor Expressed on Myeloid cells 1; MyD-188: Myeloid Differentiation 188; JAK/STAT: Janus Kinases/Signal Transducer and Activator of Transcription proteins; NF-κB: Nuclear-Factor κB; TRAM/TRIF: TIRF related TIR-domain-containing Adapter-Inducing Interferon-β; MAPK: Mitogen activated Protein Kinase; ROS: Reactive Oxygen Species; IRF-3: Interferon Regulatory Transcription Factor-3; AP-1: Activator Protein -1; IFN-γ: Interferon-γ.

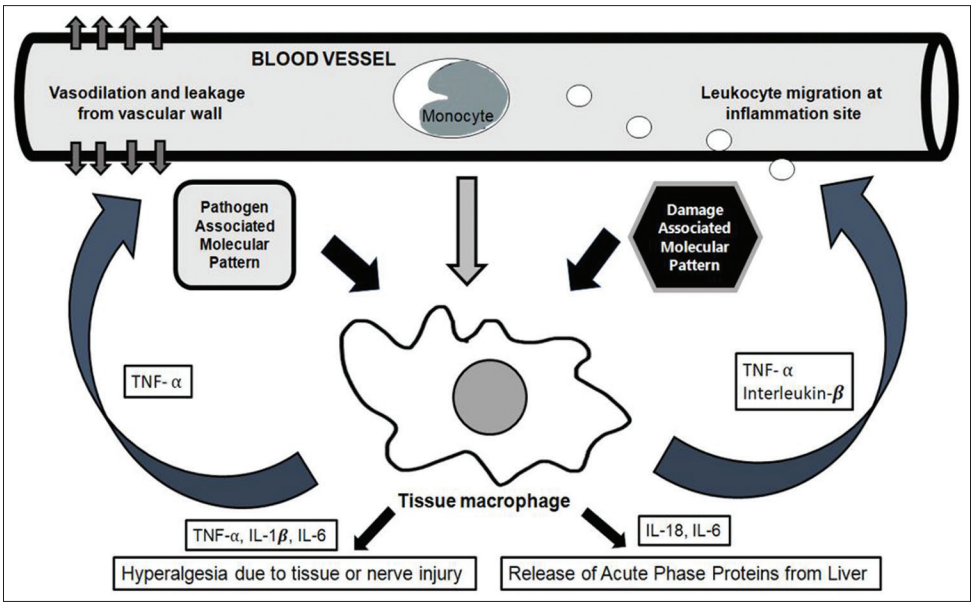

Figure 2: Events in tissue space mediated by the macrophage during acute inflammatory response. TNF: Tumor Necrosis Factor; IL: Interleukin.

(iNOS), and cyclooxygenase-2 (COX)-2, play key roles in the development of inflammation-related diseases[5,17,18] [Figure 1]. These inflammatory proteins and enzymes have been used in medicine as inflammation, infection, and trauma biomarkers. Moreover, antioxidant enzymes (i.e. SOD and GPx) play a key role in inhibiting oxidative stress. Elevated oxidative stress can induce enhanced production of ROS, malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine and isoprostanes, while every single one can activate various transcription factors, including NF-κB, AP-1, p53, and STAT.[5,17,18] Thus, oxidative stress can be a significant etiological culprit in the inflammatory process.[16-18] Under the conditions of severe oxidative stress, the body's endogenous antioxidant enzymes can be overburdened/exhausted [Figure 1].

Collectively, the inflammatory response involves a concerted response of many cell types.[16-18] at tissue injury sites; damaged

epithelial and endothelial cells release factors that trigger the inflammatory cascade, initiated by dendritic cells along with chemokines and growth factors, which attract neutrophils and monocytes. The first cells attracted to a site of injury are neutrophils, followed by monocytes, lymphocytes (natural killer cells, T cells, and B cells), and mast cells.[16-18] Monocytes can differentiate into macrophages and dendritic cells and are recruited through chemotaxis into damaged tissues. Inflammation-mediated immune cell alterations are associated with diverse diseases and disorders.[16-18] The tissue macrophages subsequently regulate a myriad of responses including hyperalgesia and release of acute phase proteins by the liver [Figures 1 and 2]. Moreover, an increase in anaerobic (oxygen-deprived) pathogenesis significantly increases the generation of ROS[16-18] and inflammatory events, which can only again be brought down by restoring cellular aerobic (glycolysis/oxidative respiration) metabolic sequel.[18] The patent-pending prodosomed nutra-phytoceutical technology has been shown to reverse anaerobic pathologies and restore healthy cellular aerobic glycolysis thereby reducing the need to initiate and/or perpetuate the extensive sequela of inflammatory events.[27-30]

THE ROLE OF GUT MICROBIOTA

The intestinal microbes living as commensals play a major role both in development of the body's immune network as well as in fending off the harmful pathogens. Lipopolysaccharides (LPSs) produced by the Gram-negative bacteria are an important component for development of the innate immune response, especially the gut associated lymphoid tissue.[14] Many microbial metabolites, especially the short chain fatty acids, also bring about differentiation of the T cells and are responsible for suppression of antigen presenting cells and pro-inflammatory cytokines. In this way, the immune cells can convert the secondary metabolites released by the gut bacteria into appropriate physiological response.[15]

EFFECTIVE PHYTONUTRIENT INTERVENTIONS

Selected botanicals rich in a wide range of phytonutrients, including bioflavonoids, stilbenes, and others active components, have been shown to improve the structural strength and functional competence of cells, tissues, organs, and systems of the body. Improving these properties lowers the need for, and potential, incidence, and extent of inflammatory events. Following are select water-extracted botanicals that have individually and collectively (in a Prodosomed® VMP35 multinutrient formulation) demonstrated antioxidative potential, inhibition of cell mutations, significant improvement in immune competence, hemoglobinization (collectively in the VMP35 formulation), and in reducing the need for initiating and/or prolonging inflammatory events.[27-30]

Astragalus membranaceus (family *Fabaceae*) root extract

This novel water-extracted medicinal plant [Figure 3] 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.[31,32] It also functions as an antioxidant and an immune modulator. Lee *et al*.[32] demonstrated that *A. membranaceus* root is enriched in five cycloartane glycosides including agroastragaloside I, agroastragaloside II, isoastragaloside II, astragaloside IV, and astragaloside V, which demonstrated potent anti-inflammatory potential as demonstrated by their potent inhibitory effect on LPS-induced nitric oxide production in RAW264.7 macrophages. In another independent investigation, Lai *et al*.[33] reported that *A. membranaceus* contains five isoflavonoids and eight saponins, which exhibited potent anti-inflammatory efficacy by inhibiting the release of inflammatory mediators and inactivation of NFκB through MAPK signaling pathway.

It is well established that *A. membranaceus* 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[34,35] demonstrated that *A. membranaceus* strengthened immunological function, promoted the discharge of pus, and the growth and regeneration of new tissue.

This novel medicinal plant is comprised flavonoids, saponins, phytosaccharides, amino acids, and isoflavan glycosides.[31,35] Ono *et al*. reported[36] that AM exhibits potent anti-viral and immunostimulatory properties and inhibits murine retroviral reverse transcriptase and human DNA polymerase activities.

Figure 3: *Astragalus membranaceus* (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/astragalus-membranaceus.html

Astragalus-based treatments have demonstrated significant amelioration of toxicity induced by other concurrently administered immunosuppressants and cancer chemotherapeutics.[37] Furthermore, Auyeung *et al*. (2016) elaborated its antitumorigenic mechanisms in ameliorating various gastrointestinal cancers and disorders.[37] 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, *A. 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[38] that *P. multiflorum* [Figure 4] 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.[38,39] Furthermore, Fo-Ti promotes rejuvenating effects on the nerves, brain cells, and endocrine glands.[40] It supports and promotes competent adrenal function and helps detoxify the body.[41] It is also reported to boost immune function and increase sexual vigor;[42] be a blood toner, improve cellular energetics, and fortify muscles, tendons, and bones.[43]

P. multiflorum significantly inhibited LPS-iNOS and COX-2 protein and mRNA expression, as well as inhibited nitric oxide and prostaglandin E2 production. LPS-induced NF-κB transactivation and nuclear translocation were significantly inhibited.[44] Concomitantly, phosphorylation of JAK-signal transducers and activators of transcription and LPS markedly upregulated MAPKs; however, it was dose-dependently inhibited by *P. multiflorum* extract. These researchers also demonstrated that *P. multiflorum* can induce Phase II antioxidant enzymes, including heme oxygenase-1 (HO-1) and NADPH dehydrogenase quinone-1 (NQO-1). *P. multiflorum* treatment activated Nrf2 pathway, while it exerted anti-neuroinflammatory efficacy mediated through Nrf2, HO-1, and NQO-1 siRNA. These molecular mechanisms exhibited potent anti-inflammatory efficacy of *P. multiflorum*.[44]

Figure 4: *Polygonum multiflorum* (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/polygonum-multiflorum.html

Water-extract of *Camellia sinensis* (family *Theaceae*) (well-known as Green Tea) leaf [GTE]

Green tea [Figure 5] has powerful antioxidant properties owing to its potent content of polyphenols, especially epigallocatechin gallate (EGCG).[45-47] These polyphenols are beneficial bioflavonoids that 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.[45,48,49] Chronic consumption of the decaffeinated form of a standardized green tea extract removes the genetically adversarial stimulatory effects of caffeine. In rodents, *C. sinensis* potently inhibited arachidonic acid-induced paw edema and this anti-inflammatory efficacy is mediated through inhibition of COX and lipoxygenase pathways of arachidonic acid metabolism.[50]

Matricaria chamomilla (family *Asteraceae*) (well-known as Chamomile) flower water extract

M. chamomilla [Figure 6] 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,

Figure 5: *Camelia sinensis* (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/camellia-sinensis.html

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.[51] 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.[52,53] Miraj and Alesaeidi[54] discussed the potent anti-inflammatory efficacy of chamomile flavonoid apigenin-7-glucoside in mice through a reduced production of TNF-α following LPS treatment. These researchers also demonstrated potential antimicrobial and anti-inflammatory properties.

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

The phytochemical constituents in *R. canina* [Figure 7] include 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 COX-2. *R. canina* 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 sequel.[55-58] 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 *R. canina* exerts potent analgesic, anti-arthritic, anti-inflammatory, anti-oxidative, and bone-preserving activities.[5-58] These citrus bioflavonoids exhibit repair, re-structuring, regenerative, re-vitalizing, and rebuilding of tissues, as well as strengthening connective tissues.[57-61] *R. canina* reduces the fragility and susceptibility of connective tissues to injury from airborne, topical contact, and orally ingested allergens,[61,62] and therefore reduces the potential for initiating and/or prolonging inflammatory events. Larsen *et al*.[63] isolated galactolipid (2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-O-beta-d-galactopyranosyl glycerol from *R. canina*, which exhibited potent anti-inflammatory efficacy in peripheral human blood neutrophils *in vitro*. In another study, Rose hip constituents were demonstrated significant efficacy in protecting protection by modulating cytokine, and chemokine expression.[64] Concurrently, Lattanzio *et al*.[65] demonstrated potent anti-inflammatory efficacy of *R. canina* and indicated its possible potential role in therapeutic treatment inflammatory diseases.

Water extract of *Eleutherococcus senticosus* (family *Araliaceae*) (known as Eleuthero) root extract

E. senticosus [Figure 8], a novel functional food from ancient times has been reported to 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.[66] *E. senticosus* is widely used in China, Korea, Japan, and Russia. *E. senticosus* 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

Figure 6: *Matricaria chamomilla* (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/matricaria-chamomilla.html

Figure 7: *Rosa canina* (Source: pixabay.com: Google image). https://pixabay.com/photos/search/rosa%20canina/

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.[67,68]

E. senticosus has long been used as a potent immunomodulator, an anti-inflammatory agent and an anti-rheumatic agent in oriental medicine. Jung *et al.*[69] assessed the protective efficacy of *E. senticosus* root extract on the expression of iNOS and COX-2 in LPS-activated macrophages, as well as investigated its involvement in MAPKs and Akt signaling pathways. These researchers demonstrated that downregulation of inflammatory iNOS expression occurs by *E. senticosus* mediated through by blocking JNK and Akt activation.[69]

Water-extract of *Crataegus oxyacantha* (family *Rosaceae*) berry (known as Hawthorn berry [HB]) extract

HB [Figure 9] 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, 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.[70,71] HB supports digestion and cardiovascular function.[72] 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."[70,73]

Tadic *et al.*[74] demonstrated the potent dose-dependent anti-inflammatory efficacy of HB extract in carrageenan-induced rat paw edema.

Figure 8: *Eleutherococcus senticosus* (Source: dreamstime.com: Google image). https://www.dreamstime.com/acanthopanax-senticosus-also-called-siberian-ginseng-eleutherococcus-senticosus-berries-widely-used-herb-traditional-image100716623

In another independent study, Li *et al.*[75] exhibited the inhibitory efficacy of HB extract on IL-6. IL-1b, TNF-α, and COX-2 genes, as well as NO production in RAW 264.7 cells. Nazhand *et al.*[76] summarized the potent anti-inflammatory mechanisms of HB.

Water-extract of *Centella asiatica* (family *Apiaceae*) (known as Gotu Kola) whole herb extract

C. asiatica [Figure 10], a triterpene-rich medicinal plant, and has been extensively used in both traditional Ayurvedic medicine and in Traditional 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"[77] as

Figure 9: *Crataegus oxyacantha*, also known as Hawthorn berry (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/crataegus-oxyacantha.html

Figure 10: *Centella asiatica*, also known as Gotu kola (Source: dreamstime.com: Google image). https://www.dreamstime.com/photos-images/centella.html

well as diverse neurological, dermatological, and metabolic dysfunctions.[78] CA 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.[77,78] Overall, CA exerts potent cardioprotective, anti-atherosclerotic, antihypertensive, antihyperlipidemic, antidiabetic, antioxidant benefits. Moreover, it reduces fatigue, 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, CA is reported to exert a calming effect and thus helps support restful sleep. It is widely used in yoga and meditative practices.[79] Diverse therapeutical and anti-inflammatory properties of *C. asiatica* have summarized by numerous independent researchers.[80] Another investigation exhibited that C. asiatica inhibits inflammation and promotes insulin sensitivity in LPS-induced 3T3-L1 adipocytes and RAW 264.7 macrophages.[81] Park *et al.*[82] demonstrated that *C. asiatica* potently inhibited LPS-induced NO production, i-NOS, COX-2 and NF-κB as well as release of TNF-α, IL-1β, and IgE.

Water-extract of *Zingiber officinale* (family *Zingiberaceae*) (well known as Ginger) root

The rhizomes (i.e. "roots") of ginger [Figure 11] 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 such as constipation, dyspepsia, belching, bloating, gastritis, epigastric discomfort, gastric ulcerations, indigestion, nausea, and vomiting.[83-85] 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.[83-85] 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.[86] Ginger also supports controlled and voluntary muscle strength and stability, as well as boosts sports performance.[87,88]

Figure 11: *Zingiber officinale*, also known as Ginger (Source: kindpng.com: Google image). https://www.kindpng.com/imgv/wJoJTR_ginger-transparent-free-png-use-ginger-for-arthritis/

Jafarzadeh and Nemati[89] exhibited that supplementation of ginger inhibited the LPS-induced NO production, as well as iNOS and COX-2 expression in RAW 264.7 macrophage cells. Furthermore, ginger inhibits the release of TNF-α, NF-κB signaling, IL-1β, and IgE. Kulkarni and Deshpande[90] demonstrated that ginger supplementation potentially inhibited TNF alpha, ferritin and MDA in human volunteers.

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

Elderberry [Figure 12] 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.[91,92]

Elderberry promotes cellular integrity and overall health by mitigating inflammatory events, boosting immune function, reducing the need for water retention and congestion.[93] 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.[92]

S. nigra exhibited anti-inflammatory efficacy in both *in vitro* and *in vivo* models.[94] Tiboc Schnell *et al.*[95] demonstrated

Figure 12: *Sambucus nigra,* also known as Elderberry (Source: pixabay.com: Google image). https://pixabay.com/photos/elder-elderberries-sambucus-nigra-1609129/

that *S. nigra* reduced oxidative stress and inflammatory response by modulating IL-6, TNF-α, and IL-1β. Furthermore, it modulated MMPs expressions, suggesting its beneficial role in tissue remodeling in systemic inflammatory response.

Furthermore, VMP35 is enriched in two proprietary phytochemical ingredients including BioAloe® DSR0114 and Proligna (poly-phenylpropanoid polysaccharide complex [PPC]), an LPC108 with potent anti-inflammatory and immunomodulatory benefits.

BioAloe®, a DSR0114 inner leaf water extracted freeze-dried gel from aloe vera rich in polysaccharides and acemannan (~18%)

This immunomodulatory, water-soluble, Aloin free (<0.00142%), safety-affirmed aloe polymannose multinutrient complex, with no laxative effects or bitter taste, was shown to enhance immune competence, anti-inflammatory efficacy, and cognitive function. Lewis *et al*.[96] conducted a human clinical study in 34 subjects (n = 34, male = 6, female = 28, Mean age = 79.9 years) over a period of 12 months. All subjects orally consumed one teaspoonful BioAloe powder 4 times/day over a period of 0, 3, 6, 9, and 12 months of treatment. Subjects exhibited remarkable decreases in TNF-α, vascular endothelial growth factor, and IL-2 and-4. CD90+, CD95+CD3+, CD95+CD34+, CD95+CD90+, CD14+CD34+, CD14+CD90+, and CD14+CD95+ decreased significantly, whereas CD14+ significantly increased. Thus, BioAloe demonstrated significant enhancement of immune competence, anti-inflammatory efficacy, and cognitive performance.

Proligna (PPC), a LPC108 scotch pine-cone water extracted freeze dried powder rich in lignans and monosaccharides

Bradley *et al*.[97] conducted extensive investigation on this aqueous extract of pine cones termed PPC, which demonstrated that PPC promotes immune cell development in both human and animal models and has pronounced ability of rapid differentiation of human peripheral blood mononuclear cells into mature dendritic cells.[97,98] A battery of toxicological assessments demonstrated its broad-spectrum safety. In another independent study, Abe *et al*.[99] exhibited the potent anti-parasitic activity of PPC as demonstrated by oral administration in mice.

PPC supplementation (oral) remarkably inhibits serum IgE levels in naïve mice and in ovalbumin-sensitized mice, as well as enhance the production of antigen-specific CD8+ T cells in mice immunized with DNA, dendritic cell, and soluble protein vaccines.[100] Moreover, antigen-stimulated splenocytes from PPC-treated mice exhibited that inhibition of IgE is associated with a decrease in IL-4 secretion with the enhanced production of IL-12 and IFNγ. In aged mice, PPC reduced the Th2 response and elevated Th1 response in the splenocytes. In another independent study, PPC-exhibited potent inhibitory effect on LPS-induced activation of TLR-2 and TLR-4/MyD88/NF-κB pathway. This mechanistic event exhibits its potent inhibitory effect in rheumatoid arthritis patients. Because elevated levels of TLR-2 and inflammatory cytokines were observed in the macrophages of rheumatoid arthritis patients.[101]

VITAMINS

Vitamin B complex

Vitamin B complex consists of eight B vitamins including Vitamin B1 (thiamin hydrochloride), Vitamin B2 (riboflavin), Vitamin B3 (niacin and 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.[102-105] 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.[103-105]

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.[106,107] 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; and (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.[106-109] 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.[108,109]

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.[110-112] Vitamin C is a well-established antioxidant, a potent free radical scavenger with remarkable immune enhancing properties and prevents cellular oxidative damage.[110-112] 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.[111-113] 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. Meng *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.[113-115]

Vitamin D

Approximately 75% people in the USA have low levels of vitamin D,[116] 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.[116-119] 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.[116-119] 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.[119] In a clinical investigation, Okereke and Singh exhibited the efficacy of Vitamin D in improving mood and lowering depression risk in older adults.[118]

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).[120-124] 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.[122-125]

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, and (g) diverse environmental stressors including UV radiation, cigarette smoke and environmental pollutants, and furthermore, Vitamin E boosts immune health.[123-125] 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.[125-128]

MACRONUTRIENTS AND MICRONUTRIENTS [TABLE 2]

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 (Ca^{2+}). 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,[129,130] 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.[130,131] 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.[131,132]

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 should not be used for deep cuts, animal bites, or burns.[133,134]

Iodine plays an important role in thyroid health, cognitive performance, and hormone production, which regulates metabolism, cardiovascular, and immune health.[133-135] 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.[133-135]

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.[134,135] 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, so ubiquitously abundant in our modern society.[133-135]

Selenium (as Sodium selenite)

It is an essential trace element, well demonstrated to scavenge ROS, 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.[136] Moreover, selenium supplementation helps the production of thyroid hormones. Furthermore, selenium provides antioxidant protection mediated through selenoproteins, mainly through GPx 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.[136-139] Studies have demonstrated that selenium supplementation reduces inflammatory marker CRP, and increases the levels of GPx. 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.[138,139] 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.[139-141]

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.[142,143] 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.[144] Metallothionine binds to copper to facilitate absorption across the GI mucosal border. Cellular uptake of dietary copper takes place through 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.[144,145]

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.[145,146] 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-h urinary excretion of copper levels. Copper deficiency afflicts diverse physiological pathologies including bone marrow hematopoiesis, optic nerve function, and the nervous system.[146] Copper-deficient anemia is mitigated either by oral or intravenous copper supplementation in the form of copper gluconate, copper sulfate, or copper chloride.[145-147] In general, hematological deficiencies are reversible following supplantation of dietary copper over a period of 4–12-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, muscle performance, skeletal muscle contraction, and functioning and relaxation of selected smooth muscles;[148,149] specifically, the muscles surrounding the bronchial tubes in the pulmonary tissues as well as the excitation of neuronal cells.[148-151] 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.[149-151] Magnesium is absorbed from a human diet through 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.[152]

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.[148-151] 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.[151-153] 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.[149-153]

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.[154,155] 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.[155,156] 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.[156,157] 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.[158]

Bagchi, *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 $Lepr^{db}$ mice by high-throughput whole mouse genome expression utilizing microarrays in an unbiased genome-wide interrogation of the transcriptome.[157,159] 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 upregulated, 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 upregulated 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 downregulated 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. In addition, 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, which facilitates muscle contraction. Expression of these upregulated niacin-bound chromium (III)-specific myogenic genes in adipocytes has exhibited to reduce these fat cells.[157,159]

Niacin-bound chromium (III) suppressed genes including cell-death-induced DNA fragmentation factor (CIDEA), thermogenic uncoupled protein 1 (UCP1), and TTP. Incidentally, CIDEA is expressed at high levels in brown adipose tissue (BAT), which is the major site of adaptive thermogenesis.[155] 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 a-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.[159] 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, downregulation of TTP may decrease the lipid-phase antioxidant defense in the adipose tissue thereby facilitating adipose tissue breakdown. Overall, these data suggest[159] 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.[160-162] 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.[160,161]

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 through transmembrane sodium-potassium pump mediated through ATPase enzyme.[161,162] 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 and 5 mmol/L.[162] 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.[160-162]

Hypokalemia, a physiological condition of low potassium level, causes diverse adverse effects.[161-163] Although no signs and symptoms are observed in mild hypokalemia, moderate hypokalemia causes muscle weakness, fatigue and cardiovascular arrhythmias, 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.[161-162]

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 key role in the activity of a host of zinc metalloenzymes.[164-167] 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.[164-166]

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.[165-168] 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.[164] More than twenty different DNA and RNA polymerases are known, which are integral for the maintenance of genetic integrity.[164,168,169] Zinc plays a key 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.[164-168]

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.[165,166,169] 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.[165,166]

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.[165,167-169]

Manganese (as Manganese sulfate)

The trace mineral manganese performs several biochemical and pathophysiological functions, including the metabolism of amino acids, cholesterol, glucose, and carbohydrates, and plays a pivotal role in bone formation, immune boosting, anti-inflammatory status, blood sugar regulation, and in the prevention of blood clotting.[170,171] This is a vital counterpart of MnSOD, which is integral for scavenging ROS in mitochondrial oxidative stress.[171] Manganese also is required for the synthesis of amino acid proline, which plays an important role in wound healing through enhanced collagen formation. Although, it should be used in requisite dose as higher dose can induce oxidative stress and cellular injury.[170,171]

APPLICATION OF NOVEL PRODOSOME TECHNOLOGY IN VMP35 FORMULATION

The prodosome technology is an important segment of a patent-pending VMP35 MNC technology to ensure the greatest potential absorption of the nutra/phytoceutical ingredients, including vitamins, macro- and trace-minerals, bioflavonoids, and other phytoceuticals. This process involves the creation of structured water, the impregnation and saturation of phosphatidylcholine-rich phospholipids with free ions; their incorporation into the structured water; the nano-emulsification of all the active ingredients; and their incorporation into the ion-impregnated phospholipid medium to ensure the formation of a highly absorbable multi-lamellar clustoidal Prodosomed nutraceutical technology.[27-30,172]

MECHANISTIC EVENTS

Oxidative damage is a universal antecedent to inflammatory sequel.[1,9] While inflammation catalyzes downstream events, it is not the initiating event; it is a responsive event.[2-7,16-18] Other than blunt force trauma and other types of acute injury, the etiological factor that initiates the entire sequence of immunological and inflammatory events is the progressive transition from cellular aerobic metabolism to oxygen deprivation-induced anaerobic metabolism, which distresses pH homeostasis and creates a chain reaction of immunological events.[39,75,76] Inflammation is a complex variety of processes carried out through a sequela of events that result from a loss in the availability of oxygen (e.g. in the case of blunt force trauma) or a loss in the ability to effectively utilize oxygen; the latter case being far more prevalent.[16-18] Essentially, the terms anaerobic, hypoxic, and acidic all indicate an inability to effectively utilize cellular oxygen; that is, involving both acute and chronic oxygen deprivation. The inability to effectively utilize oxygen results in an increase in oxygen free radicals, called ROS.[28,29]

As oxygen cannot be effectively utilized in an anaerobic environment, it still oxidizes/damages biological components (i.e. cell membranes, lipids, cross links proteins, and damages DNA) and upregulates activation of endogenous antioxidant enzymes such as SOD, GSH, GPx, and NOX.[9-13] Moreover,

Table 2: Macronutrients and micronutrients.

Micronutrients and Macronutrients	Constituents	Physiological Performance and Metabolic Function
Calcium[129-132]	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[133-135]	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[136-141]	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[142-147]	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[148-153]	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[154-159]	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[160-163]	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[164-169]	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
Manganese[170,171]	Manganese sulfate	1. Immune Booster 2. Metabolism of amino acids, cholesterol, glucose and carbohydrates 3. Bone formation 4. Insulin sensitizer 5. Anti-inflammatory 6. Enhance collagen synthesis 7. Promotes wound healing 8. Antioxidant

cell and tissue damage are directly proportional to the fragility of cells and the tissues in which they reside. The more fragile the tissues are, the more consequential the oxidative damage will be on the cells/tissues, and the greater the

resulting inflammatory response will be.[1,2] This paradigm is also evident for exacerbation of allergy sensitivities and allergic reactivity's.[21,44]

Following an insult that impairs cellular aerobic metabolic events, compensatorily increasing anaerobic events, cytokines are activated. They initiate an important role in mediating the innate immune response and as antecedents that catalyze inflammatory sequel.[1,4,5] Cytokines regulate inflammation itself through a complex network of interactions. Immune cells release different inflammatory cytokines including monocytes, macrophages, and lymphocytes. Inflammatory cytokines are classified as ILs, CSF, IFNs, TNF, TGF, and chemokines, all of which are generated mainly by cells that recruit leukocytes to the site of infection or injury.[3-8,11,12]

Chemokines are specialized cytokines that are chemoattractant molecules, inducing cell migration (chemotaxis) through the microcirculatory capillaries (i.e. "venules") from the blood into tissues and back out into the blood again.[9-12] In addition, chemokines have a function in the nervous system as neuromodulators and regulate lymphoid organ ontogeny and T-cell differentiation.[9-12]

Inflammatory mediators including cytokines such as IL-1β, IL-6, and TNF-α, induce inflammatory responses through interaction with TLRs, IL-1 receptor (IL-1R), IL-6R, and TNF receptor.[4-8] Several intracellular signaling pathways such as MAPK, NF-κB, and JAK-STAT pathologies are involved.[24,25] Moreover, transcription factors regulate a variety of inflammatory genes, such as IL-1, TNF-α, IL-6, CSF, IFNs, and TGF, among others. Chemokine messages are decoded by specific receptors that initiate signal transduction events leading to a multitude of cellular responses, leukocyte chemotaxis, and adhesion molecule activation in particular.[9-12]

The process of adhesion of leukocytes to the vascular endothelium is a key step in the inflammatory process. An array of cell adhesion molecules, including ICAM-1 and ICAM-2, VCAM-1, ELAM-1, selectins (E-, P- and L-selectins), receptors of the Ig superfamily as well as integrins, is all intricately involved in diverse inflammatory responses.[12,13] Cytokine dysregulation, and the sequential and collateral downstream consequences are hallmarks of unremittent inflammatory pathologies characteristic of CDD.[5-9]

DISCUSSION

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.[2] These populations experience a much greater incidence of anaerobically induced inflammatory disorders and diseases than other populations. 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, and coloring agents), food processing (including blanching, preservatives, flavor enhancers, functional food additives, and food colorings), 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 dietary practices and meet nutrition requirements 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 CDD is the increase in anaerobic events and pathologies, that is, 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 ROS.[1,2] Given this, in addition to making healthier food choices, supplementation should include ingredients/products that have been shown to restore aerobic metabolic events, thereby minimizing free-radical generation, and provide additional antioxidants to neutralize ROS as well.

The patent-pending iron-free VMP35 MNC has demonstrated a remarkable ability to restore iron dependent hemoglobin to RBCs, improving aerobic metabolism, neutrophil morphology, and functionality, and improving performance output in well-trained athletes among other benefits.[28-31,172] Rich in phytonutrients, including flavonoids and a comprehensive range of other phytochemicals, the VMP35 MNC enhances the structure and function of cells and reduces oxidative damage also reducing the need to induce the sequela of inflammatory events.[1-7]

CONCLUSION

When our cells are unable to efficiently and effectively utilize oxygen to facilitate aerobic glycolysis and other cellular metabolic events, the oxygen instead oxidizes cell membranes, lipids, neurons, cross-links proteins, damages DNA, and initiates inflammation among other consequences. These anaerobic events are hallmarks of CDD. Inflammation is triggered when a cellular insult is greater than the strength of cellular membranes and intracellular structures to withstand it. Inflammation occurs because of

cellular/tissue damage following a harmful stimulus, such as pathogens, toxic manifestations and compounds, irradiation, as well as blunt force trauma and other types of cellular injury including infection. The sequela of inflammatory events involved in acute and chronic inflammation, include the production of a range of immune molecules such as leukocytes, cytokines, chemokines, adhesion molecules, and an array of enzymes, such as matrix metalloproteinases, and others. The patent-pending Prodosomed iron-free VMP35 MNC, rich in phytonutrients, including flavonoids and a comprehensive range of other phytochemicals has demonstrated a remarkable ability to restore iron dependent hemoglobin to RBCs, improving aerobic metabolism, neutrophil morphology, and functionality, and improving performance output in well-trained athletes among other benefits.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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