

Nutrients For Immune Support

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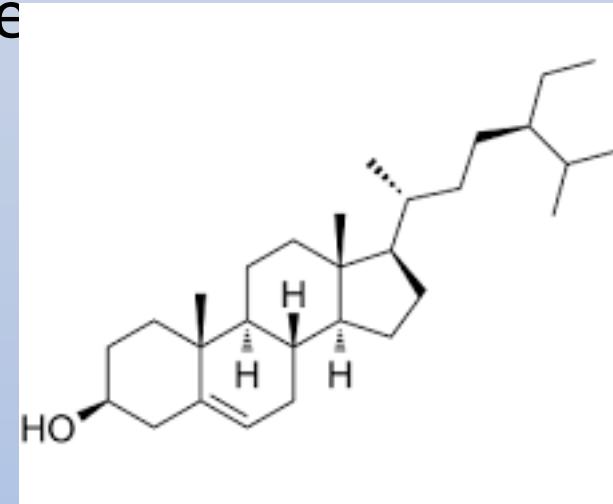
“The states of health or disease are the expressions of the success or failure experienced by the organism in its efforts to respond adaptively to environmental challenges”

- 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



Plant Sterols/Sterolins

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

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

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

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

Zinc Immunity

- Essential micronutrient
- Involved in regulation of innate and adaptive immune responses
 - Modulates NF- κ B – 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

Zinc Adjunct in Pneumonia Mortality

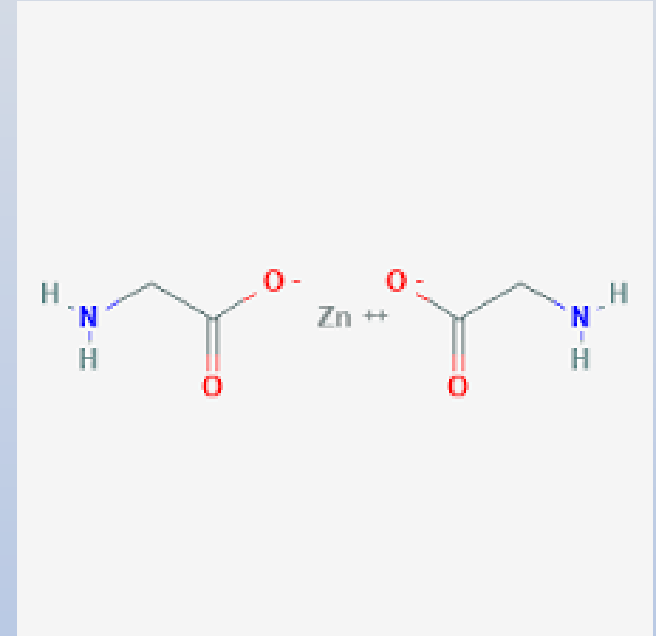
- Meta analysis, 6 randomized double-blind placebo controlled
- n = 2216 patients w/ severe pneumonia
- Zinc tx as adjunct to antibiotic tx
- Significantly reduced mortality
- No change in treatment failure

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

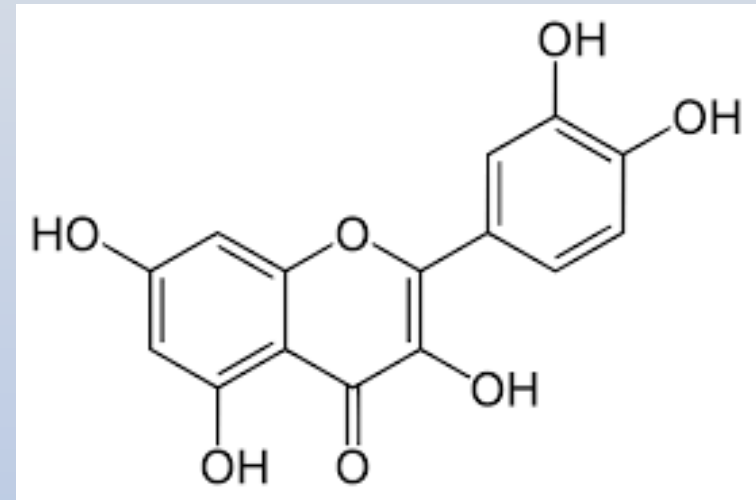
Zinc

- 30-50mg elemental zinc daily
- Zinc glycinate more bioavailable
- Zinc can alter iron and copper absorption, so dose independently if possible
- 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

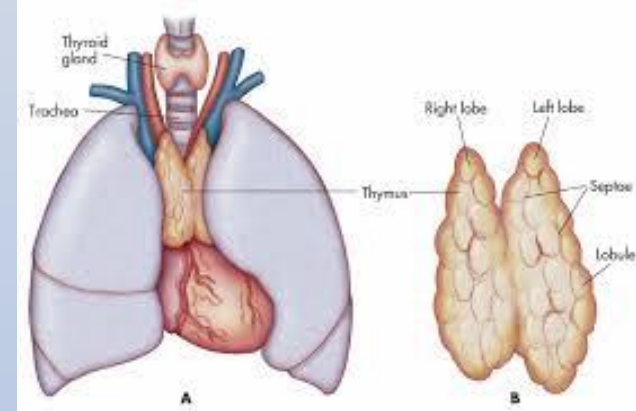
- Cardioprotective
 - Neuroprotective
 - ↓ inflammatory mediators including NO synthase, COX-2, and CRP, lipoxygenase
 - Reported to : ↓ Total Cholesterol, Trigs, LDL, oxLDL , ↑ HDL
 - Important antiviral activity
 - Viruses commonly responding to quercetin include (***in-vitro***):
 - H5N1 avian, H1N1 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

Thymus glandular

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



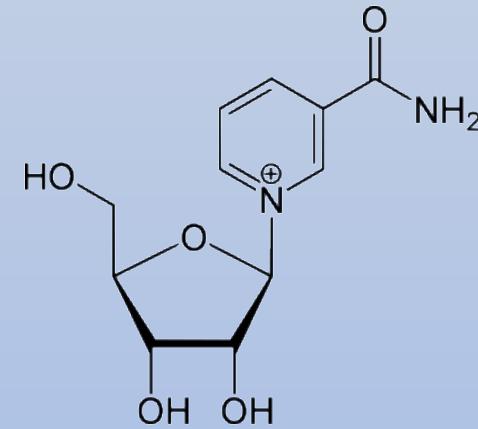
Zdrojewicz Z, et al. The thymus: a forgotten, but very important organ. *Adv Clin Exp Med*. 2016;25(2):369-75.

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**

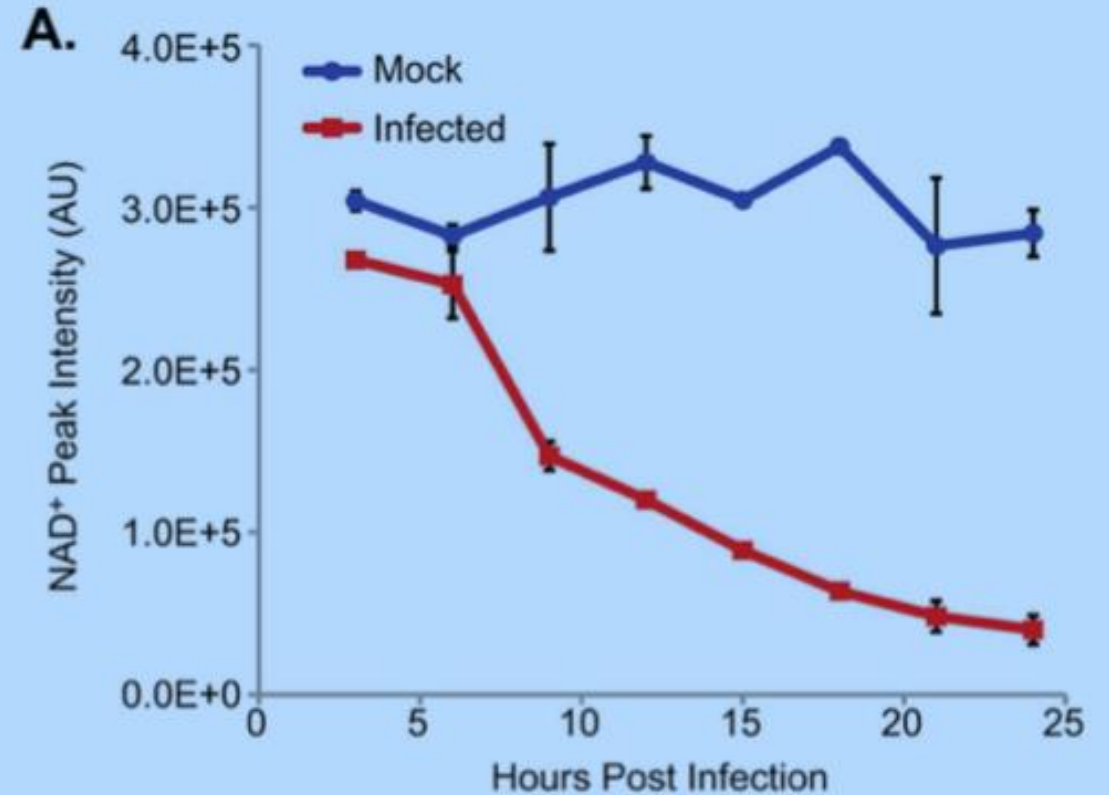


*Yang SJ, L, et al. Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes. *J Nutr Biochem.* 2014;25(1):66-72.

*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 ADP-ribosylation, a form of protein posttranslational modifications
- PARPs activated *in-vivo* post viral infection
- Leads to depleted NAD⁺



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% andrographolides



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

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 decreases fatigue in patients with relapsing-remitting 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



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.

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



- 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

- 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 phytochemicals
- 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):125-129.

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 Ivy 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% ↑ 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



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

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.

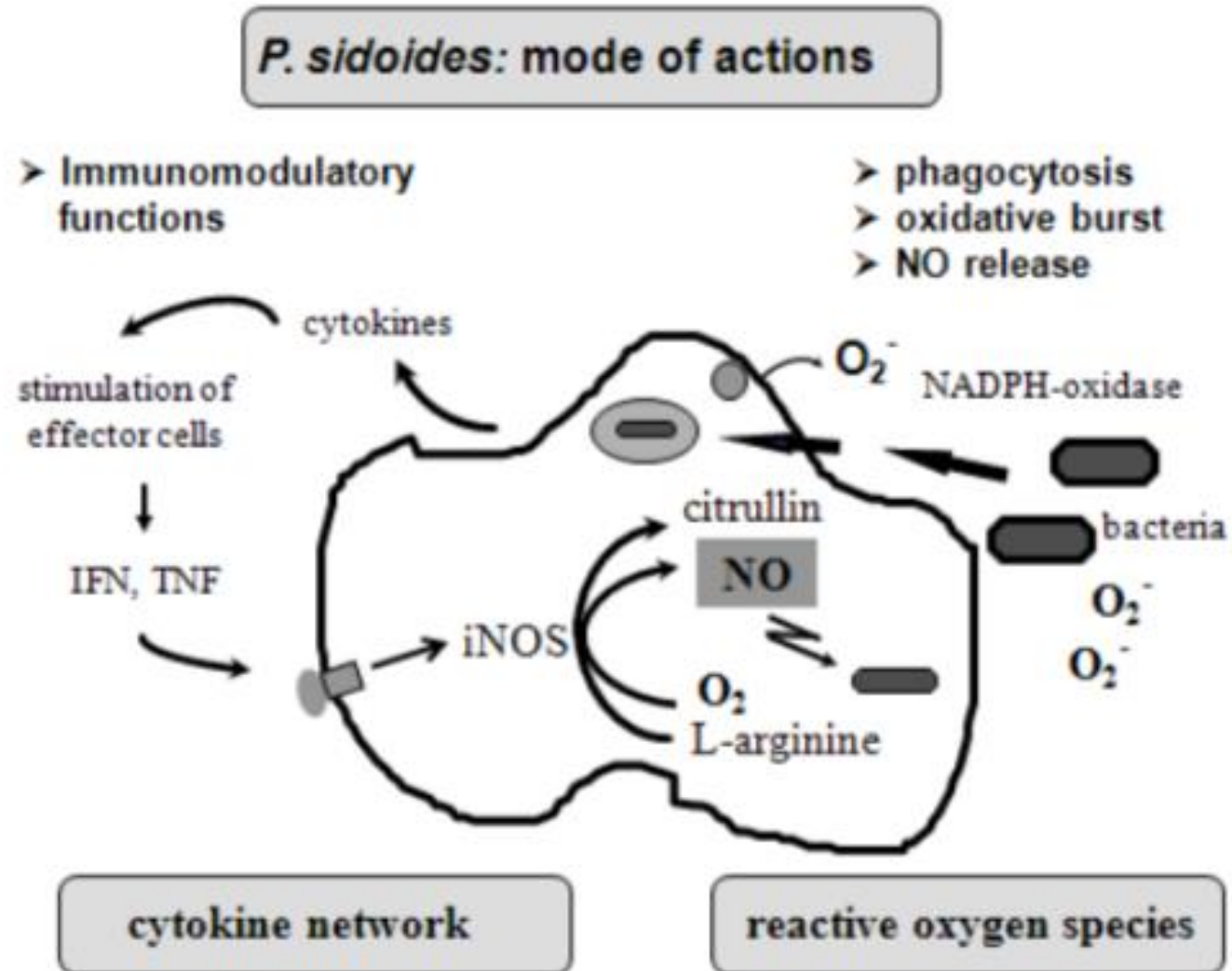
Pelargonium sidoides root

- Increases release of defensins - antimicrobial peptides – from neutrophilic granulocytes
- Stimulates ciliary beat 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 7-day treatment with Pelargonium reduced severity and duration of bronchial symptoms significantly over placebo

Pelargonium Clinical Effectiveness

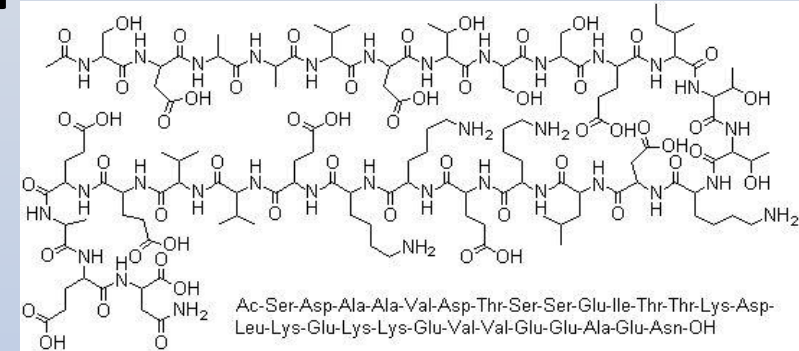
- Cough
 - 2003 randomized, double-blind placebo-controlled trial 143 children ages 6-10 with non-stress sore throat ; EPs 7620 or placebo x 6 days. Day 2 decreased symptoms, day 6 80.8% of treated returned to school vs. 21.4% placebo
- Nasal irritation
- Common Cold
 - Multiple studies report efficacy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

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

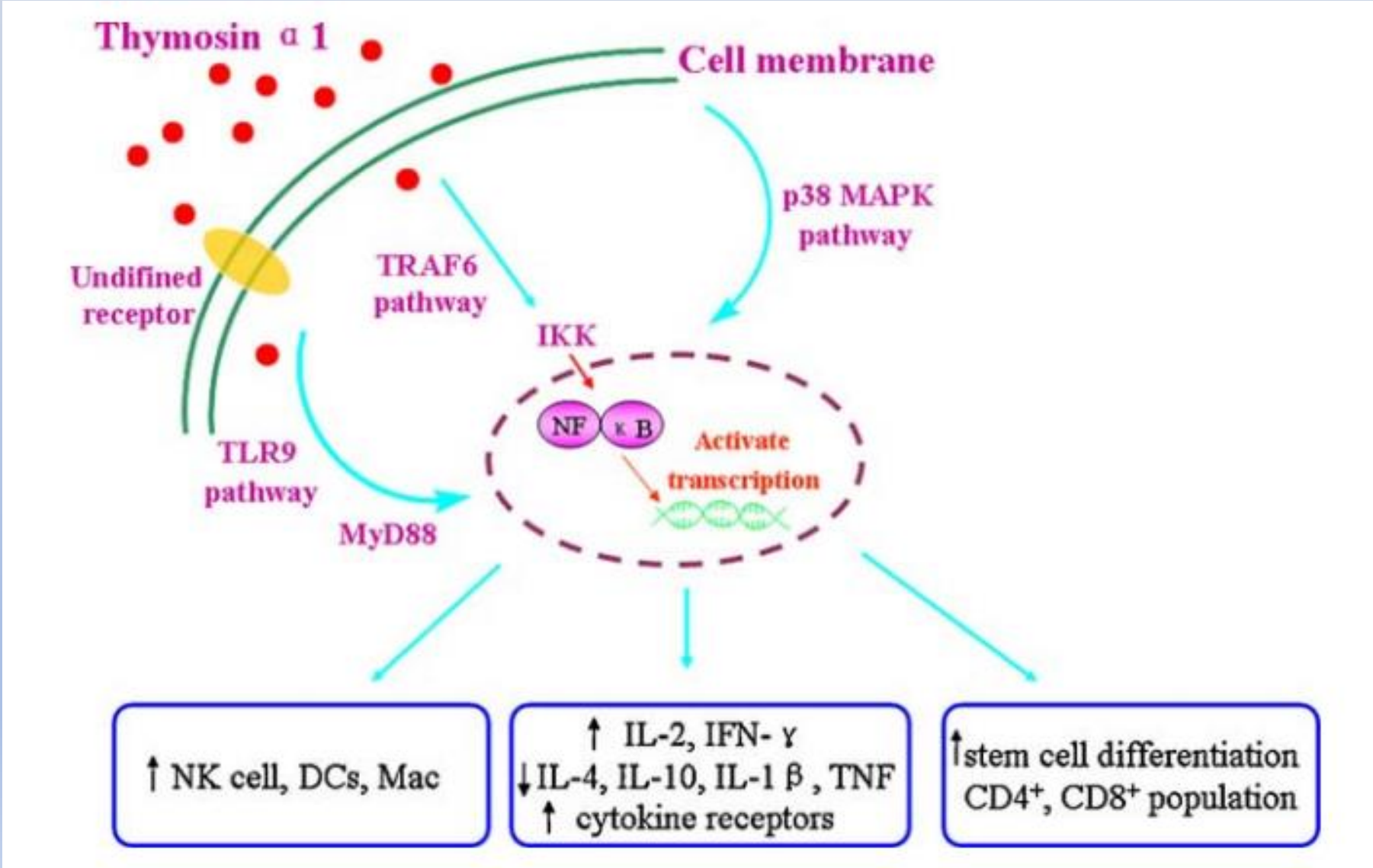


Ershler WB, et al. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. *Ann NY Acad Sci.* 2007;1112:375-84.

Zadaxin prescribing information SciClone Pharmaceuticals. www.scicloneinternational.com

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

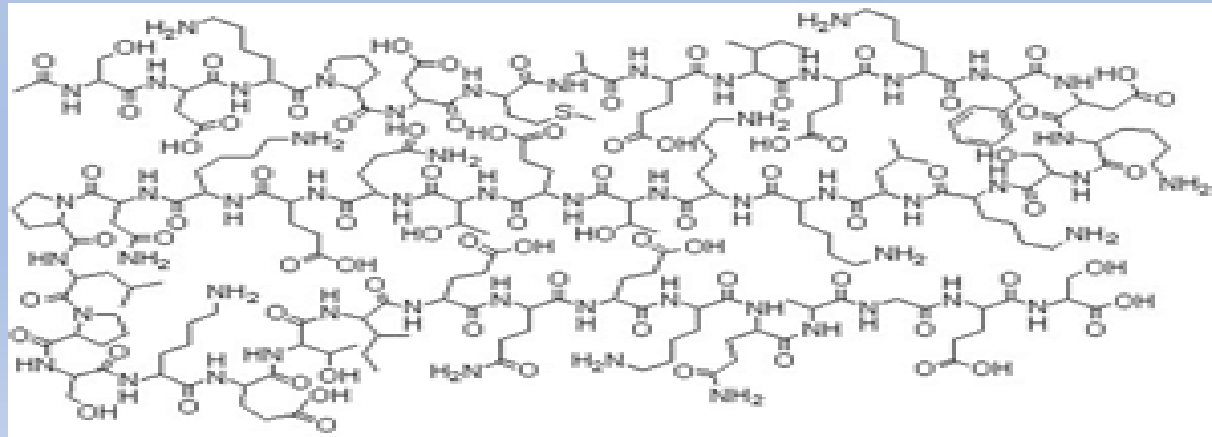


Peptide Immune Support - TA1

- 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

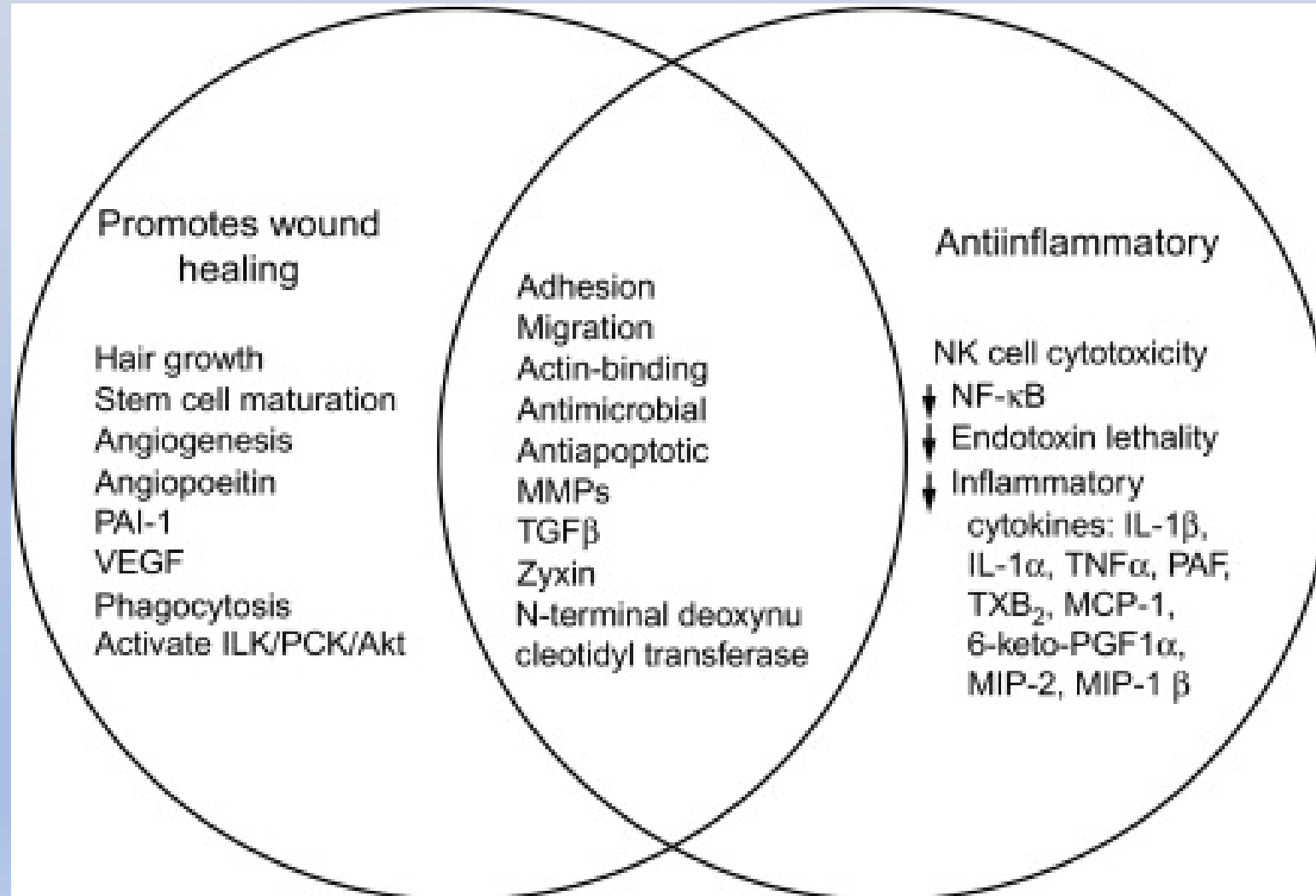


TB4

- 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

Eltsur 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 of G-actin into F-actin
- Improves mortality rate in sepsis

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