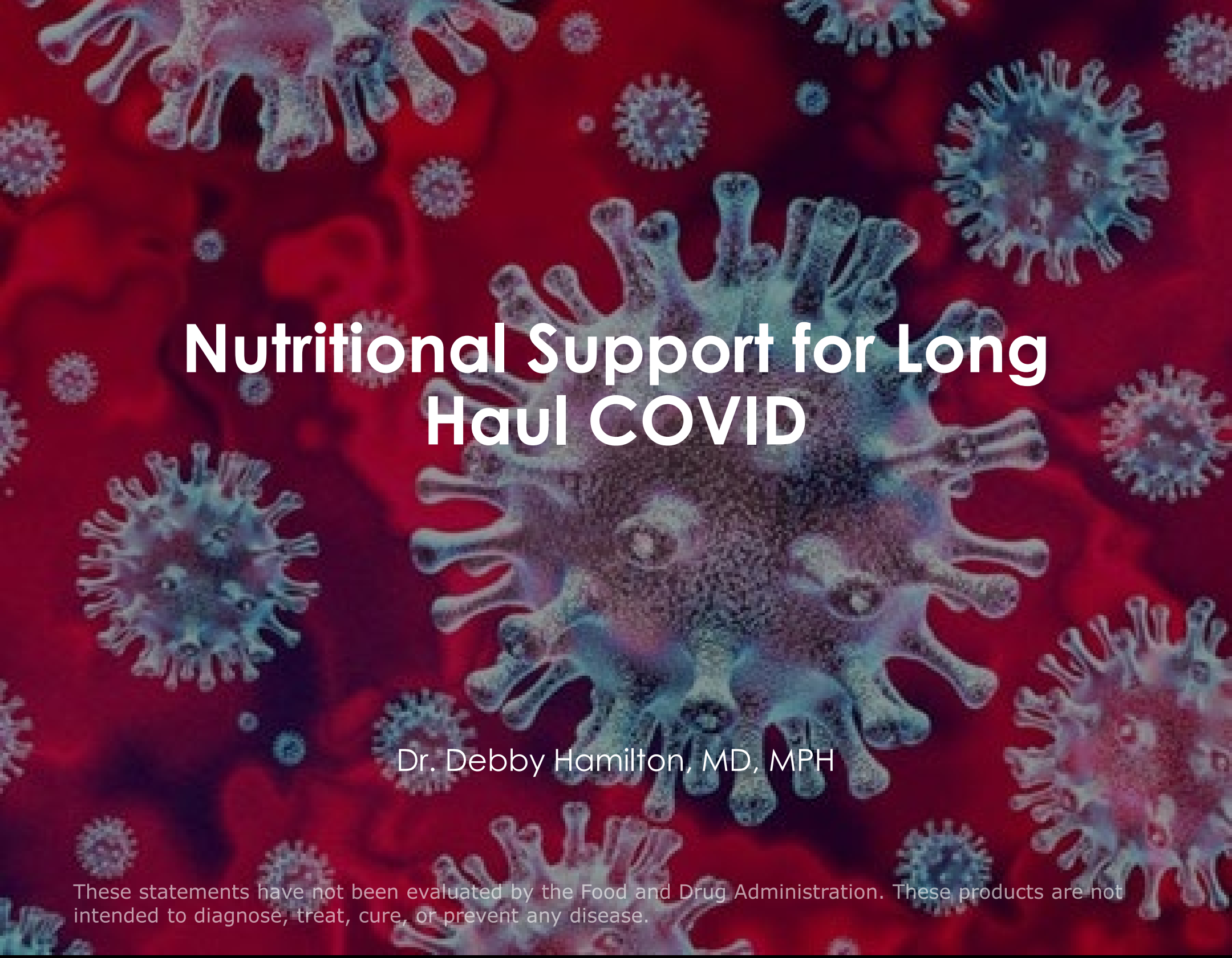


Nutritional Support for Long Haul COVID

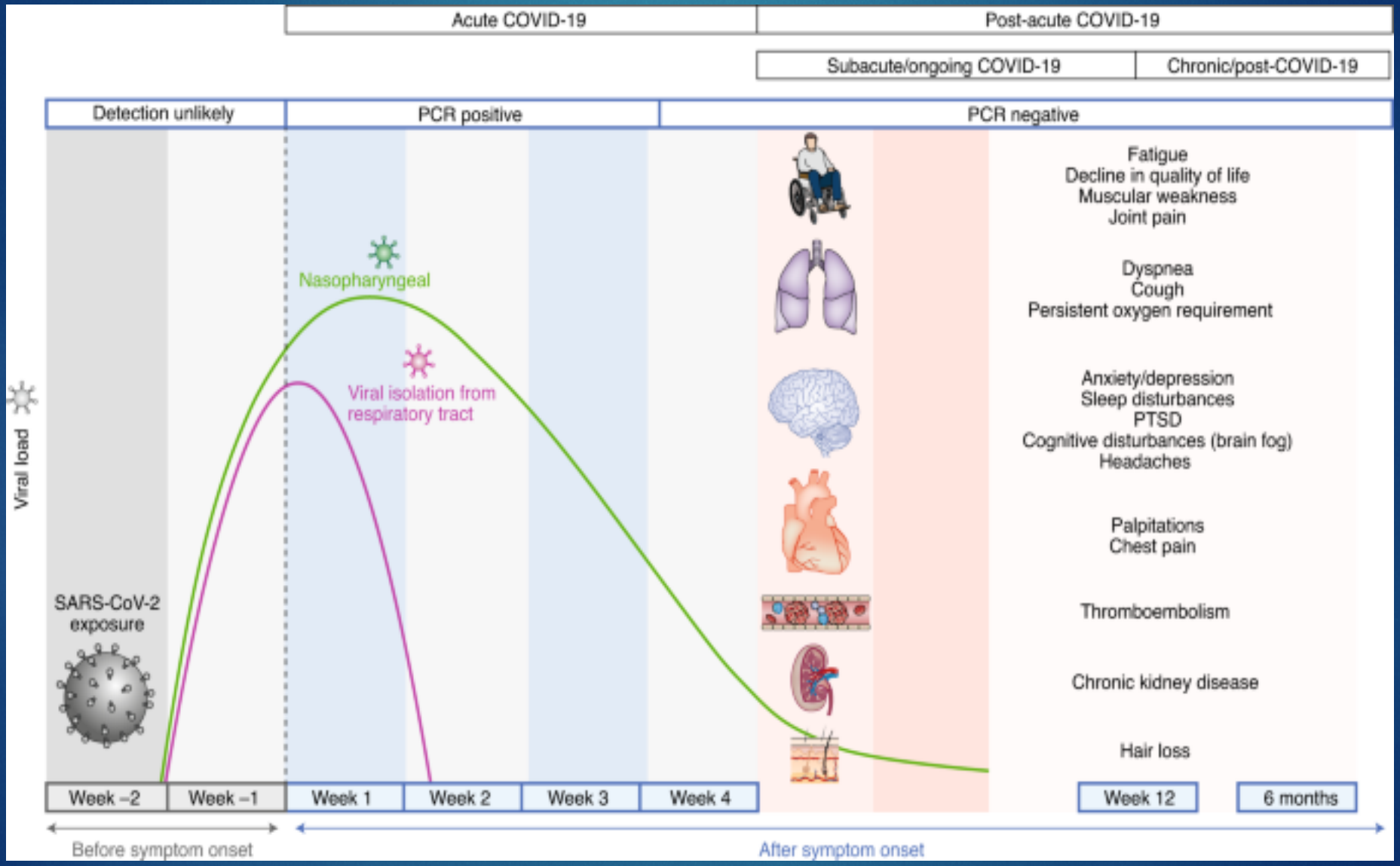
Dr. Debby Hamilton, MD, MPH

Risk Factors for Post COVID (Long Haul) Symptoms

- More severe COVID infection with hospitalization
- All people exposed at risk
- Five early symptoms
- Early Dyspnea
- Prior psychiatric disorders
- Specific biomarkers: Elevated D-dimer, CRP, Lymphocyte count
- Increased age

- Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments [published online ahead of print, 2021 May 22]. *Infect Dis (Lond)*. 2021;1-18. doi:10.1080/23744235.2021.1924397

Nalbandian, A., Sehgal, K., Gupta, A. *et al.* Post-acute COVID-19 syndrome. *Nat Med* **27,** 601–615 (2021).

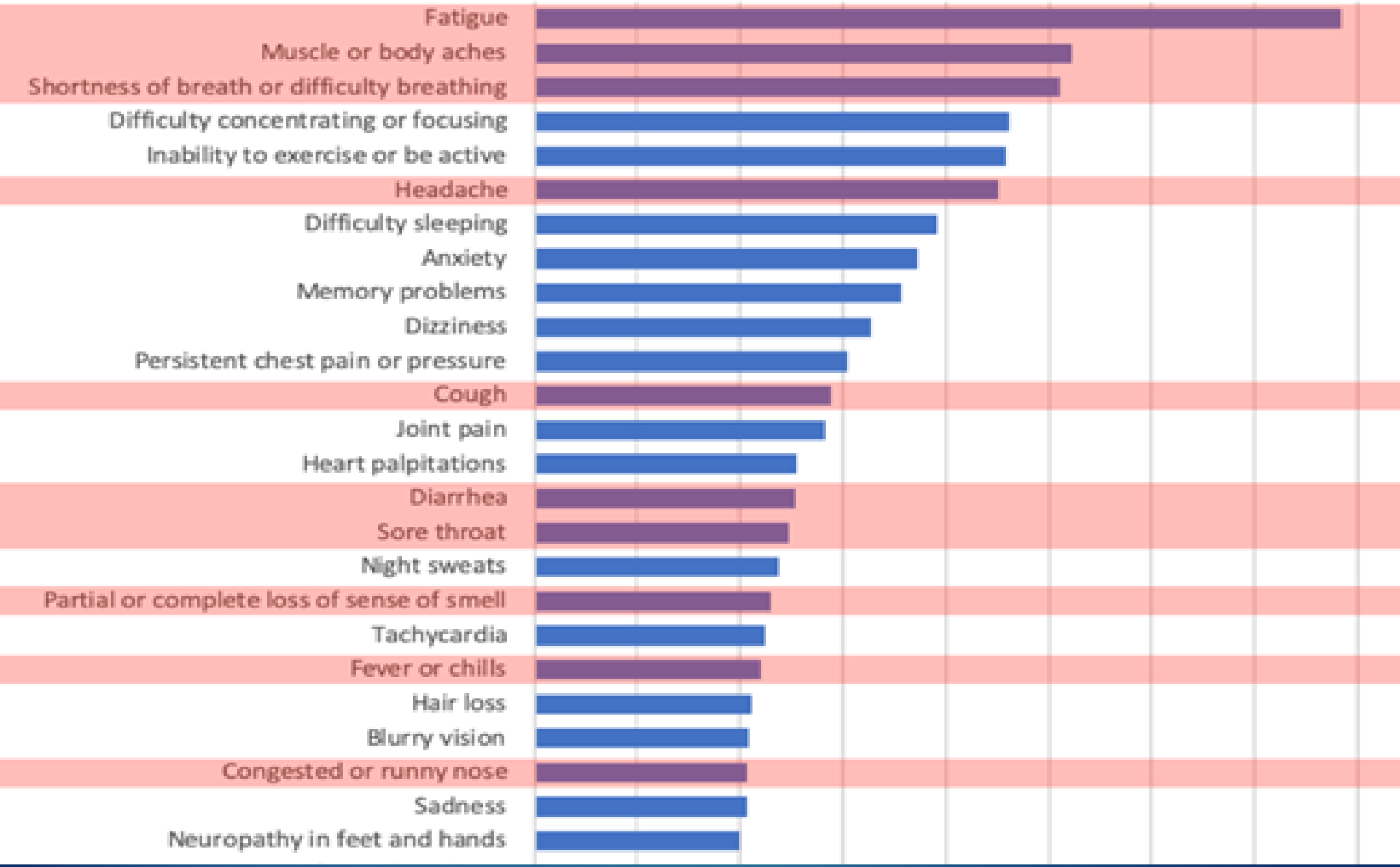


Post COVID Syndrome Definition

- Long Haul COVID: symptoms that persist 4 weeks after infection from people with serious COVID to asymptomatic COVID infection
- Effects from hospitalization treatment: post intubation, muscle loss, PTSD, etc.
- Multi-organ symptoms from COVID including autoimmune, Multisystem Inflammatory Syndrome (MIS)

- https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

CDC (shaded) vs. Long Hauler Reported COVID-19 Symptoms



Cardiovascular Issues

- Vascular inflammation
- Endothelial damage
- Systemic microangiopathy
- Blood clotting: inflammation induced
- Stroke
- Elevated fibrinogen
- Elevated D-dimer
- Right ventricular dysfunction
- Myocarditis
- Pericarditis

- Sarfraz Z, Sarfraz A, Barrios A, et al. Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care. *J Prim Care Community Health*. 2021;12:215013272110237 26

Neuro-PASC DIAGNOSTIC CRITERIA

At least 2 or 3 of following manifestations are also required in a single category

Neurologic:	Smell/taste disturbance, myalgia, muscle weakness, motor disturbance, generalized hyperalgesia, neuromuscular pain, new headaches, disturbed sleep patterns, unrefreshing sleep drowsiness
Neurocognitive:	Difficulty thinking/processing, short-term memory loss, difficulty to focus, depression/anxiety,hypersensitivity to noise/light, tinnitus, double vision, PTSD
Neuroendocrine:	Thermostatic instability, anorexia
Autonomic dysfunction:	Orthostatic intolerance, cardiovascular, respiratory gastro-intestinal (GI), genito-urinary (GU)
Immune system:	Fever or chills, flu-like symptoms, susceptibility to virus, sore throat, lymph node pain/tenderness, sensitivity to chemicals (foods,medications, or odors)
Laboratory findings:	Consistent with a hyperinflammatory and/or hypercoagulability conditions kidney insufficiency

Patient has at the least 3 of the following 4 symptoms

ADL reduction:	A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 4-6 weeks after diagnosis
Fatigue:	The fatigue is of new or definite onset (not lifelong) and is not the result of ongoing excessive exertion. The fatigue is not substantially alleviated by rest and is often profound.
Neuromuscular symptoms:	Chronic, debilitating pain, numbness or weakness in their hands, feet, arms and legs due to unexplained nerve damage.
Neuropsychiatric symptoms:	dementia, delirium, anxiety, psychotic disorder, depression, and post-traumatic stress disorder

Documented history of COVID19 according to WHO criteria or SARS-CoV2 infection defined by the specific diagnostic techniques
AND
Negative PCR

Exclusion Criteria

Medical conditions causing chronic fatigue
Psychiatric disorders
Primary brain disorders
Substance abuse
Eating disorder
Active process of disease
History of depression and anxiety

Neurologic Issues

Neuro-Post-Acute Sequelae of SARS-COV2 infection

Neuro-PASC

Moghimi N, Di Napoli M, Biller J, et al. The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 infection. *Curr Neurol Neurosci Rep*. 2021;21(9):44.

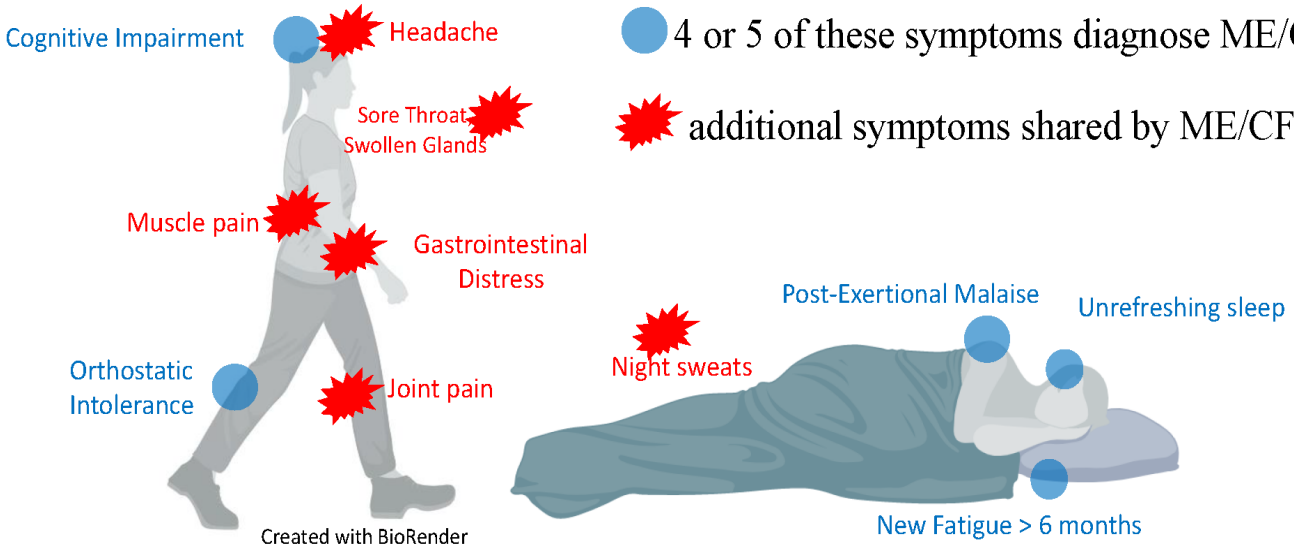
Fatigue: Definition: "*the decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors due to the COVID-19 disease*"

- Causes: still investigating
- Changes in neurotransmitter levels
- Inflammation
- Stress and anxiety
- Physical deconditioning
- Substrate metabolism/availability: mitochondrial function
- Persistent viral infection

- Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 Fatigue: Potential Contributing Factors. *Brain Sci*. 2020;10(12):1012. Published 2020 Dec 19.

Long-Haul COVID and Other Chronic Illnesses

Long COVID19 victims share symptoms with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) patients



4 or 5 of these symptoms diagnose ME/CFS: shared by Long COVID19

additional symptoms shared by ME/CFS and Long COVID19

Institute of Medicine clinician's guide to ME/CFS:

http://www.nationalacademies.org/hmd/Reports/2015/ME-CFS.aspx

Symptoms of Long COVID19 not like ME/CFS:

- Shortness of breath
- Chest pain/pressure
- Cough
- Heart palpitations
- Reduced sense of smell
- Rash
- Tinnitus


LYME DISEASE IN THE AGE OF
COVID-19

Multisystem Inflammatory Syndrome in Children (MIS-C)

- Overlapping symptoms with Kawasaki disease (KD), toxic shock syndrome (TSS), and acute rheumatic fever
- Signs and Symptoms: fever, systemic inflammation, abdominal pain and cardiac involvement
- Post-acute immune reaction
- Negative PCR, Positive SARS-COV2 AB's
- Treatment: IVIG and steroids

- Buonsenso D, Riitano F, Valentini P. Pediatric Inflammatory Multisystem Syndrome Temporally Related With SARS-CoV-2: Immunological Similarities With Acute Rheumatic Fever and Toxic Shock Syndrome. *Front Pediatr*. 2020;8:574.

Pathology of COVID and Post-COVID Illness: Summary

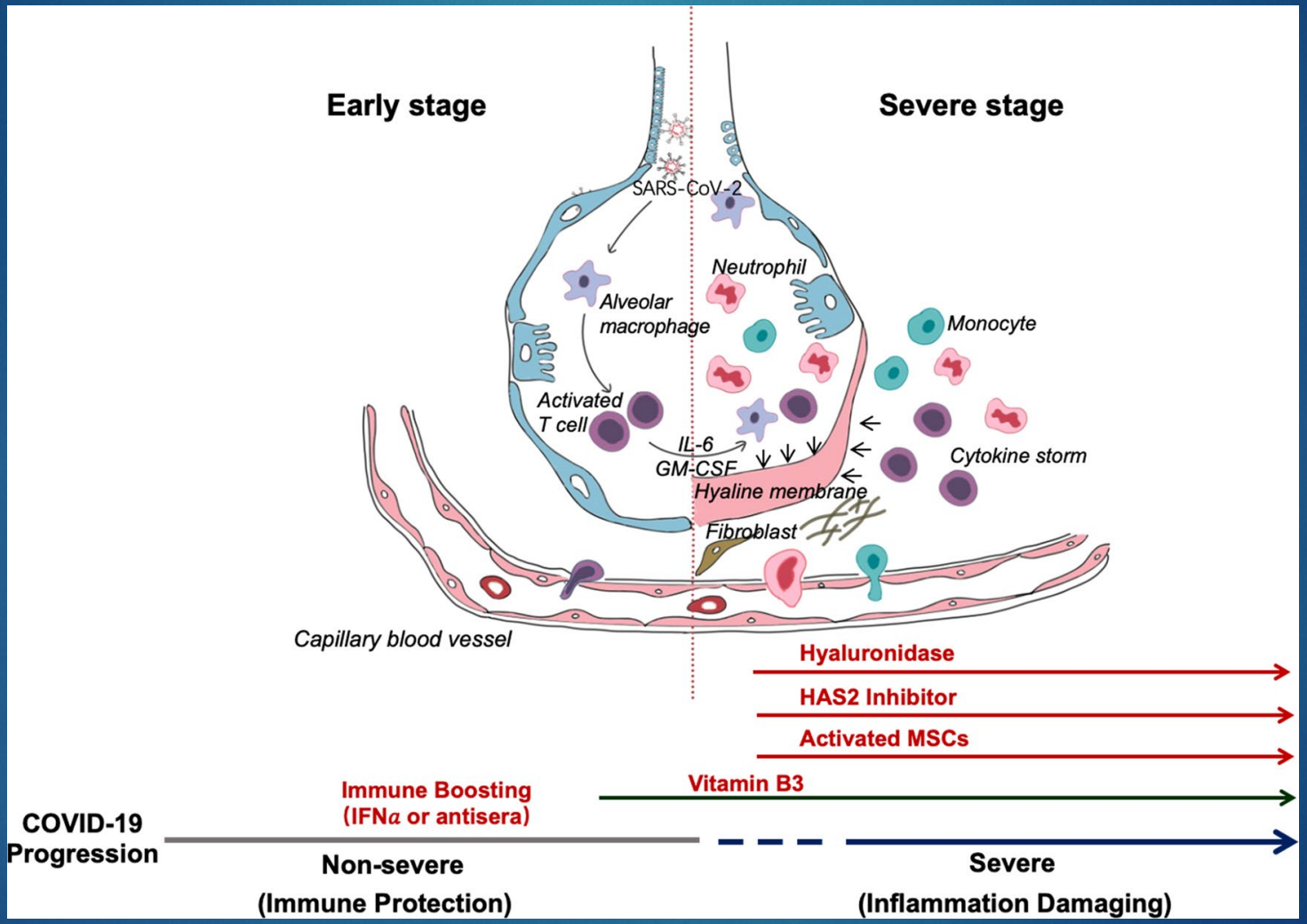
- Inflammation
- Oxidative Stress
- Mitochondrial dysfunction
- Anti-oxidant depletion
- Immune dysregulation
- Direct tissue damage
- Persistent low-grade infection
- Possible Reactivation of chronic infections

The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. Newton AH et al. Semin Immunopathol (2016) 38:471–482.

- These clinical observations and a growing body of experimental data suggest that the host response to infection rather than direct viral injury of respiratory cells primarily accounts for the clinical and pathologic changes observed during respiratory viral infections

COVID-19 infection: the perspectives on immune responses. She Y. et al.

Yufang Shi. Cell Death and Differentiaion. March 2020



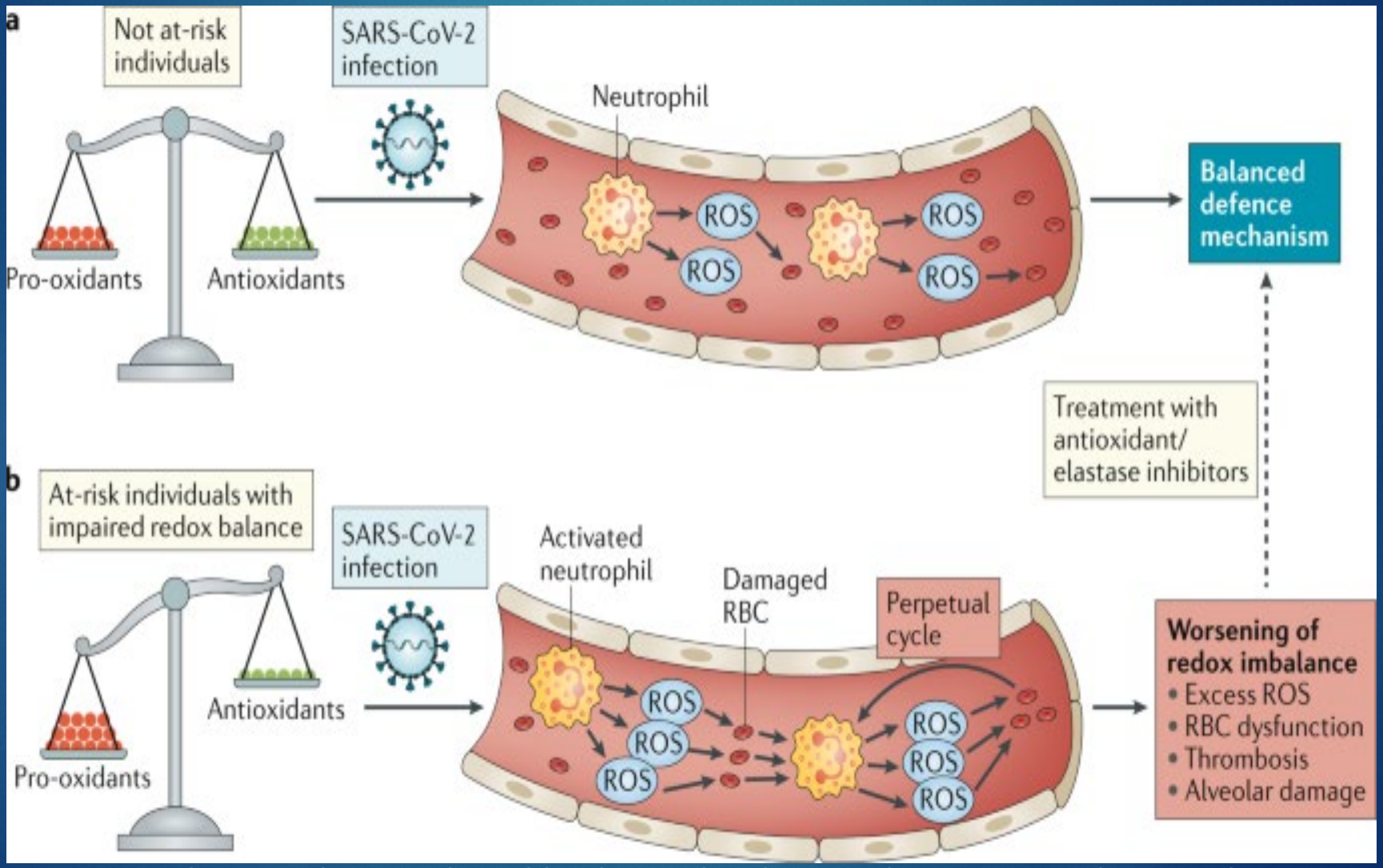
Inflammation in COVID

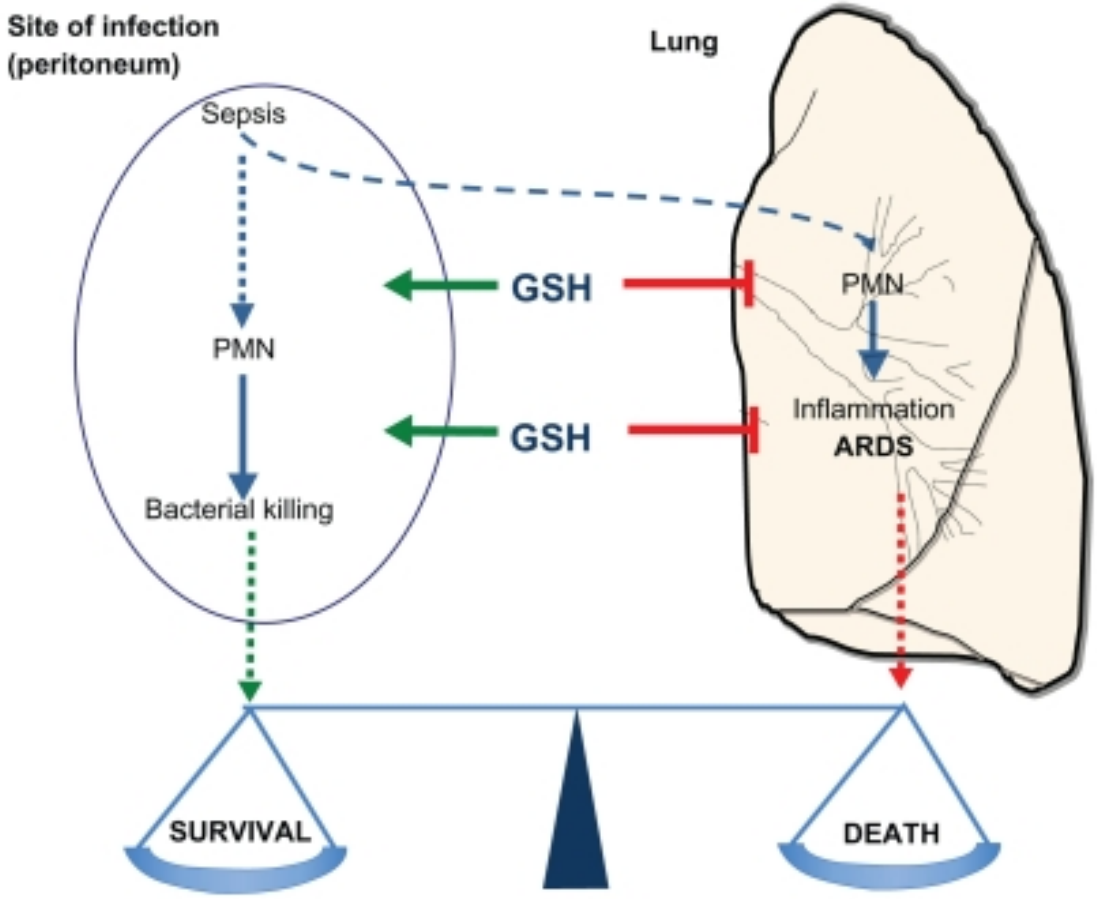
- IL-1β, IL-6, IL-8, and TNF increased in COVID
  - Pro-inflammatory
- Higher levels of these cytokines than in other pneumonias
- Decreased levels of IL-10
  - Anti-inflammatory
- Neutrophils with altered immunometabolism

- McElvaney OJ. Et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness

Oxidative Stress

Laforge, M., Elbim, C., Frère, C. *et al.* Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nat Rev Immunol* 20. 2020 515–516.





Role of glutathione in immunity and inflammation in the lung. Ghezzi P. *Int J Gen Med*. 2011;4:105–113.

Lung diseases associated with glutathione deficiency

- Acute lung injury/acute respiratory distress syndrome
- Chronic bronchitis
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Idiopathic pulmonary fibrosis
- Various bacterial and viral infections (including AIDS)
- Toxicity of various foreign compound (smoke, pollutants, drugs ...)

Role of glutathione in immunity and inflammation in the lung. Ghezzi P. *Int J Gen Med*. 2011;4:105–113.

Mitochondrial Dysfunction

- Mitochondrial hijacking by SARS-COV-2 virus
- Increase in glycolysis and use of glucose as primary fuel in the mitochondria: metabolic disturbance from virus
- Increase in mitokines such as fibroblast growth factor in mononuclear cells
- Impacts innate immunity

- Ajaz S, McPhail MJ, Singh KK, et al. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. *Am J Physiol Cell Physiol*. 2021;320(1):C57-C65.

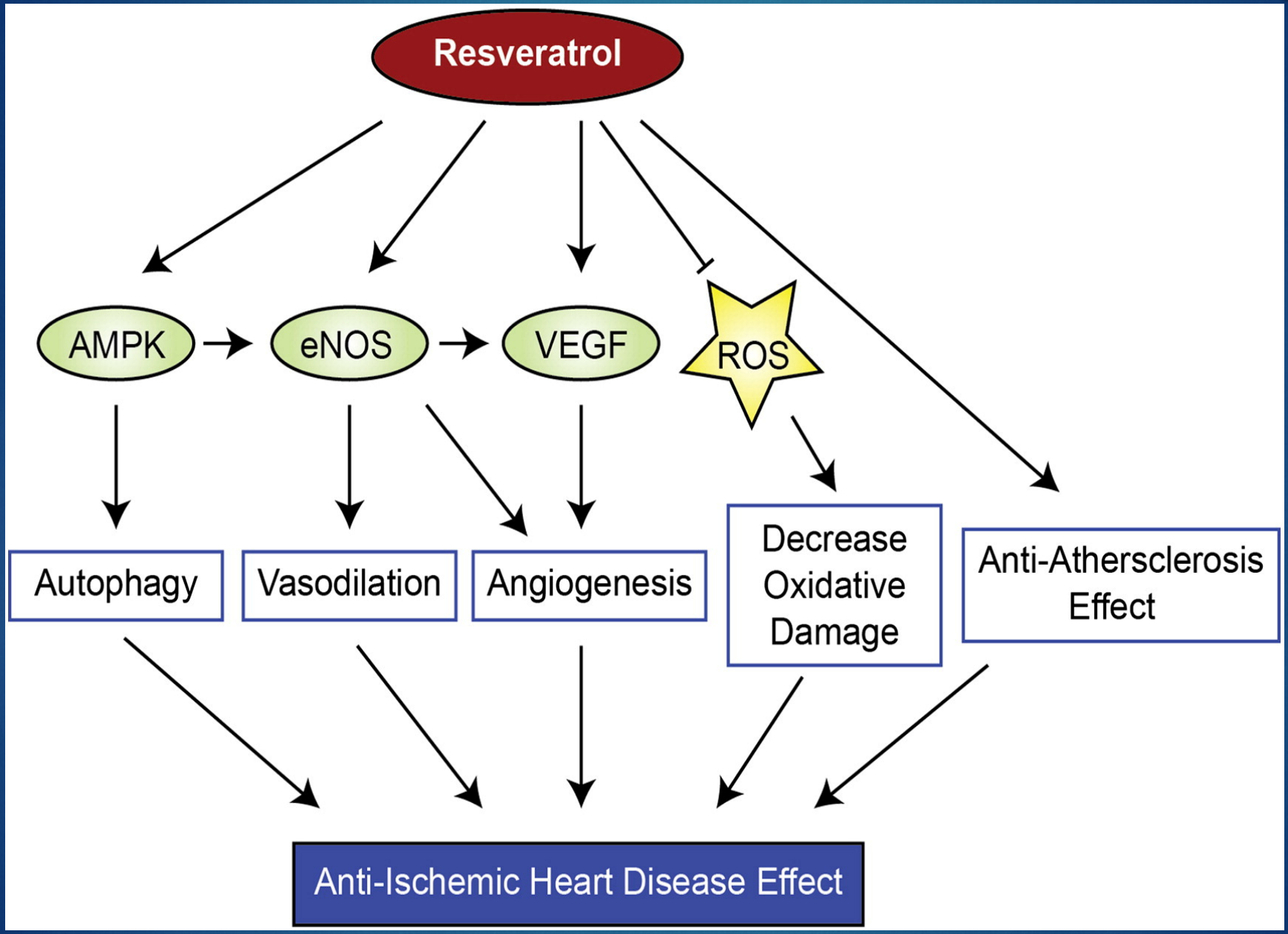
Mitochondrial Dysfunction

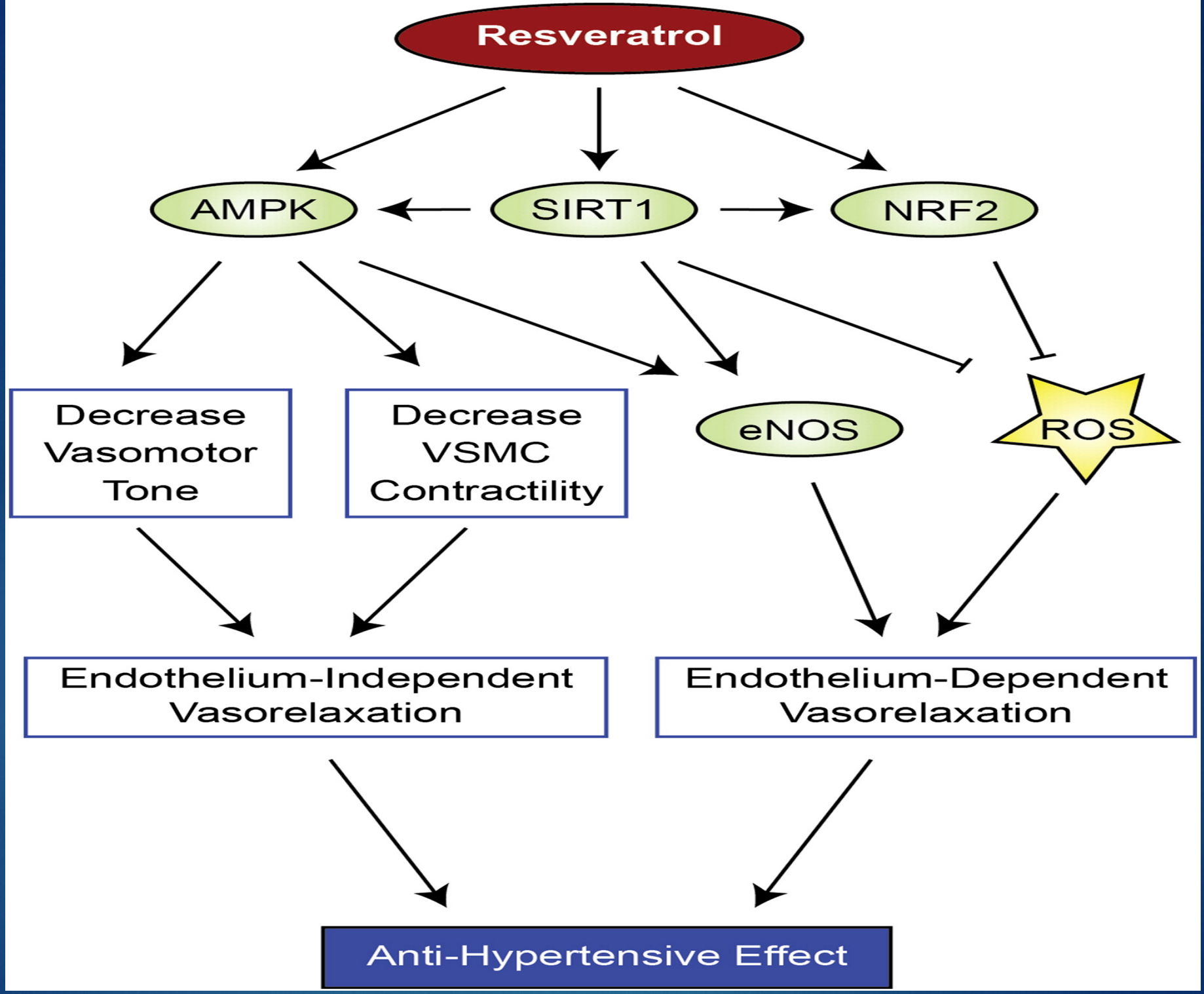
- Damaged mitochondrial membranes = no energy
- Membranes damaged by inflammation and oxidative stress
- Need to repair membranes so other mitochondrial nutrients can be supportive.
- Energy is created within the mitochondrial membrane so poor membrane health reduces electron transport chain ATP production

Nutritional Support for Post-COVID through Support of Pathologic Mechanisms

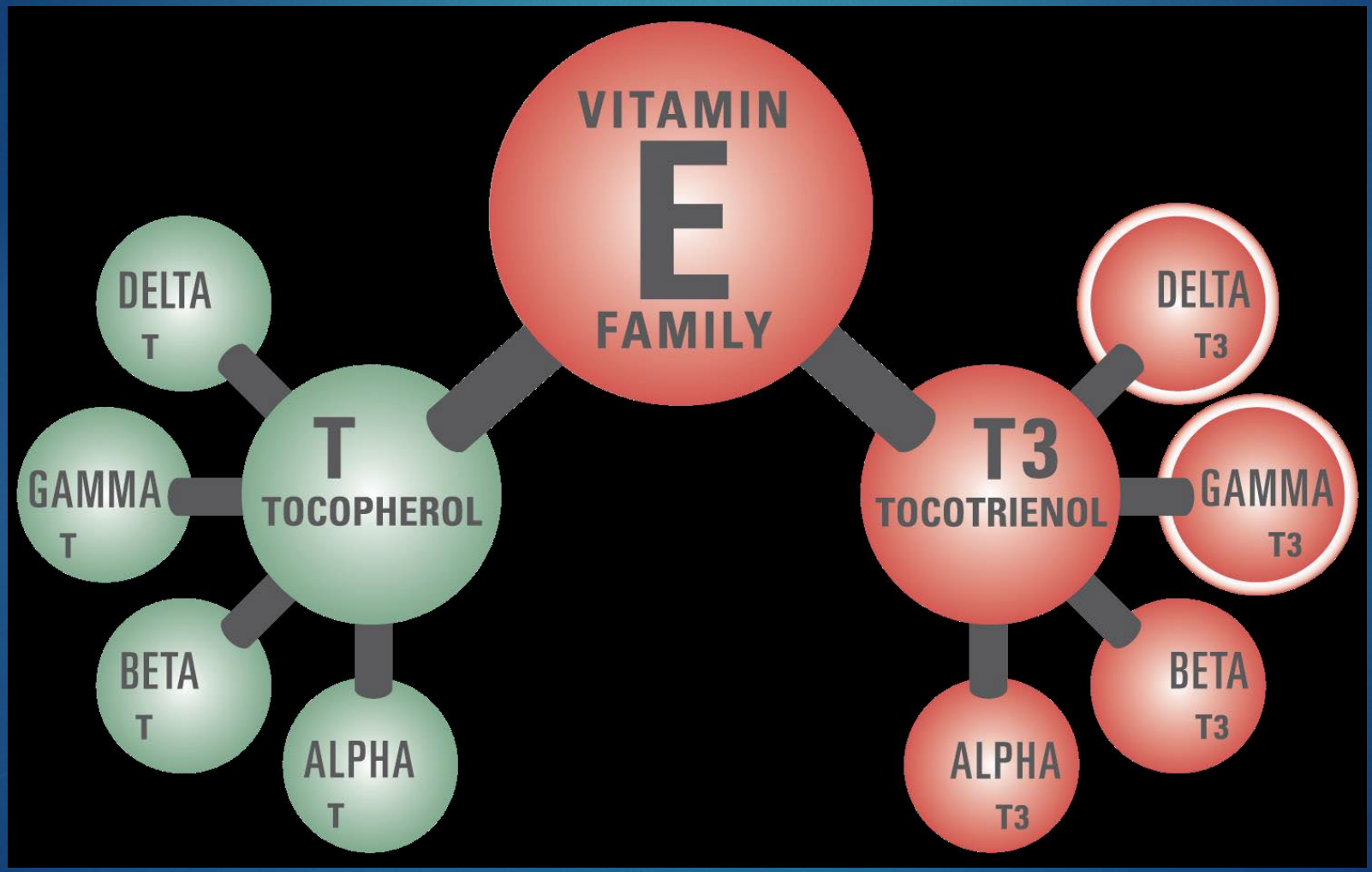
- Inflammation
- Oxidative Stress
- Anti-oxidant Deficiency
- Mitochondrial Dysfunction
- Immune Regulation

Zordoky B. Et al. Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular disease. BBA-Molecular Basis of Disease. 2015:1155-1177.





Vitamin E:
Tocopherols and Tocotrienols



These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Tocotrienols

- Protection against:
  - Oxidative Stress
  - Inflammation
  - Neurodegeneration
  - Cancer
  - Cardiovascular disease

International Journal of *Molecular Sciences*

MDPI

Review

Biological Properties of Tocotrienols: Evidence in Human Studies

Puvaneswari Meganathan and Ju-Yen Fu *

Nutrition Unit, Product Development and Advisory Services Division, Malaysian Palm Oil Board, 6 Persiaran Institusi, Bandar Baru Bangi, 43000 Kajang, Selangor, Malaysia; mpuvaneswari@gmail.com
* Correspondence: fujuyen@gmail.com or fujuyen@mpob.gov.my; Tel.: +60-3-8769-4592

Academic Editor: Maurizio Battino
Received: 14 July 2016; Accepted: 28 September 2016; Published: 26 October 2016

Abstract: Vitamin E has been recognized as an essential vitamin since their discovery in 1922. Although the functions of tocopherols are well established, tocotrienols have been the unsung heroes of vitamin E. Due to their structural differences, tocotrienols were reported to exert distinctive properties compared to tocopherols. While most vegetable oils contain higher amount of tocopherols, tocotrienols were found abundantly in palm oil. Nature has made palm vitamin E to contain up to 70% of total tocotrienols, among which alpha-, gamma- and delta-tocotrienols are the major constituents. Recent advancements have shown their biological properties in conferring protection against cancer, cardiovascular diseases, neurodegeneration, oxidative stress and immune regulation. Preclinical results of these physiological functions were translated into clinical trials gaining global attention. This review will discuss in detail the evidence in human studies to date in terms of efficacy, population, disease state and bioavailability. The review will serve as a platform to pave the future direction for tocotrienols in clinical settings.

Keywords: tocotrienols; human studies; clinical trial; biological properties; palm oil

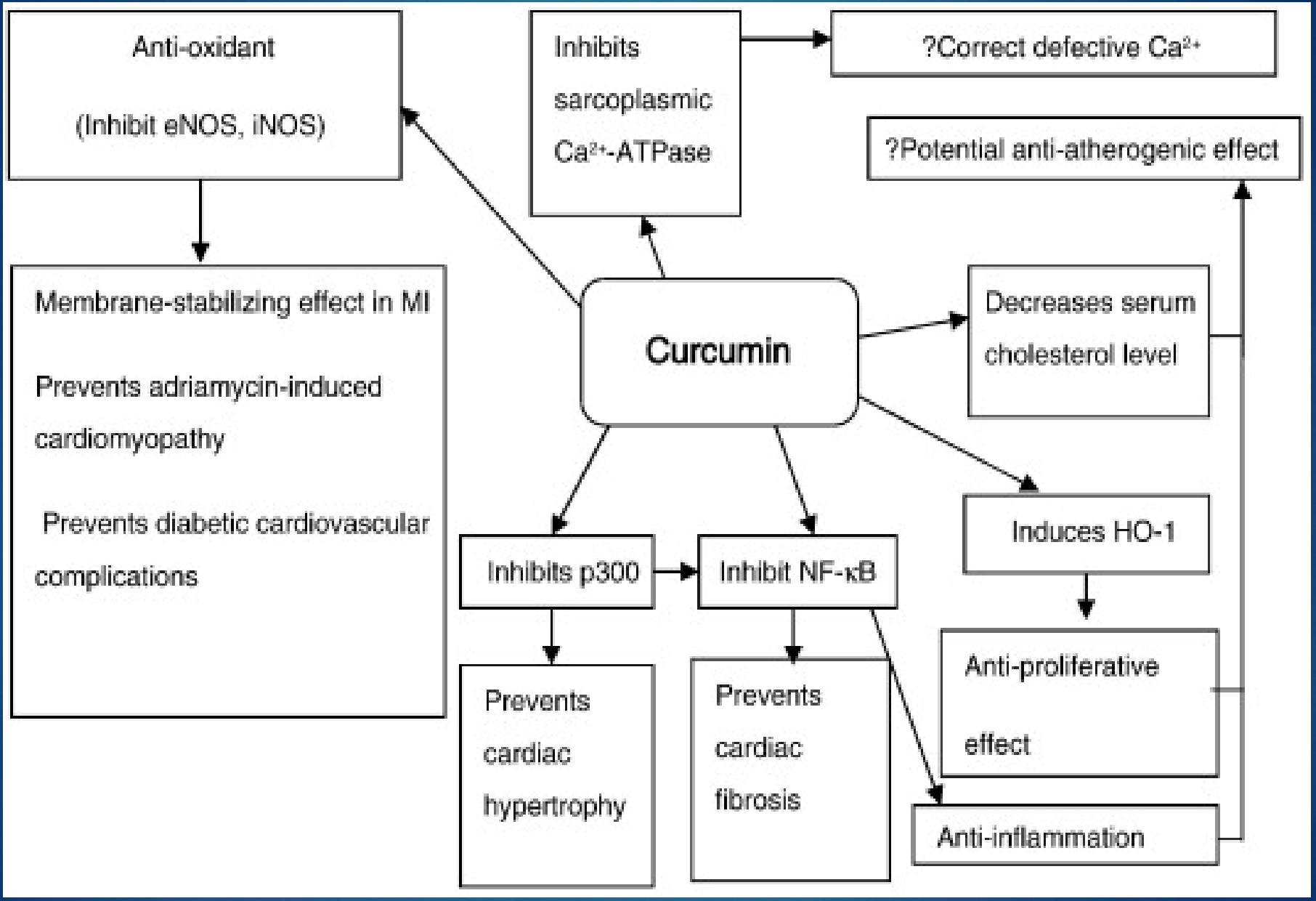
1. Introduction

Due to the increasing trend of life expectancy and awareness towards lifestyle-related diseases, the nutraceutical industry is gaining prominence and has penetrated into consumers' average daily diet. While the term nutraceutical has not been well defined, it generally refers to any food or supplements that have a beneficial nutritional effect. The current market trend has segmented the nutraceutical industry into two major categories, i.e., functional foods and dietary supplements. The global market size is estimated at USD 140.1 billion in 2010 [1]. Among the major global ingredients, vitamin E has market revenue of USD 83.4 million, alongside with omega-3 fatty acids, amino acids, probiotics and soy proteins [1]. While vitamin E is generally referred to α-tocopherol, the role of tocotrienols in human nutrition is frequently underestimated.

Vitamin E is a family of compounds consisting of two categories: tocopherols (TP) and tocotrienols (T3). Structurally, TP and T3 share a similar chromanol head. While tocopherols are attached with a saturated tail at the C2 position, tocotrienols have three double bonds in the side chain. Both TP and T3 have four homologs, namely alpha (α), beta (β), gamma (γ) and delta (δ). Nomenclature of the homologs is dependent on the degree and position of methylation at C5 and C7 position at the chromanol head. Although α-TP is widely known for its function in maintaining cardiovascular health, T3 tend to exhibit various health benefits beyond the antioxidant properties. Among the major sources of T3 are palm oil, annatto and rice bran oil [2].

Global trend of nutraceutical ingredients is moving towards disease or condition specific formulations. Among the highly demanded formulations are those targeted for cardiovascular diseases, weight management, cognitive function, and bone/joint health. In this review, the clinical effects of

Wongchoroen W. et al. the protective role of curcumin in cardiovascular disease. Int. Jr. of Cardiology. 2009



CytoQuel® healthy cytokine support

- **Black Tea Extract**
  - Much stronger antioxidant than green tea
  - Highest EGCG Content - 50%
- **CurcuWin®**
  - 46X absorption of standard curcumin*
  - 35X absorption of BCM-95®*
  - 6X absorption of Meriva®*
- **Delta Gold® Tocotrienols**
  - Pure delta & gamma
  - No tocopherols = better absorption
- **N-Acetyl-cysteine (NAC)**
- **Resveratrol (Natural Trans-Resveratrol)**

* Comparative Absorption of Curcumin Formulations. Jager R. Et al *Nutr J* 2014 Jan 24;13(1):11.

Study CytoQuel®

- Small pilot study of 21 individuals with one area of chronic pain for 6 months: excluded patients with previously diagnosed cardiovascular disease
- An open-label study design: either 3 capsules daily
- CytoQuel® designed to decrease inflammation: Evaluations: Baseline, 2 weeks, 8 weeks
  - Pain and activities of daily living questionnaires
  - Blood pressure was measured in both arms and ankles, and the ankle-brachial index calculated
  - Blood markers associated with inflammation and cardiovascular health.

Journal of Pain Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend

Debby E Hamilton, MD[1]
Gitte S Jensen, PhD[2]

[1]Researched Nutritionals, Los Olivos, CA, USA; [2]NIS Labs, Klamath Falls 1437, OR, USA

Purpose: The objective for this clinical pilot study was to evaluate changes to chronic pain, vascular health, and inflammatory markers when consuming a dietary supplement blend (DSB, CytoQuel®), containing curcumin, resveratrol, tocotrienols, N-Acetylcysteine, and epigallocatechin gallate.

Materials and methods: An open-label study design was used where 21 study participants were evaluated at baseline and at 2 and 8 weeks after consuming DSB. Participants were randomized to consume 3 capsules once daily versus 2 capsules twice daily. Pain and activities of daily living questionnaires were used to gather subjective data on pain levels and interference with daily living. Blood pressure was measured in both arms and ankles, and the ankle-brachial index (ABI) calculated. Blood samples were used to evaluate markers associated with inflammation and cardiovascular health.

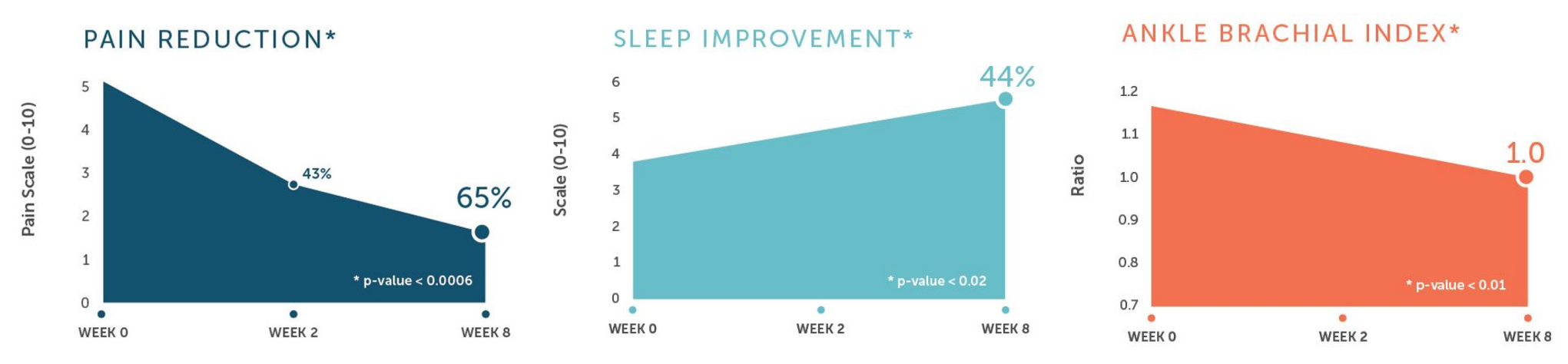
Results: Highly significant reduction of chronic pain was seen after 8 weeks ($p<0.01$), both at rest and when physically active. Faster improvement was seen when consuming 3 capsules once daily, compared to 2 capsules twice daily. The pain reduction resulted in improved sleep quality ($p<0.1$), and improved social functioning ($p<0.01$), and less need for support from others ($p<0.05$). Normalization of mildly elevated ABI at study start was seen after 2 weeks. Plasma fibrinogen and von Willebrand Factor and serum matrix metalloproteinase-9 (MMP-9) showed reduction after 2 weeks (not significant), whereas a reduction in serum interleukin-1 receptor antagonist-a (IL-1ra) was statistically significant after 2 weeks ($p<0.05$). Correlation between pain reduction and changes to MMP-9 after 8 weeks was highly significant ($P<0.01$), whereas correlation between pain reduction and changes to IL-1ra reached significance at 2 weeks for the group consuming 3 caps once daily ($p<0.04$).

Conclusion: Consuming DSB helped manage pain, increased comfort during daily activities, and improved vascular function. This was associated with selective effects on specific blood biomarkers associated with inflammation and vascular health.

Keywords: ankle-brachial index, cardiovascular disease, fibrinogen, interleukin-1 receptor antagonist, matrix metalloproteinase-9, von Willebrand factor

CytoQuel® Research Highlights

Peer-reviewed Clinical Research[1]



- 9.6% reduction in MMP-9 ($p<0.05$)
- Highly significant correlation between MMP-9 & pain ($p<0.01$)

[1]Hamilton, D., Jensen, G., Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend. *J Pain Res. 2019 May 15;12:1497-1508.*

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Results Summary: Inflammation and Hemostasis Factors

Plasma fibrinogen and von Willebrand Factor showed reduction after 2 weeks: Decreased clotting potential

Serum matrix metalloproteinase-9 and interleukin-1 receptor antagonist-a (IL-1ra) were reduced

Reduction of IL-1ra was statistically significant already after 2 weeks ($p<0.05$).

Oxidative Stress Support

Glutathione, Vitamin C, and Alpha Lipoic Acid improving COVID symptoms

Horowitz RI, Freeman PR, Bruzzese Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. J.Respir Med Case Rep. 2020 Apr 21;30:101063.

Tri-Fortify® Liposomal Glutathione
Published, Peer-Reviewed Research

Research Summary

In just 2 weeks…

- **28%** increase in red blood cell glutathione levels
- **400%** increase in natural killer cell activity
- **25%** reduction in lipid peroxidation (oxidative stress marker)
- Research conducted at Penn State University
- Published in European Journal of Clinical Nutrition..2017

ORIGINAL ARTICLE

Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function

R Sinha[1], I Sinha[1], A Calcagnotto[2], N Trushin[2], JS Haley[3], TD Schell[3] and JP Richie Jr[2]

BACKGROUND/OBJECTIVES: Glutathione (GSH) is the most abundant endogenous antioxidant and a critical regulator of oxidative stress. Maintenance of optimal tissues for GSH levels may be an important strategy for the prevention of oxidative stress-related diseases. We investigated if oral administration of liposomal GSH is effective at enhancing GSH levels *in vivo*.

SUBJECTS/METHODS: A 1-month pilot clinical study of oral liposomal GSH administration at two doses (500 and 1000 mg of GSH per day) was conducted in healthy adults. GSH levels in whole blood, erythrocytes, plasma and peripheral blood mononuclear cells (PBMCs) were assessed in 12 subjects at the baseline and after 1, 2 and 4 weeks of GSH administration.

RESULTS: GSH levels were elevated after 1 week with maximum increases of 40% in whole blood, 25% in erythrocytes, 28% in plasma and 100% in PBMCs occurring after 2 weeks ($P < 0.05$). GSH increases were accompanied by reductions in oxidative stress biomarkers, including decreases of 35% in plasma 8-isoprostane and 20% in oxidized:reduced GSH ratios ($P < 0.05$). Enhancements in immune function markers were observed with liposomal GSH administration including Natural killer (NK) cell cytotoxicity, which was elevated by up to 400% by 2 weeks ($P < 0.05$), and lymphocyte proliferation, which was elevated by up to 60% after 2 weeks ($P < 0.05$). Overall, there were no differences observed between dose groups, but statistical power was limited due to the small sample size in this study.

CONCLUSIONS: Collectively, these preliminary findings support the effectiveness of daily liposomal GSH administration at elevating stores of GSH and impacting the immune function and levels of oxidative stress.

European Journal of Clinical Nutrition advance online publication, 30 August 2017; doi:10.1038/ejcn.2017.132

INTRODUCTION

Glutathione (GSH) is the most abundant nonprotein thiol in cells and has an array of critical functions, which include detoxifying drugs, protecting macromolecules from oxidative damage and maintaining immune functions.[1–7] GSH is synthesized from cysteine (Cys), glutamic acid and glycine with Cys most often being the rate-limiting substrate.[8,9] As a result, GSH levels can be depleted when Cys levels are limited such as during periods of fasting.[10,11] GSH depletion has numerous detrimental effects, including impaired immune function[6] and increased susceptibility to xenobiotics[12] and oxidants.[13] Maintenance of optimal tissue levels of GSH is thought to be an important factor for maintaining health and low GSH levels have been associated with increased risks for diseases, including cancer, cardiovascular diseases, arthritis and diabetes.[14–16]

GSH enhancement represents a potentially important approach in the treatment and prevention of disorders associated with GSH depletion. Studies linking dietary GSH intake with increased blood levels and reduced risk for cancer[17,18] support the use of orally administered GSH for this purpose. Studies in laboratory animals have demonstrated that oral GSH is bioavailable and effective at enhancing blood and tissue GSH levels[19–24] and can be protected against aging-related impairments in immune function,[25] influenza infections[26] and cancer.[27–30] In a recent clinical trial, we demonstrated that daily oral supplementation of GSH was effective at enhancing GSH levels in oral buccal cells and a variety of intra- and extracellular blood compartments.[31]

Liposomes have been used as an effective means of drug delivery allowing for more efficient absorption and delivery of both hydrophilic and lipophilic substances and greater protection against oxidation and degradation. Since GSH is subject to destruction in the acid environment of the stomach, we proposed that oral liposomal GSH might be an effective means of GSH delivery *in vivo*. While liposomal GSH preparations are commercially available, there have been few clinical reports on their effectiveness and no data on their ability to enhance body GSH stores. Thus, our current objectives were to conduct a pilot study to determine the short-term (1 month) effects of daily oral supplementation with liposomal GSH on the levels of GSH in different intracellular and extracellular blood compartments in healthy adults. In addition, the effects on specific immune functions and biomarkers of oxidative stress were assessed.

SUBJECTS AND METHODS

Study protocol

The study (ClinicalTrials.gov identifier: NCT02278822) was approved by the Institutional Review Board of the Penn State College of Medicine in accordance with the Helsinki Declaration of 1975, as revised in 1983. Subjects were recruited from the local Hershey/Harrisburg, PA, USA area using fliers, online announcements and word of mouth. Interested individuals were prescreened by telephone and eligible subjects were asked to visit the Clinical Research Center at the Penn State Cancer Institute, Hershey, PA, USA. After providing informed consent, the subjects were further screened for eligibility based on the following criteria: healthy

[1]Department of Biochemistry and Molecular Biology, Penn State University College of Medicine, Hershey, PA, USA; [2]Department of Public Health Sciences, Penn State University College of Medicine, Hershey, PA, USA and [3]Department of Microbiology and Immunology, Penn State University College of Medicine, Hershey, PA, USA. Correspondence: Dr R Sinha or Dr JP Richie, Penn State College of Medicine, 500 University Drive, Hershey, PA 17033, USA.
E-mail: rus15@psu.edu or jrichie@psu.edu

Received 27 February 2017; revised 25 May 2017; accepted 19 July 2017

Tri-Fortify® Liposomal Glutathione

Heat stable, no refrigeration necessary

CLINICALLY RESEARCHED

Supplement Facts

Serving Size: 1 teaspoon (5 mL)
Servings per Container: Approx. 48

	Amount Per Serving	% Daily ** Value
Calories	30	
Total Fat	1 g	1%
Vitamin C (Ascorbic Acid)	50 mg	56%
Reduced Glutathione	450 mg	†

** Percent Daily Value based on a 2,000 calorie diet
† Daily Value not established.

Other Ingredients: Glycerin, phospholipids (soy), medium chain triglycerides, natural flavor.

Contains: Ingredients partially derived from soy and tree nuts (coconut).

Free of: Milk, eggs, fish, crustacean shellfish, peanuts, wheat and gluten.

Suggested Use: As a dietary supplement, gently squeeze the tube to fill 1 teaspoon (5 mL). Hold under tongue for 30-60 seconds, and then swallow or use as directed by your health care professional. Additional doses may be taken.

C-RLA™

Liposomal High Dose Vitamin C and R-Lipoic Acid

GMO Free – Vegan – Soy Free

Original Flavor

Supplement Facts

Serving Size: 2 teaspoons (10 mL)
Servings Per Bottle: 30

Amount Per Serving		%Daily Value**
Vitamin C (as sodium ascorbate)	1500 mg	1667%
Sodium (as sodium ascorbate)	197 mg	9%
R-Lipoic Acid	70 mg	†

** Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Purified water, non-GMO sunflower phospholipids, glycerin, natural flavors, potassium sorbate.

Free of: Milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, soy, corn and gluten.

Vanilla Caramel

Supplement Facts

Serving Size: 2 teaspoons (10 mL)
Servings Per Bottle: 30

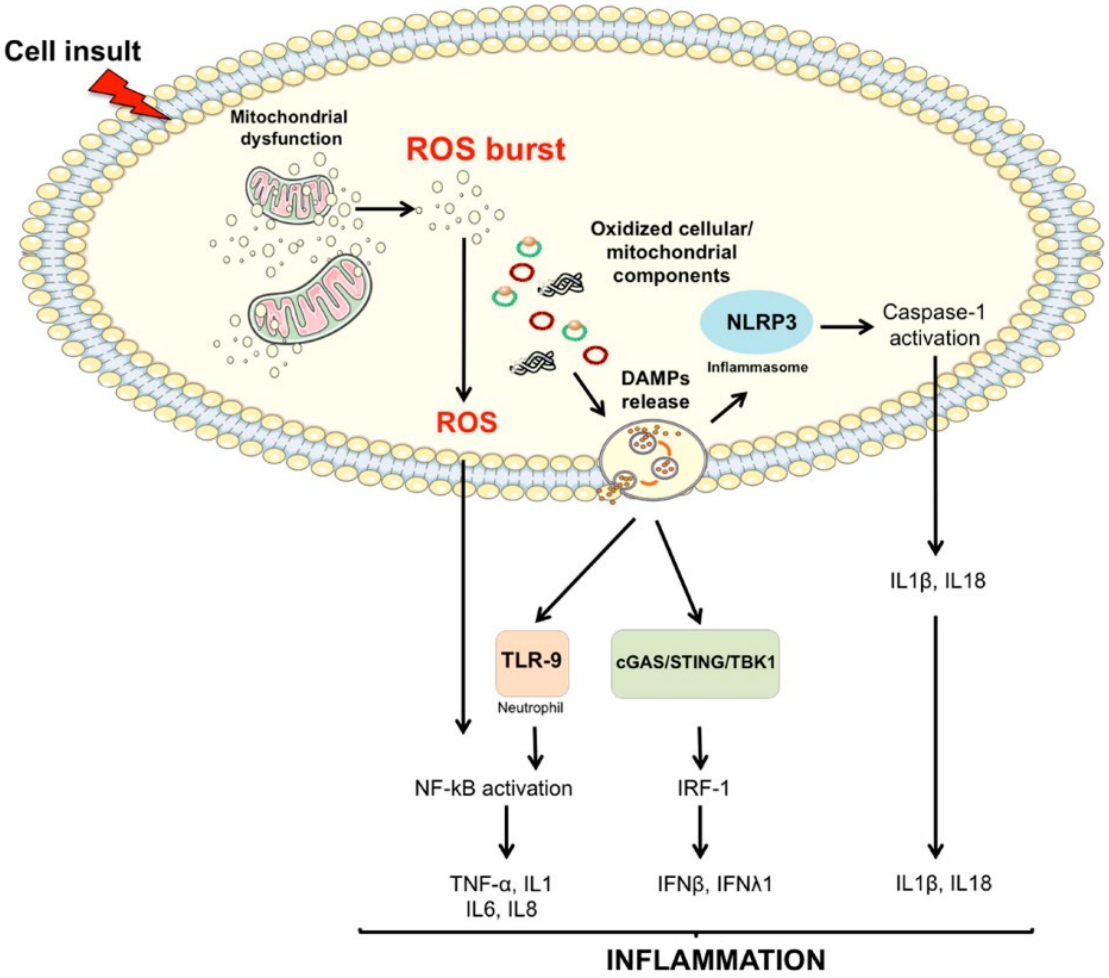
Amount Per Serving		%Daily Value**
Calories	5	
Carbohydrates	6 g	2%
Total Sugars 6g		
Vitamin C (as Sodium Ascorbate)	1500 mg	1667%
Sodium (as Sodium Ascorbate)	197 mg	9%
R-Lipoic Acid (as Sodium R-Lipoic Acid)	70 mg	†

** Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Other Ingredients: Allulose, deionized water, sunflower lecithin, vanilla extract, grapefruit seed extract, stevia extract.

Free of: Milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, soy and gluten.

Suggested Use: Take 2 teaspoons daily.
May be taken straight or mixed in water.

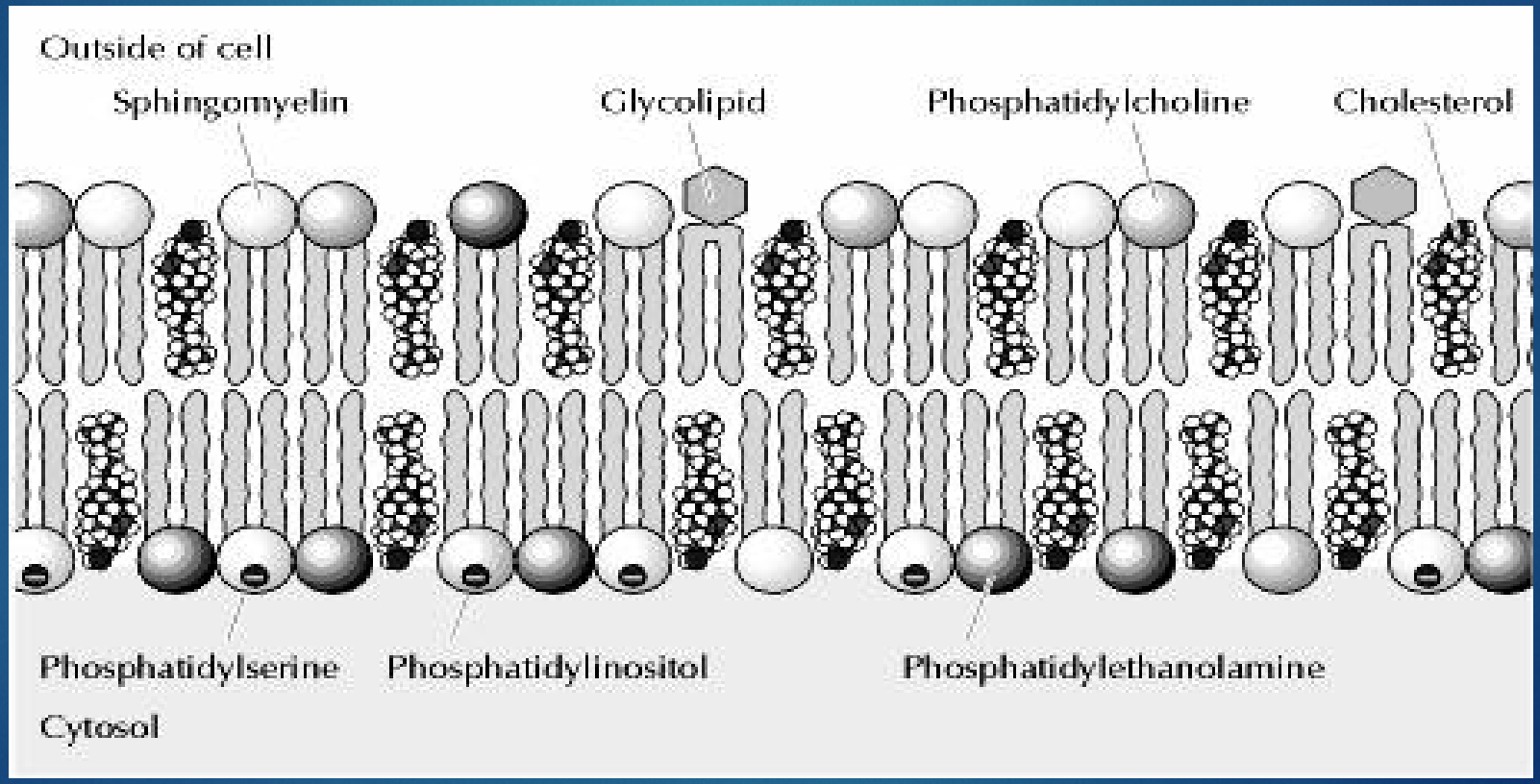


Correlation between Mitochondrial Dysfunction, Oxidative Stress and Inflammation

Picca A. et al. Fueling Inflamm-Aging through Mitochondrial Dysfunction: Mechanisms and Molecular Targets. International Journal of Molecular Sciences. 2017; 18(5):933.

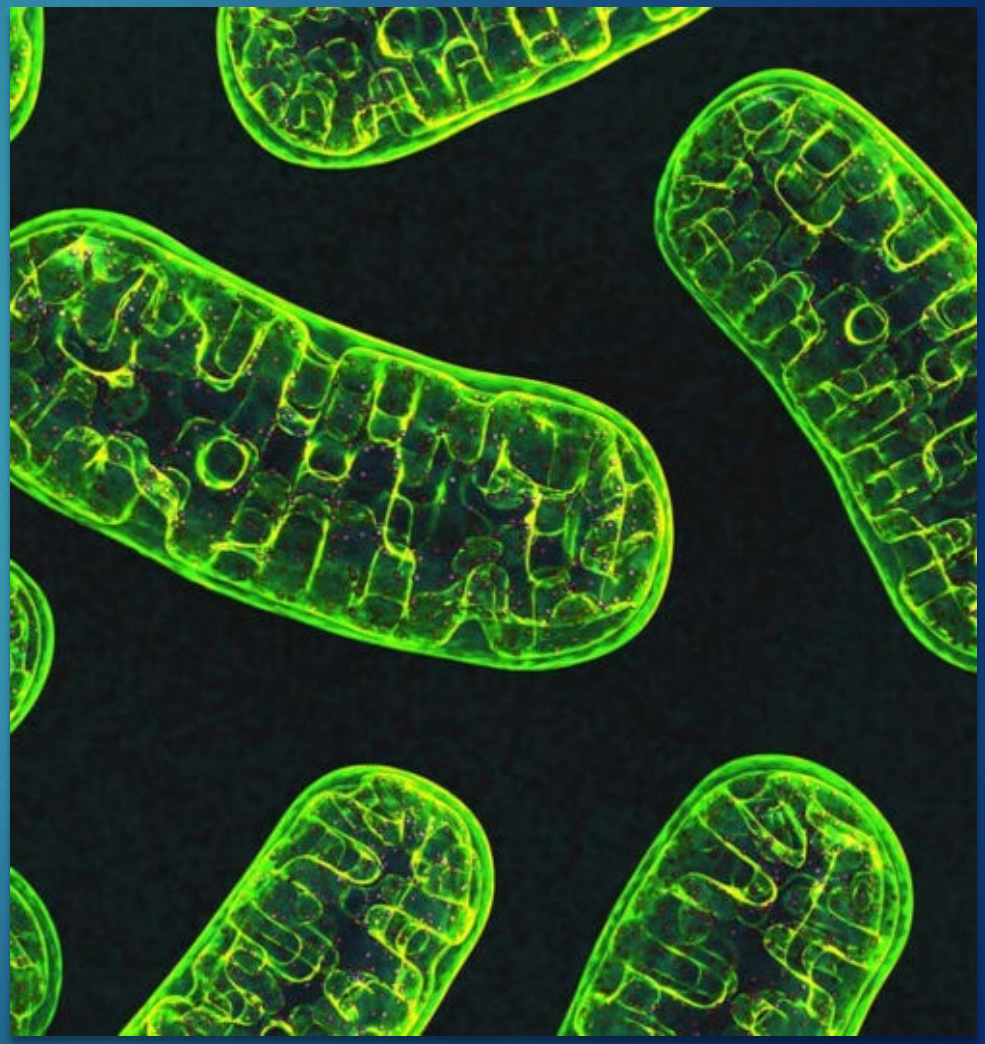
Treatment for Mitochondrial Dysfunction

- Repair mitochondrial membrane
  - Phospholipids



Treatment for Mitochondrial Dysfunction

- Support mitochondrial function
  - Phospholipids
  - CoQ10/Ubiquinol
  - Carnitine
  - NADH
  - Alpha-lipoic acid
  - B vitamins
  - Vitamin E
  - PQQ
  - Vitamin C



- Hamilton D, Jensen G. Nutraceutical support of mitochondrial function associated with reduction of long-term fatigue and inflammation. *Altern Ther Health Med.* 2021 May; Vol 27 (3):8-17.

ORIGINAL RESEARCH

Nutraceutical Support of Mitochondrial Function Associated With Reduction of Long-term Fatigue and Inflammation

Debby Hamilton, MD, MPH; Gitte S. Jensen, PhD

ABSTRACT

Objectives • To evaluate the effects of ATP 360, a nutraceutical energy formula, in people experiencing long-term fatigue affecting daily living. To explore the use of ex vivo mitochondrial stress testing to evaluate cellular energy improvements with nutraceutical support.

Study Design • An open-label study design was used with screening for long-term fatigue, scoring 50% or higher on the Piper Fatigue Scale. Eleven participants (8 women, 3 men) consumed the nutraceutical energy formula for 8 weeks, with a 1-week online evaluation and 4-week and 8-week follow-up visits. Eleven healthy people of similar age and BMI range donated blood for comparative evaluation of mitochondrial function in non-fatigued subjects.

Methods • Fatigue scoring was performed using the Piper Fatigue Scale. Other data included blood pressure readings and questionnaires for pain and wellness. Blood draws were performed. Serum was tested for cytokines using bead-based immunoassays. Leukocytes were tested for mitochondrial mass and mitochondrial membrane potential after 2-hour ex vivo inflammatory challenges with bacterial lipopolysaccharide using fluorescent probes, along with flow cytometry analysis.

Primary Outcome Measures • Change in fatigue and pain levels from baseline to 8 weeks.

Results • Reduction in long-term fatigue was rapid and highly significant after 1 week. Pain reduction reached statistical significance at 4 weeks. Wellness scores improved, especially mental functioning, sleep, increased emotional wellness, and increased energy/vitality. Diastolic blood pressure was reduced. Serum levels of TNF-α and interleukin 8 were reduced. At baseline, leukocyte mitochondrial responses to ex vivo inflammation were low compared to leukocytes from healthy non-fatigued people, showing a mild 21% increase after 4 weeks (not statistically significant), and returning to baseline at 8 weeks.

Conclusion • This proof-of-concept study showed that consumption of a proprietary nutraceutical energy formula resulted in rapid and sustained fatigue reduction associated with reduced pain and inflammatory cytokines and improved wellness. A mild increase in mitochondrial response to inflammation was seen at 4 weeks. A future study with longer duration should evaluate whether mitochondrial function may approach that of a healthy population.

Trial registration • This study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration of 1975 (trial registration number NCT04261881) (*Altern Ther Health Med.* 2021;27(3):8-18).

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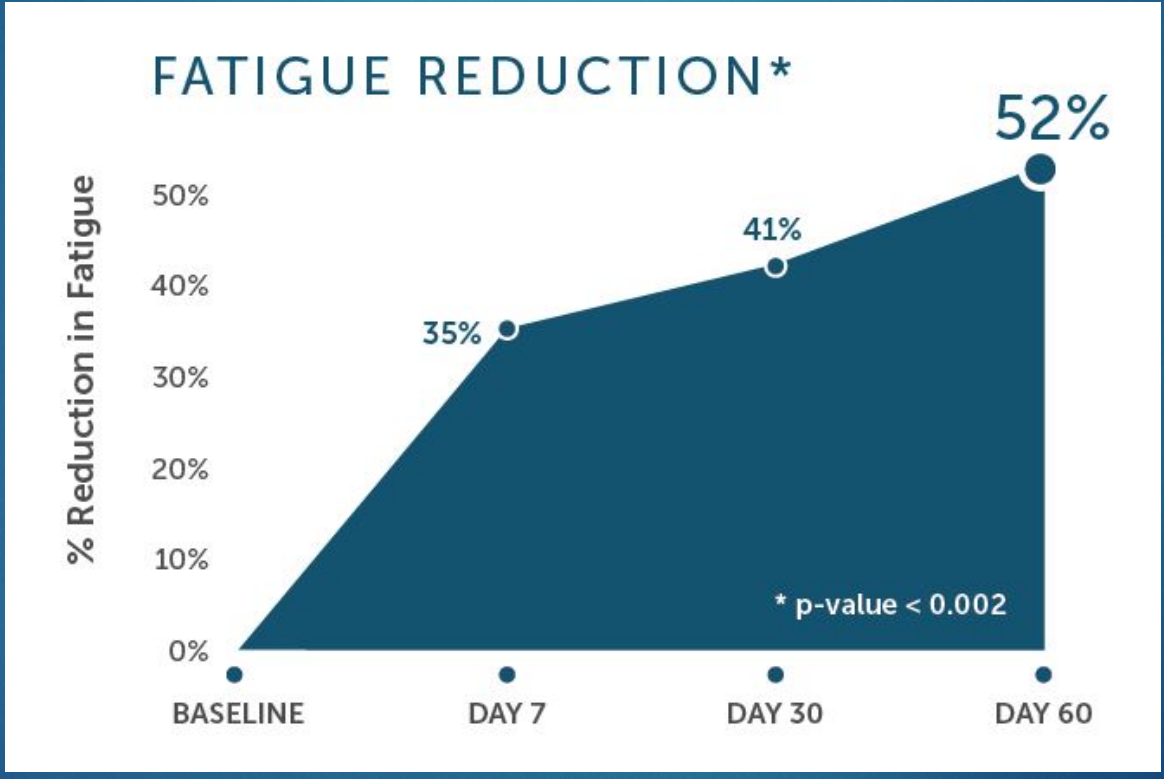
BACKGROUND

Fatigue is defined as persistent disrupted physical and/or mental tiredness that impacts quality of life and decreases the ability to perform activities of daily living. Fatigue is a 30% of visits to practitioners involve a complaint including fatigue.[1] When the general population is surveyed, the prevalence of fatigue appears to affect 30% to 50% of people. When the fatigue is persistent and severe, patients will be given the diagnosis of chronic fatigue syndrome which affects approximately 1% of the population by clinical evaluation and 3% by self-assessment.[2] Long-term fatigue can be an isolated symptom or a part of chronic disease. Children with significant long-term disease may also present with fatigue in up to 21% causing a negative impact on their lives.[3] While many patients suffer from fatigue, it is difficult to successfully treat. Infections and autoimmune diseases

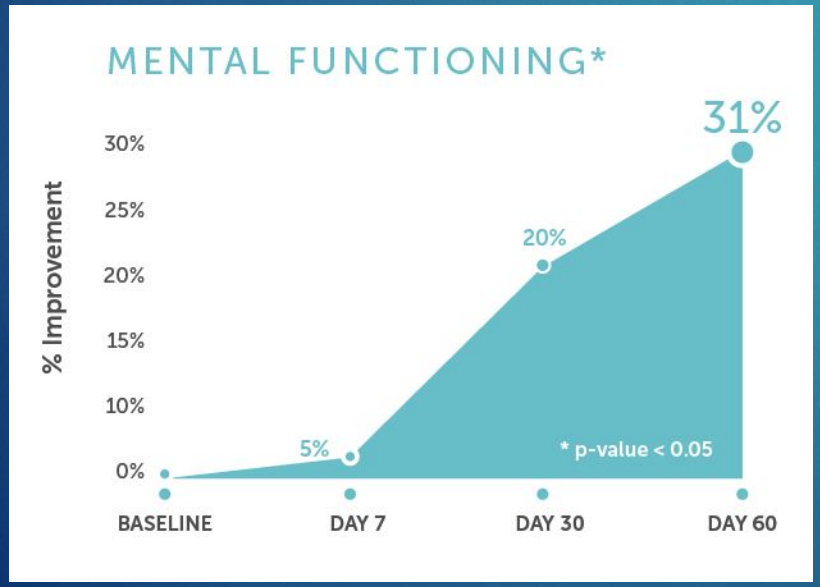
Results: Fatigue

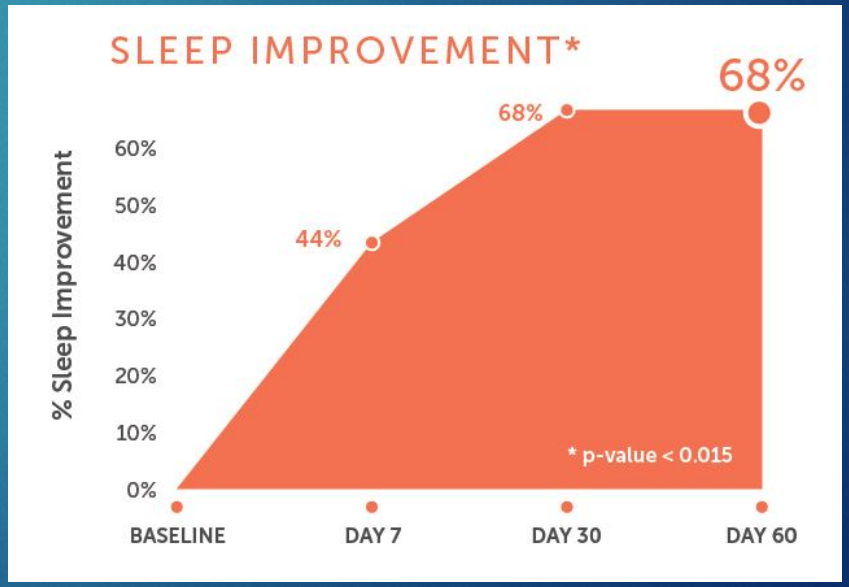
- Reduction in long-term fatigue was rapid and highly significant after 1 week. (35%)
- 52% reduction in fatigue after 8 weeks



Results: Pain, Sleep, and Mental Functioning

- Pain reduction reached statistical significance at 4 weeks.
- Wellness scores improved, especially mental functioning, increased emotional wellness, and increased energy/vitality.
- Sleep improvement 68% by 8 weeks

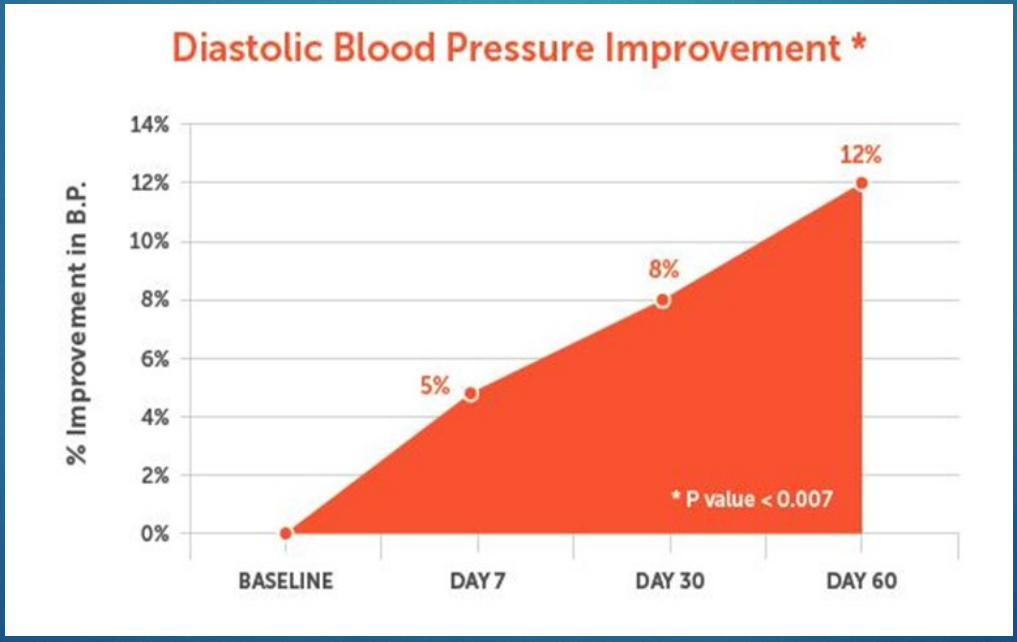




These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Results: Reduced Diastolic Blood Pressure and Inflammatory Markers

- Diastolic blood pressure was reduced 12% by 8 weeks
- Serum levels of TNF-a decreased by 19%
- Interleukin 8 was also reduced.



Results: Mitochondria

- At baseline, leukocyte mitochondrial responses which included increasing mitochondrial mass and membrane potential to ex vivo inflammation were low compared to leukocytes from healthy non-fatigued people, showing a mild 21% increase after 4 weeks (not statistically significant)

ATP 360®

Supplement Facts

Serving Size 3 Capsules Servings Per Container 30

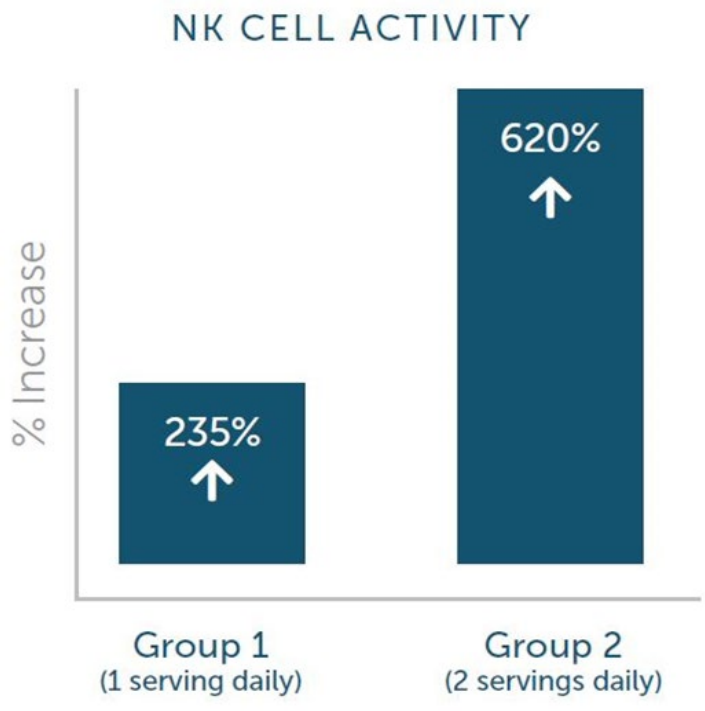
Amount Per Serving		% Daily Value**
Vitamin C (from Membrane Restore™ Blend)	100 mg	111%
Thiamin (from Membrane Restore™ Blend)	50 mg	4167%
Riboflavin (from Membrane Potential™ Blend)	42 mg	3250%
Choline (from RN Lipid Concentrate™ Blend)	27 mg	5%
Magnesium (from Krebs Plus Foundation™ Blend)	50 mg	12%
Membrane Potential™ CoQ10, Riboflavin-5-Phosphate, Panmol® (NADH).	215 mg	†
Membrane Restore™ Ascorbic Acid, DeltaGold® Tocotrienols.	130 mg	†
RN Lipid Concentrate™ (Phosphatidylcholine, Phosphatidylethanolamine, Phytoglycolipids, Phosphatidylinositol)	200 mg	†
Krebs Plus Foundation™ R-Lipoic Acid, Alpha Ketoglutaric Acid, Magnesium (as Di-Magnesium Malate), Thiamine HCl.	225 mg	†
Mitogenesis RN™ Acetyl L-Carnitine, PQQ (Pyrroloquinoline Quinone).	210 mg	†

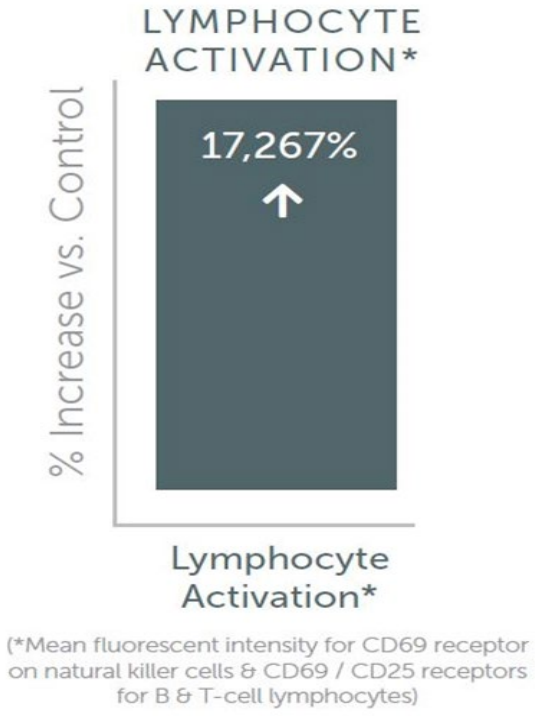
** Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

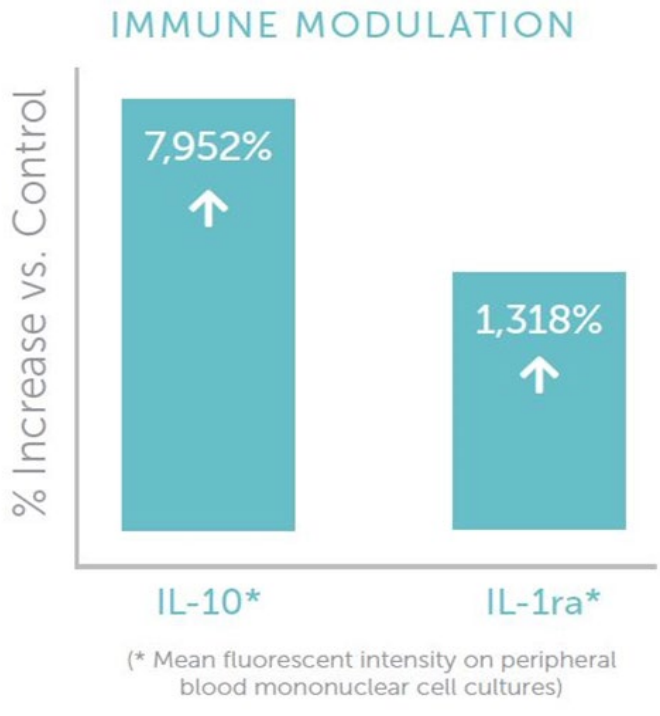
Other Ingredients: Hypromellose (vegetable capsule), rice hull extract, calcium carbonate, and mineral silica.

Contains: Ingredients derived from soy.

Transfer Factor Multi-Immune® Clinical Research[1]







[1]Currently in peer-review process

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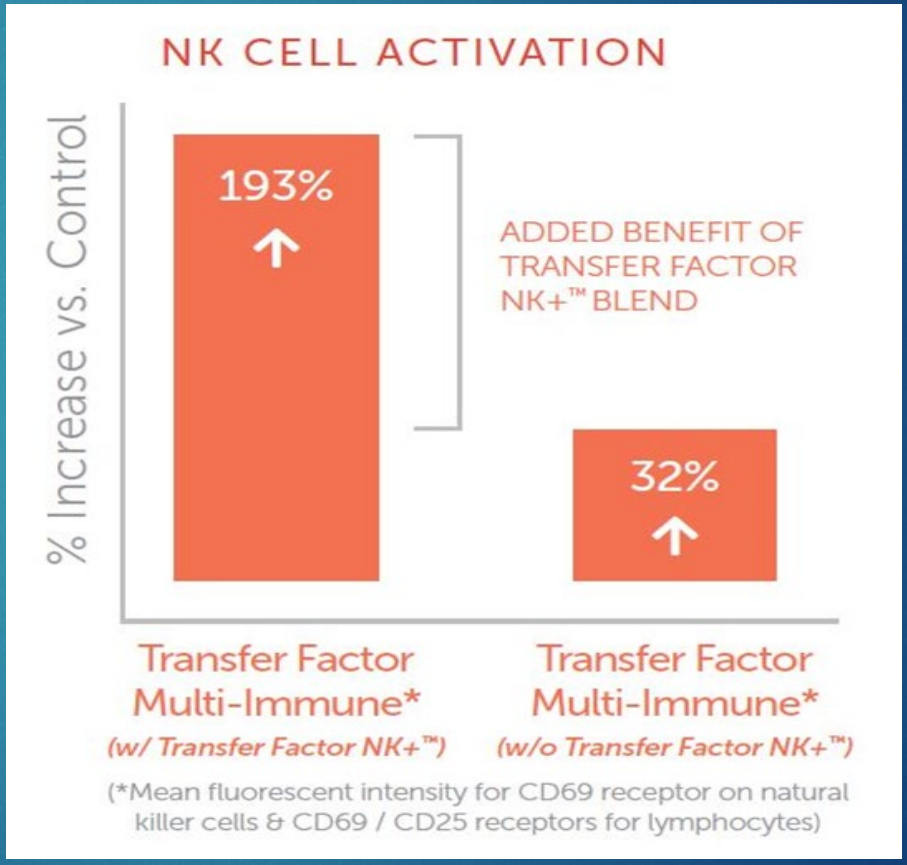
Transfer Factor Multi-Immune®

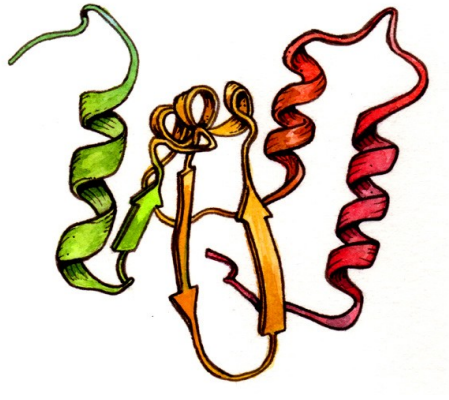
Transfer Factor vs. herbal blend with mushrooms and beta-glucan

Transfer Factor Multi-Immune™ vs. Same Product without Transfer Factor Ingredient



Transfer Factors

- Small proteins with RNA (nucleotide material)
- Made by activated T-helper cells
- Increases natural killer cells
- Promotes stronger Th1 immune response



Treating Long Haul COVID through Treating Chronic Pathology

- **Immune Dysregulation**
  - **Transfer Factor Multi-Immune™** - optimize and balance the immune system
- **Inflammation:**
  - **CytoQuel®** - support healthy cytokine activity and manage oxidative stress and inflammation, decrease clotting potential and support cardiovascular health
- **Mitochondrial Dysfunction:**
  - **ATP 360®** - repair mitochondrial membranes and support mitochondrial function
- **Oxidative Stress:** neutralize free radicals
  - **Tri-Fortify® Liposomal Glutathione**
  - **C-RLA™:** Liposomal vitamin C with R-lipoic acid
  - **H2Absorb™:** Molecular Hydrogen