Nutrients For Immune Support

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"The states of health or disease are the expressions of the success or failure experienced by the organism in its efforts to respond adaptively to environmental challenges"

> - Rene Dubose, Famed Microbiologist 1965

DEFENSIVE/PREVENTATIVE MEASURES

Plant Sterols/Sterolins

- Proprietary mixture of plant sterols and sterolins including beta-sitosterol and beta-sitosterol glycoside
- 100:1 optimal ratio
- Superior immune modulation
- Helps balance Th1 / Th2 immune arms
- Autoimmune thyroiditis



Bouic PJD. Sterols and sterolins: new drugs for the immune system? Drug Discovery Today 2002; 7:775–78.

Plant Sterols/Sterolins

- Decreases IL6, a pro-inflammatory cytokine
- Decreases TNF-alpha secretion, also proinflammatory
- Chronic inflammatory observed in the following:
 - Rheumatoid arthritis
 - SLE (Lupus)
 - Psoriasis
 - Insulin-dependent diabetes Type I

Bouic PJ, et al., The effects of B-sitosterol (BSS) and B-sitosterol glucoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation.Nnt J Sports Med. 1999 May;20(4):258-62.

Plant Sterols/Sterolins

Dose = 2 caps (20mg sterols/0.2mg sterolins/cap) in the morning, 1 cap at bedtime daily

May increase to 2 caps, 3 times daily if needed or if > 200 lb

Bouic PJ, et al., The effects of B-sitosterol (BSS) and B-sitosterol glucoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation.Nnt J Sports Med. 1999 May;20(4):258-62.

Medicinal Mushroom Blends

- Immune supportive water extracted beta-glucans (polysaccharides)
- Antibacterial, Antiviral, antifungal activity
- Supports microbiome
- 500mg BID-TID

- Chaga (Inonotus obliquus) (Scierotium)
- Cordyceps (Cordyceps sinensis or militaris) (Fruiting bodies)
- Shiitake (Lentinus edodes) (mushroom)
- Lions Mane (*Hericium* erinaceus)(fruiting bodies)
- Maitake (Grifola frondosa) (mushroom)
- Reishi (Ganoderma lucidum) fruiting body
- Turkey tail (Coriolus versicolor) mushroom

Lindequist U, Kim HW, Tiralongo E, Van Griensven L. Medicinal Mushrooms. Evidence-Based Complementary and Alternative Medicine. 2014;2014:2.



Vitamin A

- Vitamin A is the name of a group of fat-soluble retinoids, including retinol, retinal, and retinyl esters
- Immune supportive
- Also vision, reproduction, cellular communication
- Alters inflammatory response
- Vitamin A and retinoids reported to lead to compositional changes in microbiota
 - Improves Lactobacillus sp.
 - Partial reason for immune support
- Response to virus mediated by INF-beta upregulation

Lee H, et al. Antiviral effect of vitamin A on norovirus infection via modulation of the gut microbiome. Sci Reports. 2015;6:25835.

Vitamin A

- Both provitamin A and preformed vitamin A must be metabolized intracellularly to retinal and retinoic acid the active forms of vitamin A, to support the vitamin's important biological functions
- Most of the body's vitamin A is stored in the liver in the form of retinyl esters
- Vitamin A depleted by:
 - Aminoglycosides
 - Bile acid sequestrants (reduced absorption)
 - Colchicine

Lee H, et al. Antiviral effect of vitamin A on norovirus infection via modulation of the gut microbiome. Sci Reports. 2015;6:25835.

Vitamin A Dosage, Depletions

- 5,000 25,000 IU (1,500 7,500 RAE, retinol activity equivalents) vitamin A daily
- No more than 10,000 IU (3,000 RAE) in pregnant women daily
- Make sure to account for multivitamin/mineral amounts of vitamin A for total daily dosage needs

NIH National Institutes of Health. <u>https://ods.od.nih.gov/factsheets/VitaminA-</u> <u>HealthProfessional</u>. Accessed April 2020.

Zinc Immunity

- Essential micronutrient
- Involved in regulation of innate and adaptive immune responses
 - Modulates NF-kB master regulator of proinflammatory responses
 - Controls oxidative stress
- Zn deficiency leads to cell-mediated immune dysfunctions
- Deficiency associated with chronic inflammation
 - Increased infections and poor outcomes

Gammoh N.Z., Rink L. Zinc in infection and inflammation. Nutrients. 2017;9:624

Zinc Adjunct in Pneumonia Mortality

- Meta analysis, 6 randomized double-blind placebo controlled
- n = 2216 patients w/ severe pneumonia
- Zinc tx as adjunct to antibiotic tx
- Significantly reduced mortality
- No change in treatment failure

Wang L, et al. Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: a meta-analysis of randomized double blind and placebo controlled trials. Clin Resp J. 2018;12(3):857-64.

Zinc Autoimmunity

- 2018 Database review
- 62 studies included
- Relationship of Zinc status in autoimmune conditions
- For all models, Zn concentration in serum autoimmune patients significantly lower than controls

Sanna A, et al. Zinc status and autoimmunity: a systematic review and meta analysis. Nutrients. 2018;10(1):pii.E68.

• 30-50mg elemental zinc daily

• Zinc glycinate more bioavailable



 Zinc can alter iron and copper absorption, so dose independently if possible

Zinc

Copper needed by lysyl oxidase in collagenesis and elastic tissue formation

Quercetin

- Flavonoid (subclass flavonols) found in many fruits veggies and Botanicals examples....
 - Brassica veggies, tomatoes, spinach
 - Apples, berries, grapes
 - Onions, shallots, garlic, ginger
 - Seeds, nuts, flowers, barks, leaves
 - Ashwagandha, Holy basil, Bitter melon, Ginkgo, St. John's wort, Elder (Sambucus), Amla (Emblica), Licorice, others
- Av. Western diet takes in only 14mg daily quercetin
- Antioxidant supportive
- Immuno-supportive
- Anti-inflammatory metaflammation
 - Kelly GS. Quercetin. Alt Med Rev. 2011;16(2):172-94.

- David AVA, et al. Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn Rev. 2016;10(20):84-89.





Quercetin

- Cardioprotective
- Neuroprotective
- Inflammatory mediators including NO synthase, COX-2, and CRP, lipoxygenase
- Reported to : \downarrow Total Cholesterol, Trigs, LDL, oxLDL , \uparrow HDL
- Important antiviral activity
- Viruses commonly responding to quercetin include (in-vitro):
 - H5N1 avian, H1N1 swine, Ebola, adenovirus, herpes simplex virus, Japanese encephalitis virus, respiratory syncytial virus, Zika virus
- Chopra M, et al. Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clin Chem. 2000;46(8 Pt 1):1162–70. Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents. 2005;26:343–56.

Quercetin

- Disrupts HIV latency allows HIV to be more susceptible to Tx
- Interacts with viral HA2 (hemagglutinin) subunits decreases viral entry
- Inactivates viral NS3 protease
- Sirtuin activity upregulates SIRT1 and SIRT2 in vivo
- Sirtuins are evolutionary conserved viral restriction factors
- Broad-spectrum antiviral activity
- Dose = 500mg 1-3 times daily

Peredo-Escarcega AE, et al. The Combination of Resveratrol and Quercetin Attenuates Metabolic Syndrome in Rats by Modifying the Serum Fatty Acid Composition and by Upregulating SIRT 1 and SIRT 2 Expression in White Adipose Tissue. Evid Based Complement Alternat Med. 2015;2015:474032.

Thymus glandular

- New Zealand bovine Thymus tissue
- High quality, tested purity, contaminants
- Improves innate immunity
- Dosage 250mg 2 am, 1 afternoon

Zdrojewicz Z, et al. The thymus: a forgotten, but very important organ. Adv Clin Exp Med. 2016;25(2):369-75. Reggiani PC, et al. The Thymus-neuroendocrine axis. Ann NY Acad Sci. 2009;1153:98-106.





Diagnosed with Virus

Nicotinamide Riboside (NR)

- Form of vitamin B3 (niacin) found mainly in Cow's milk / yeast
- Statistically significantly increases NAD+ levels*
- Supports ongoing mitochondrial health*



- Promotes cellular resilience and repair*
- Neuroprotective activity

*Yang SJ, L, et al. Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes. J Nutr Biochem. 2014;25(1):66-72.

*Bieganowski P, et al. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a Preiss-Handler independent route to NAD+ in fungi and humans. Cells. 117;495-502.

Nicotinamide Riboside (NR)

- NAD+ plays key role in innate immunity
- Viral infections deplete intracellular NAD+ pools
- Polyadenosine diphosphate-ribose polymerases (PARPs) promote ADPribosylation, a form of protein posttranslational modifications
- PARPs activated *in-vivo* post viral infection
- Leads to depleted NAD+

Mesquite, et al. Cell. Mol. Life Sci. (2016) 73:1225-1236



Grady et al. Journal of Virology (2012) 86(15): 8259-8268

NAD-dependent enzymes play a key role in all stages of COVID-19 Viral Infection



The molecular story of COVID-19; NAD⁺ depletion addresses all questions in this infection

Shirin Kouhpayeh^{1†}, Laleh Shariati^{2,3†}, Maryam Boshtam⁴, Ilnaz Rahimmanesh⁵, , Mina Mirian⁶, Mehrdad Zeinalian⁵, Azhar Salari-jazi⁷, Negar Khanahmad⁸, Mohammad Sadegh Damavandi⁷, Parisa Sadeghi⁷, Hossein Khanahmad^{5*}

NR

- Supports neuronal NAD⁺ synthesis without inhibiting sirtuins
 - Sirtuins important regulators of metabolism and longevity
 - Sirtuins also evolutionary components of immunity viral restriction factors
 - NAD⁺ is a rate-limiting co-substrate for sirtuin enzymes
 - NR regulates sirtuin function and subsequent regulation of oxidative metabolism
 - * Canto C, et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high fat diet-induced obesity. Cell Metab. 2012;15(6):838-47.
 - * Suave AA. Nicotinamide and vitamin B3: from metabolism to therapies. J Pharmacol Exp Ther. 2008;324(3):883-93

NR

- Orally available commercial product containing nicotinamide riboside is patented
- Oral dose 300-500mg daily
- 300mg NSF certified for sport
- May also be used intranasally and / or sublingually

Andrographis paniculata aerial parts

 "King of Bitters" – SE Asian botanical for immune/inflammatory conditions



- Andrographalide phytochemical w/ Broad spectrum antibacterial, antiviral, antifungal, antiparasitic activity
- Hepatoprotective antioxidant
- Antiinflammatory
- Reported to help improve Th1/Th2

and Th17 modulation

• Dose = 300mg BID std 10-50% and rographolides

Jayakumar T, et al. Evid Based Complement Alternat Med. 2013; 2013;846740.

Andrographis Upper Respiratory Tract Infections (uRTIs)

- 2010 randomized, double blind placebo controlled
- N=223 patients with uncomplicated URTI
- 200mg / day standardized andrographis or placebo
- RESULTS:
 - Significant reduction in symptoms scores for andrographis vs placebo
 - 2.1 x more effective than placebo in reducing symptoms of URTI

Saxena RC, et al. Phytomedicine. 2010;17(3-4):178-85.

Andrographis Autoimmune Associated Fatigue

- 2016, 12 month double blind placebo-controlled pilot study
- N=25 Multiple Sclerosis patients (relapsing-remitting)
- 170mg BID standardized andrographis BID
- Andrographis significantly improved Fatigue Severity Scores (FSS) in patients receiving interferon

Bertoglio JC, et al. Andrographis paniculata decraeses fatigue in patients with relapsingremitting multiple sclerosis: a 12 month double blind placebo controlled pilot study. BMC Neurol. 2016;16:77.

Thai Ginseng (*Kaempferia parviflora*) root

- aka Black Ginger in the ginger family
- Contains high level of antioxidant polymethoxyflavones specifically 5,7 dimethoxyflavone
- Improves mitochondrial biogenesis increased energy
- SIRT 1 upregulation 3-4x that of resveratrol
- Sirtuins are evolutionarily viral restriction factors antiviral

Koynucu E, et al. Sirtuins are evolutionary conserved viral restriction factors. mBio. 2014;5(6):e02249-14.



Thai Ginseng (*Kaempferia parviflora*) root

- Reported to inhibit viral proteases
- Reported strong activity vs. pathogenic H5N1 avian influenza virus
- Upregulates of TNF- α and IFN- β mRNA expressions
- Inhibition of virus replication
- Active against cytokine response to virus infection cytokine "storm"

Sookkongwaree K, et al. Inhibition of viral proteases by Zingiberaceae extracts and flavones isolated from Kaempferia parviflora. Sompet B, et al. Antiviral activity of five Asian medicinal plant crude extracts against highly pathogenic H5N1 avian influenza virus. Asian Pac J Trop Med. 2017;10(9):871-76.





Yoshino S, Kim M, Awa R, Kuwahara H, Kano Y, Kawada T. 2014. Kaempferia parviflora extract increases energy consumption through activation of BAT in mice. Food Sci Nutr 2: 634–637.
Promthep K, et al. Effect of Kaempferia parviflora extract on physical fitness of soccer players: A randomized double blind placebo controlled trial. Med Sci Monit Basic Res. 2015;21:100-108.

Thai Ginseng root

- Improves weight management
 - SIRT1 and PPAR gamma regulating
 - Increases whole-body energy expenditure (EE)
 - Improves brown adipose tissue (BAT) production
- PDE5 inhibitor improves nitric oxide utilization
- Traditionally used in erectile dysfunction
- Reported to improve athletic performance based on stress response and cardiorespiratory performance

Thai Ginseng

- 50mg BID std. to 4% or > 5,7 dimethoxyflavone
- Use with caution if also prescribing PDE5 inhibitors
- 5,7-DMF markedly decreases expression of CYP3A11 and CYP3A25 in the liver

- Use with caution if prescribing medications metabolized by these enzymes including:
 - Benzodiazepines
 - Buspirone
 - Calcium channel blockers
 - Carbamazepine
 - HIV protease inhibitors
 - Fentanyl
 - Felodipine, nifedipine
 - Lovastatin, simvastatin
 - Quinidine, quinine

English Ivy Extract (Hedera helix)

- Ivy leaf used for bronchial issues in Europe for decades as Rx medicine
- Mucolytic, spasmolytic, bronchodilatory and antibacterial
- German Commission E approves Ivy extract for symptomatic relief of acute and chronic respiratory inflammation
- Antispasmodic and expectorant saponins and phenolic phytocompounds
- Saponins trigger gastric mucosal response
- Activates mucous glands in bronchi through parasympathetic signaling

Trute, A. et al. 1997. *In vitro* antispasmodic compounds of the dry extract obtained from *Hedera helix*.*Planta Med* 63(2):125129.

English Ivy Extract (Hedera helix)

- A 2009 post-marketing study in 9657 patients (5181 children) with bronchitis (acute or chronic bronchial inflammatory disease) were treated lvy extract (syrup) 11% hederacoside C
 - 0–5 years: 2.5 ml TID
 - 6–12 years: 5 ml TID
 - 12 years >: 5–7.5 ml TID
- After 7 days of therapy, 95% of the patients showed improvement or healing of their symptoms
- SE's 2.1% (1.5% transient GI discomfort)
- Note some patients got antibiotics as well, with no apparent benefit respective to efficacy but a 26% \uparrow in SEs

Fazio S, Pouso J, Dolinsky D, et al. Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. Phytomedicine. 2009;16(1):17–24.

English Ivy Extract (Hedera helix)

- Review of studies 10 trials, n=17,463 patients
- Conclusion: Ivy effective in reducing symptoms of URTI including frequency and duration of cough and improvement in mucous production
- Dosage = 5-10ml 3-4 times daily
- Std. 11% hederacoside C (4.7mg/5ml)

Trute, A. et al. 1997. *In vitro* antispasmodic compounds of the dry extract obtained from *Hedera helix*.*Planta Med* 63(2):125129.

Pelargonium sidoides root

- African geranium
- High level of polyphenols (mainly catechin and gallocatechin) also found in Green tea
- Antiviral ; antibacterial
- Cytoprotective effect against virus-induced cell destruction
- Immune modulatory
 - Increases TNF-alpha, NO
 - Stimulates interferon synthesis
 - Increases NK cell activity
 - Increases phagocytosis

Kolodziej H, et al. In vitro evaluation of antibacterial and immunomodulatory activities of *Pelargonium reniforme, Pelargonium sidoides* and the related herbal drug preparation EPs[®] 7630. Phytomedicine. 2007;14(suppl 1):18-26.



Koch E, et al. *Pelargonium sidoides* root extract EPs 7630 stimulates release antimicrobial peptides from neutrophile granulocytes in human whole blood. Planta Medica. 2007;73:846.

Pelargonium sidoides root

- Increases release of defensins antimicrobial peptides from neutrophilic granulocytes
- Stimulates ciliary best frequency in respiratory cells
- Improves respiratory cell vitality
- Most clinical studies with proprietary extract Eps 7630

Neugebauer, P. *et al*. A new approach to pharmacological effects on ciliary beat frequency in cell cultures – exemplary measurements using *Pelargonium sidoides* extract, Phytomedicine. 2005; 12: 47–52.





Pelargonium sidoides root



Pelargonium Clinical Effectiveness

- Acute Upper Respiratory Tract infections (uRTIs)
 - 2013 Cochrane Database Systematic Review: P. sidoides may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults,
- Bronchitis and bronchial irritation
 - Meta-analysis 2008 of 6 clinical trials reported in patient w/ bronchitis a 7day treatment with Pelargonium reduced severity and duration of bronchial symptoms significantly over placebo

Timmer A, et al. Pelargonium sidoides extract for treating acute respiratory tract infections. Cochrane Database Syst Revi. 2013;(10):CD006323. Agbabiaka TB, et al. Pelargonium sidoides for acute bronchitis: a systematic review. Phytomedicine. 2008;15(5):378-85. Keck T, et al. Tolerability and Treatment Effects of Pelargonium sidoides Preparation EPs 7630 in Adults Suffering from Acute Rhinopharyngitis– A Prospective, Open-Label Trial. Altern Integr Med. 2015;4:4.

Pelargonium Clinical Effectiveness

- Cough
 - 2003 randomized, double-blind placebo-controlled trial 143 children ages 6-10 with non-stress sore throat; EPs 7620 or placebo x 6 days. Day 2 decreased symptoms, day 6 80.8% of treated returned to school vs. 21.4% placebo
- Nasal irritation
- Common Cold
 - Multiple studies report efficacy and tolerability of EPs 7630 in treating symptoms of and decreasing duration of the common cold (rhinovirus)

Timmer A, et al. Pelargonium sidoides extract for treating acute respiratory tract infections. Cochrane Database Syst Revi. 2013;(10):CD006323. Agbabiaka TB, et al. Pelargonium sidoides for acute bronchitis: a systematic review. Phytomedicine. 2008;15(5):378-85. Keck T, et al. Tolerability and Treatment Effects of Pelargonium sidoides Preparation EPs 7630 in Adults Suffering from Acute Rhinopharyngitis– A Prospective, Open-Label Trial. Altern Integr Med. 2015;4:4.

Peptides in Immune Support

Peptide Immune Support -

TA1

Thymosin Alpha-1 (TA1)

Synthetic thymic peptide



 Zadaxin[®] (thymalfasin) is patented pharmaceutical version for Hepatitis B&C

and HIV

- Immune supportive modulates innate immunity (pleiotropic)
- Improves Th1/Th2 balance
- Helps modulate human GUT mucosal immune system

Ershler WB, et al. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. Ann NY Acad Sci. 2007;1112:375-84. Zadaxin prescribing information SciClone Pharmaceuticals. <u>www.scicloneinternational.com</u> Elltsur Y, et al Thymosin alpha 1 and thymosin beta 4 modulate human colonic lamina propria lymphocyte function. Immunopharmacology. 1990;20(2):89-96.

TA1 Mechanism



Peptide Immune Support -TA1

- Used in over 3,000 patients in over 70 clinical studies for immune support either alone or in conjunction w/ pharmaceuticals
- Used in conjunction with vaccines to support immunity
- Dosage TA1
 - 3,000 mcg/ml 5ml vial
 - 0.15 ml SQ daily
 - Transient increases in ALT may occur

Thymosin Beta-4 (TB4)

- Thymosin β-4 (TB4 or TB-500)
 - Originally isolated from calf thymus
 - More ubiquitous occurs in most all cells
 - 43 amino acids
 - Ac-Ser-Asp-Lys-Pro-Asp-Met-Ala-Glu-Ile-Glu-Lys-Phe-Asp-Lys-Ser-Lys-Leu-Lys-Lys-Thr-Glu-Thr-Gln-Glu-Lys-Asn-Pro-Leu-Pro-Ser-Lys-Glu-Thr-Ile-Glu-Gln-Glu-Lys-Gln-Ala-Gly-Glu-Ser
 - Higher levels in platelets and white cells



TB4

- Helps decrease scar tissue formation
 - Reduces level of myofibroblasts
- Supports immunity
 - Antimicrobial
 - Improves T cells
 - Use with Thymosin alpha 1
 - Helps modulate human GUT mucosal immune system
- Neuroprotective

Elltsur Y, et al Thymosin alpha 1 and thymosin beta 4 modulate human colonic lamina propria lymphocyte function. Immunopharmacology. 1990;20(2):89-96. Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30. Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

TB4 Summary



Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30. Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci. 2007;1112: 219–224.

TB4 Applications

- Immune support in conjunction w/ TA1
- Soft Tissue Repair tendon, ligament, muscle
 Sports/athletic injuries
- Pressure or venous stasis ulcers
- Conditions requiring immune response modulation
- Brain issues if autoimmunity suspected
- Ischemic stroke

Kleinman HK, Sosne G. Thymosin B4 promotes dermal healing. Vitam Horm. 2016;102:251-75.

Yarmola EG, Kilmenko ES, Fujita G, et al. Thymosin beta4: actin regulation and more. Ann NY Acad Sci. 2007;1112:76-85.

TB4 Applications

- Decreases endotoxemia use in sepsis
- Reported in lab studies to reduce polymerization fo G-actin into F-actin
- Improves mortality rate in sepsis

Badamchian M, et al. Thymosin beta 4 reduces lethality and down-regulates inflammatory mediators in endotoxin-induced septic shock. Int Immunopharmacol. 2003;3(8):1225-33.

TB4 Dosage

- General dosage
 - 300 mcg 1 gram daily, SubQ
 - Depending upon clinical presentation
 - Do not dose for more than 3 months
 - Cycle if needed long-term 3 months on, 1 month off
- TB4 use with Thymosin alpha 1 and BPC-157 concurrently
- Individual dosage requirements may vary based on clinical presentation

Immune Supportive Plan

- HYDRATE well
- Dietary issues
- Exercise in moderation