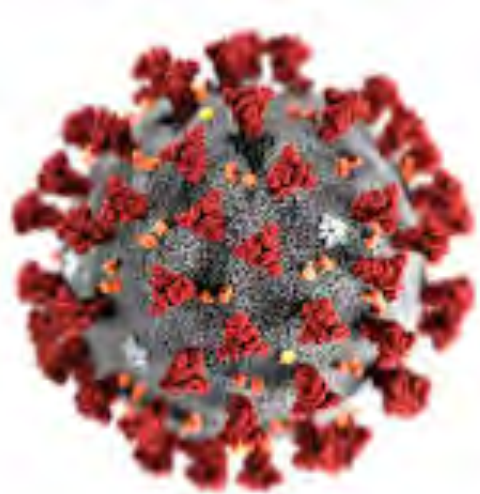
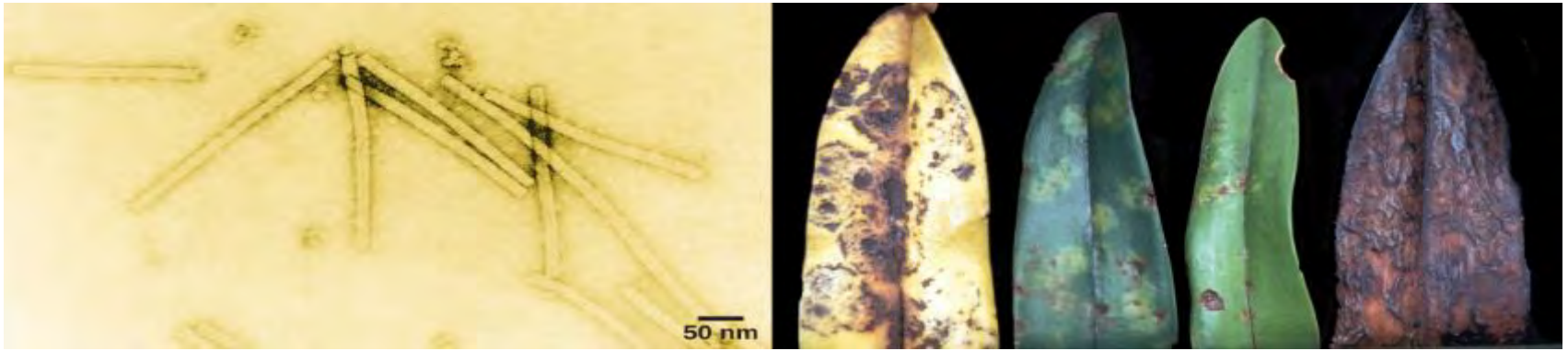
COVID-19 and Immune Support

with Dr. Gaetano A. Morello



"The body has an innate ability to heal itself, provide it with the environment and recovery will come."

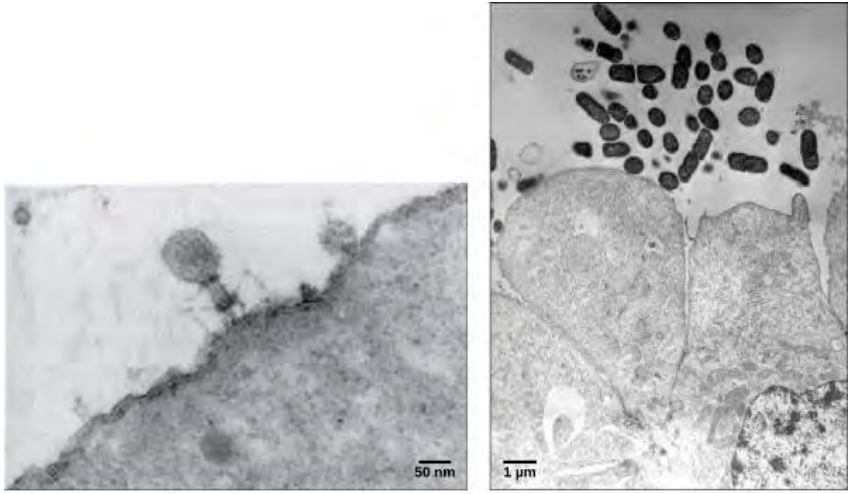
The First Virus Discovered



- The tobacco mosaic virus (left), seen here by transmission electron microscopy, was the first virus to be discovered. The virus causes disease in tobacco and other plants, such as the orchid (right)

Some Perspective

In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these *E. coli* cells are dwarfed by cultured colon cells



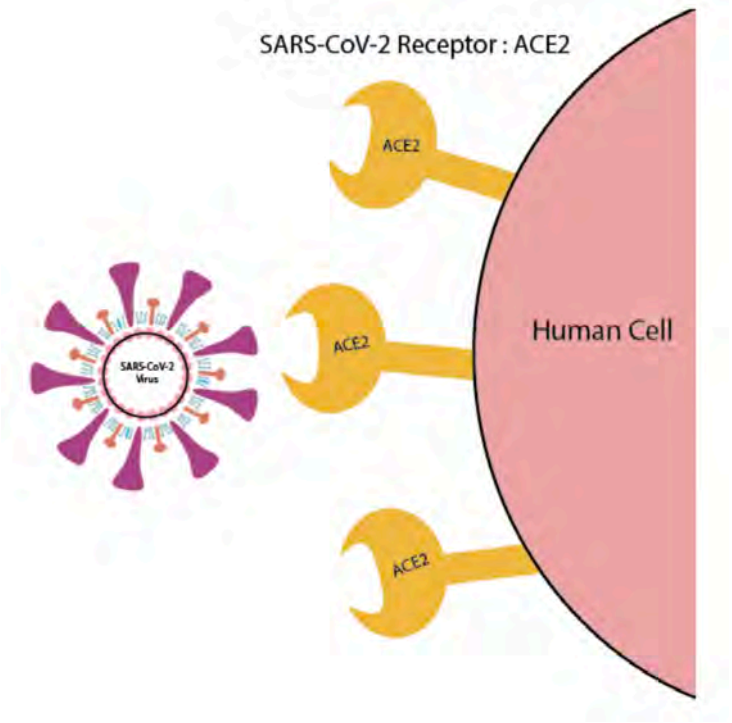
Where Did SARS-CoV-2 (Severe Acute Respiratory Syndrome) Come From?

- Current scientific consensus is a bat transferred to human; others argue that it was developed in lab
- Where did that transfer occur?
  - ***Accidental leak from Wuhan Institute of Virology***
  - "Wet" market
  - Bat feces
  - Pangolin

What Increases the Risk of Severe COVID-19?

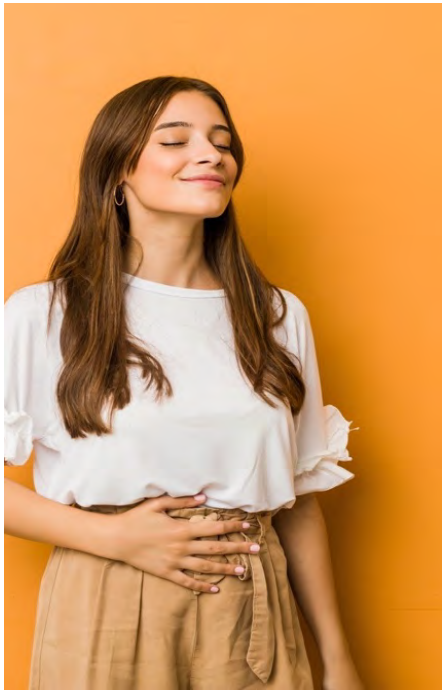
- People 65 years and older
- People who live in a nursing home or long-term care facility*
- People of all ages with underlying medical conditions, particularly if not well controlled, including:
  - COPD (chronic obstructive pulmonary dz) or moderate to severe asthma
  - Low immune function due to any reason
  - Obesity, diabetes, high blood pressure
  - Chronic kidney or liver disease
- **Medications?* ACE inhibitors, PPIs, NSAIDs, acetaminophen**
- **Influenza vaccine?***

Do ACE-Inhibitors Increase the Risk of COVID-19



- Angiotensin converting enzyme is critical in influencing blood flow throughout the body.
- ACE inhibitors are among the most popular blood pressure lowering drugs.
- By blocking ACE it leads to an increase in ACE2 receptors on cells throughout the body thereby increasing the number of portals for SARS-CoV-2

The Digestive Tract Has a Role in Lung Health and SARS-CoV-2 Infection



- The GI tract is an important route of infection with SARS-CoV-2 (Virus)
- Within the GI tract, **stomach acid and digestive enzymes** are important for immune health.
  - Stomach Acid:

    Proton Pump Inhibitors increase the gut route of coronavirus infections of the the lungs in animal models. *Sci Adv. 2017 Nov 15;3(11):eaao4966.*
  - Digestive Enzymes:

    Pancreatic enzyme insufficiency is a known risk factor for increased respiratory infections.

What About NSAIDs and Acetaminophen?

- Is reducing the fever a good idea?
- NSAIDs are known to worsen COVID-19? Why? Increase gut permeability?? Or via another mechanism?
- Acetaminophen is known to slow down viral clearance. (reduces antibody response)
- Acetaminophen could be catastrophic due to depletion of glutathione – the main antioxidant in cells and the lungs.

Vaccines

- Skip next 3 slides.

- Will a vaccine work????
- Vaccines do have an affect but will it work for COVID19??
- Do current flu shots eradicate the influenza virus??

The Effect of the Flu Vaccine on Coronavirus Infection Rate

- *Wolff GG. Influenza Vaccination and Respiratory Virus Interference Among Department of Defense Personnel During the 2017-2018 Influenza Season. Vaccine 2020;38 (2):350-354.*
- Study Objective and Design:
  - To determine the risk of vaccinated individuals for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection due to the vaccine producing "viral interference" by examining infection rates in 2,880 vaccinated vs. nonvaccinated members of the U.S. Department of Defense.
- Key Finding:
  - "Vaccine derived virus interference was significantly associated with coronavirus"
  - Vaccination was associated with a 36% increase in the relative risk of developing a coronavirus infection.

Were Early Flu Shots Effective?

- *Cochrane Database Syst Rev. 2010 Jul 7;(7):CD001269*
  - In healthy adults, vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates.
  - Industry funded studies were more likely to be positive than studies funded from public sources.

  "The review showed that reliable evidence on influenza vaccines is thin but there is evidence of widespread manipulation of conclusions and spurious notoriety of the studies."

What about in targeted groups?

- *Michiels B, et al. A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. Vaccine. 2011 Nov 15;29(49):9159-70.*
- Key Findings:
  - No quality evidence exists on the effectiveness of influenza vaccination on complications such as pneumonia, hospitalization and influenza-specific and overall mortality.
  - In healthy adults, vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates.
  - **Inconsistent results are found in studies among children younger than 6 years, individuals with COPD, institutionalized elderly (65 years or older), elderly with co-morbidities and healthcare workers in elderly homes, which can only be explained by bias.**

To Enhance Effectiveness in Elderly, Super Vaccines Were Created

Wilkerson K, et al. Efficacy and safety of high-dose influenza vaccine in elderly adults: A systematic review and meta-analysis. Vaccine. 2017 May 15;35(21):2775-2780.

Study Design:

- Reviewers independently identified RCTs comparing high-dose influenza vaccine (60µg of hemagglutinin per strain) to standard-dose influenza vaccine (15µg of hemagglutinin per strain) in adults over the age of 65years.

Key Findings:

- Patients receiving the high-dose vaccine had 24% less risk of developing influenza infections.
- Post-vaccination measures of immune response (mean titres and seroprotection rates) were also higher in the high-dose vaccine recipients.
- Researchers concluded "the high-dose influenza vaccine was well-tolerated, more immunogenic, and more efficacious in preventing influenza infections than the standard-dose vaccine.

Why do some healthy, young people suffer severe infection?

- Nutritional factors
- Genetic factors
- Load of viral exposure (inoculum level)*
  - It's a race between the virus finding enough target cells to replicate and the immune response trying to eliminate the virus. A larger dose of virus gives the virus a head start in the race.*
  - A higher dosage of SARS-CoV-2 exposure leads to higher levels of the virus in the body in multiple areas (respiratory tract and gut), greater infectivity, and more significant risk for severe disease.*

The Infection Equation

In the infection equation the interaction of the host's immune system with the infecting organism determines the equation's outcome.

Weak immune system + highly infectious virus = Severe disease

Strong immune system + highly infectious virus = Less severe to no disease

THE FOUR CORNERSTONES OF GOOD HEALTH

- ✓ **Positive Mental Attitude**
- ✓ **Health Promoting Lifestyle**
- ✓ **Diet**
- ✓ **Supplementary Measures**

Overview of the Immune System

- **First line of defense:** Physical barriers that viruses, bacteria must cross
  - Skin
  - Mucous membranes that line digestive, respiratory, reproductive tracts
- **Second line of defense:** Innate immune system (non-specific immunity)
  - Macrophages, neutrophils, natural killer (NK) cells, dendritic cells, etc.
  - Cytokines -- hormone-like proteins that mediate immunity and inflammation
  - Complement proteins
  - Serum factors
- **Third line of defense:** Adaptive immune system (adapts to defend against specific pathogens)
  - B cells make antibodies to fight infectious organism.
  - T cells regulate cell-mediated immune responses.

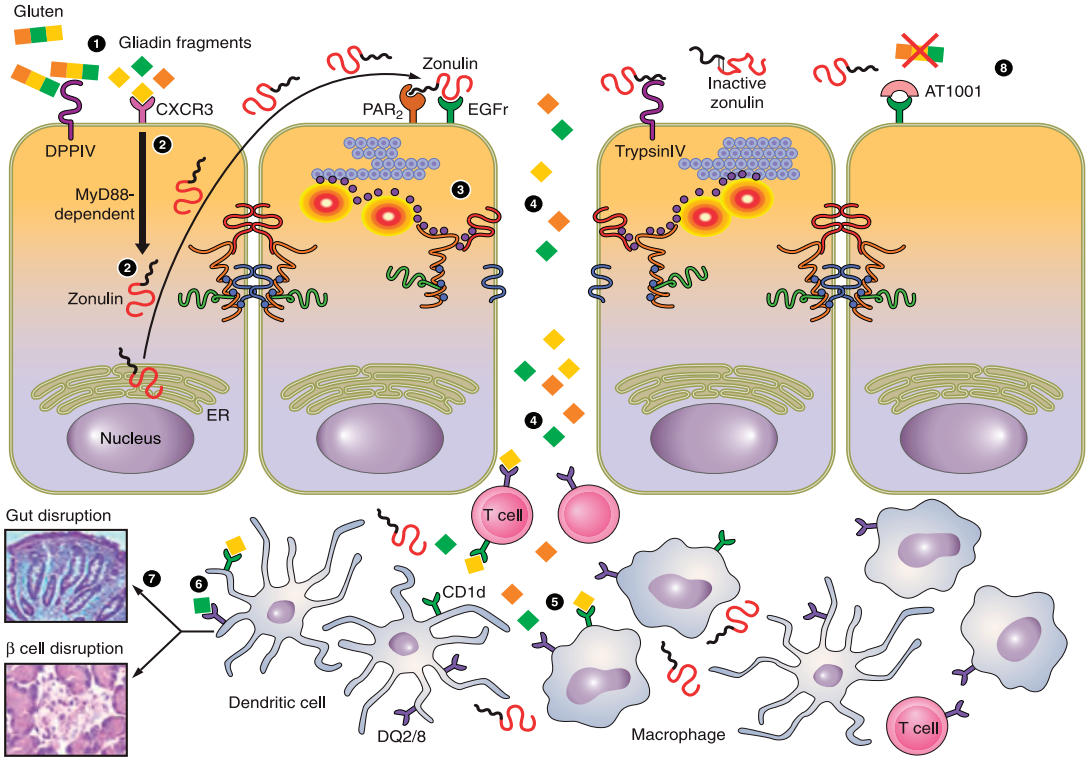
NOTE: 80% of the immune system resides in the gastrointestinal tract.

Underlying factors that contribute to decreased immunity

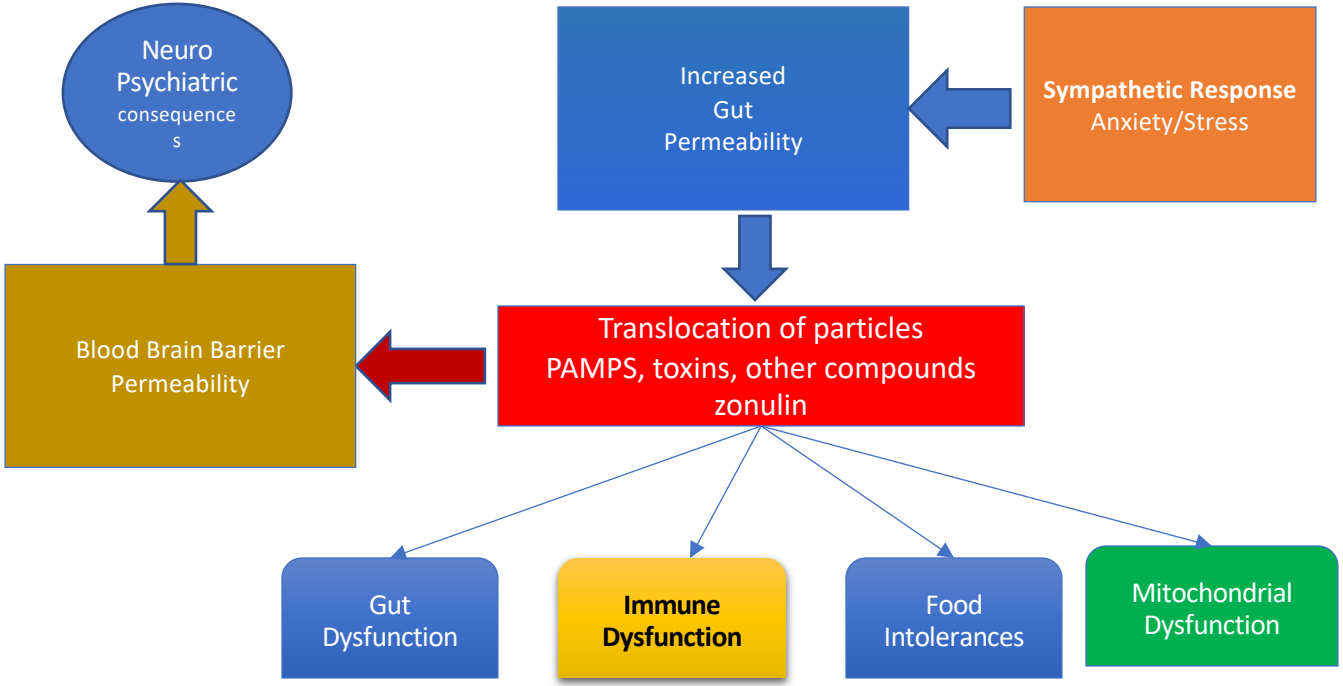
- Nutrient deficiency
- Stress
- Insulin resistance
- Chronic inflammation
- Food allergies and intolerances
- *Presence of a "leaky gut"*
- Increased toxin exposure
- Genetic predisposition

What is Leaky Gut?

"Zonulin's far reaching effects"



Etiology of Systemic Conditions



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Causes of increased intestinal permeability ("leaky gut")

- Nutrient deficiency
- Food allergies or intolerances
  - Direct irritation of the intestinal cells
  - Immune system damage leading to overgrowth of harmful microbes
- Dysbiosis
  - An alteration in the level of gut microorganisms, especially in the bacteria in the mucus layer covering the intestinal cells
- Antibiotics
  - Promotes dysbiosis and the growth of antibiotic resistant bacteria, yeast (e.g., Candida), and protozoa

Causes of increased intestinal permeability ("leaky gut") cont.

- High sugar intake
- Overeating
- Altered fats (trans fatty acids, lipid peroxides)
- Excess alcohol
- Poor digestion and absorption due to digestive enzyme insufficiency
- **Prescription and OTC drugs (especially acid-blocking drugs and NSAIDs)**

The Thymus Gland:
the "Master Gland" of the Immune System

- Functions:
  - Produces T-lymphocytes and thymic hormones
  - Thymosin - Thymopoetin - Serum Thymic Factor
  - Controls "Cell-Mediated Immunity" a type of adaptive immunity critical in fighting viral infections
- Enhancement of Thymus Activity and Function:
  - Prevention of thymic involution with antioxidants
  - Supplementation with nutrient cofactors

Foundational Supplements for Good Health

- ✓ High Potency Multiple
- ✓ Vitamin D3*
  - 2,000 to 5,000 IU daily
- ✓ Plant-based antioxidants
  - Flavonoid-rich extract, curcumin, “greens” drink, etc.
- ✓ EPA+DHA+DPA = 1,000-3,000 mg daily

Why Take a Multiple Vitamin and Mineral Formula

- Provides “nutritional” insurance
- Nutrient deficiency is common (even in Canada)
  - National Health and Nutrition Surveys
- Critically important in many specific groups
  - Pregnancy, infants, children, and elderly especially
- **Provides documented benefits in boosting immune function**, improving brain function, and protecting against oxidative damage.
- Logical approach and does no harm.

7 Key Nutrients for Immune Function

- Vitamin A (retinol) – significant antiviral effects and barrier function
- Beta-carotene and other carotenoids – support thymus function
- Vitamin D – numerous immune mechanism
- Vitamin C – critical for optimal immune function
- B vitamins, especially B1, B6, and B12 – required for antibody production
- Zinc – the ”gatekeeper” of immunity with direct antiviral activity
- Selenium – essential for thymus and cell-mediated immunity

Vitamin A and Viral Illness

- Key functions in host defense barriers especially the integrity of the mucosal epithelium.
- Plays a key role in innate immunity against viral infection.
- Essential in its role in cellular sensors for RNA viruses that ultimately signal immune system activation.
- During viral infections vitamin D antibody production; and lymphocyte proliferation and activation.
- Vitamin A supplementation to children is known to decrease the risks of mortality and morbidity from:
- - infectious diarrhea, measles, RSV, HIV, and malaria.

J Clin Med. 2018 Sep 6;7(9).
Crit Rev Biochem Mol Biol. 2019 Apr;54(2):184-192.

Vitamin A: Dosage Guidelines for Prevention and Treatment of Viral Illness

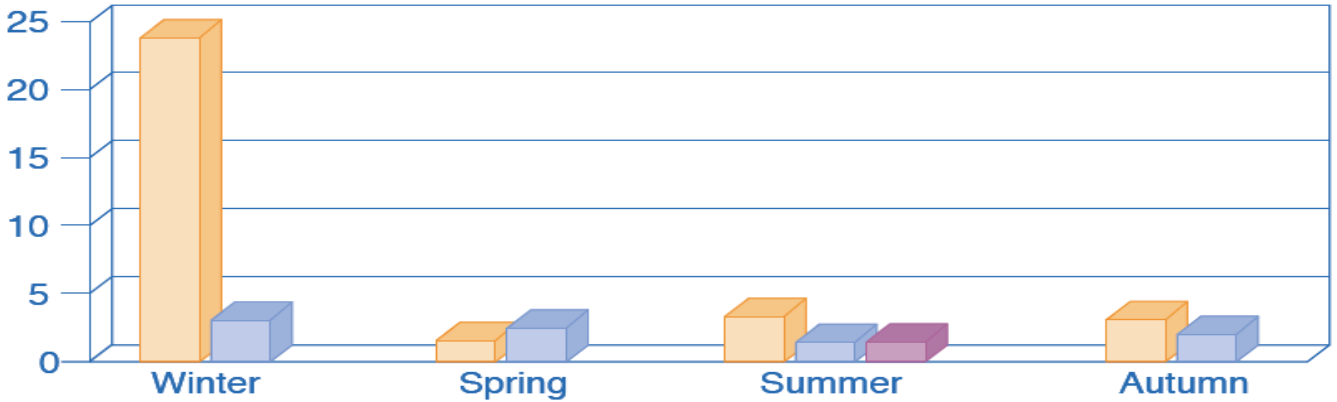
- Prevention: retinol dosage of 3,000 mcg (10,000 IU) for men and 1,500 mcg (5,000 IU) for women is safe.
- During an acute viral infection: a single oral loading dosage of 15,000 mcg or 50,000 IU is safe as long as there is ZERO chance of pregnancy.
- Pregnancy and lactation: Women of childbearing age at risk of pregnancy should not supplement with more than 1,500 mcg (5,000 IU) of vitamin A per day. The same warning applies during lactation.

Vitamin D and Viral Illness

- Intricate and complex functions on host defense barriers and immune function.
- Enhances both innate and adaptive immune cells.
- Vitamin D deficiency predisposes to respiratory tract infections.
- High quality evidence from 25 RCTs revealed that D3 supplementation reduced the risk of experiencing RTIs. D3 supplementation was effective in preventing RTIs irrespective of baseline 25(OH)-VD levels. Protective effects were greatest among subjects with more pronounced D deficiency especially the integrity of the mucosal epithelium.
- *Nutrients 2017 Jun 24;9(7).*

Vitamin D Prevents Colds and Flu

Figure 1. Incidence of Colds/Influenza After 2,000 IU Vitamin D Daily for One Year



Incidence of reported cold/influenza symptoms according to season. The placebo group reported more cold/influenza symptoms in the winter. Only one subject had cold/influenza symptoms while taking a higher dose of vitamin D (2000 IU/d).

Placebo 800 IU/d 2000 IU/d

Adapted from: Aloia JF, Li-Ng M. Epidemic influenza and vitamin D. *Epidemiol Infect* 2007; 135:1095-1096. Used with permission.

Vitamin D3 Blood Levels

- "Normal"- 30-80 ng/mL (75 to 200 nmol/L)
- Deficient - <25 ng/mL
- Insufficient - <50 ng/mL
- Optimal- 50-90 ng/mL
  - Toxic - Levels > 150 ng/mL (374 nmol/L)
  - 41.6% deficient in US/Canada
  - 69 % Hispanics deficient and 82 % African Americans

How much vitamin D?

- Most experts recommend a blood test to determine vitamin D levels.
- Serum 25(OH)D3 level should be 50-90 ng/ mL (approx. 145-200 nmol/L)
- Many experts are recommending a loading dosage of 10,000 IU daily for 3 months followed by 5,000 IU daily if no sun exposure and 2,000 IU with sun exposure
- For the latest research, go to **vitaminDcouncil.com**

Zinc and the Immune System

- Regarded as the "gatekeeper" of the immune system
- Zinc is involved in virtually every aspect of immunity especially thymus function and hormones, white blood cell function and signaling, and in our "innate immunity" as well as exerts direct antiviral actions
- The effects of chloroquine against SARS-CoV-2 is via acting as a zinc ionophore increasing the level of ionic zinc in infected cells
- Natural zinc ionophores are quercetin, EGCG, and other flavonoids
- Typical dosage for prevention: men 30 to 45 mg; women 20 to 30 mg.

Side note: Is the loss of taste and smell in COVID-19 due to an induced relative zinc deficiency?

Flavonoids and Polyphenols
Nature's Biological Response Modifiers

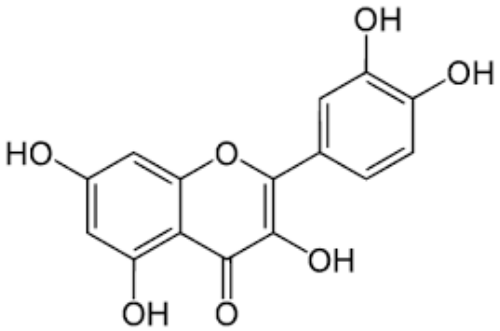
Pharmacological Actions:

- Antioxidant
- Anti-allergy
- Anti-inflammatory
- **Antiviral**
- Antineoplastic

Black elderberry
(Sambucus nigra)

Quercetin

- Consistently demonstrates greatest activity *in vitro* studies for flavonoids.
- Primary actions:
  - ✓Anti-inflammatory effects
  - ✓Anti-allergy effects
  - ✓Anticancer properties
  - ✓Antiviral activity
    - Binds to Sars-CoV-2 spike protein docking station on ACE-2 receptors.
    - Acts as a zinc ionophore similar to hydroxychloroquine with a potency roughly 40%, but no toxicity.



Commercially Available form of Quercetin

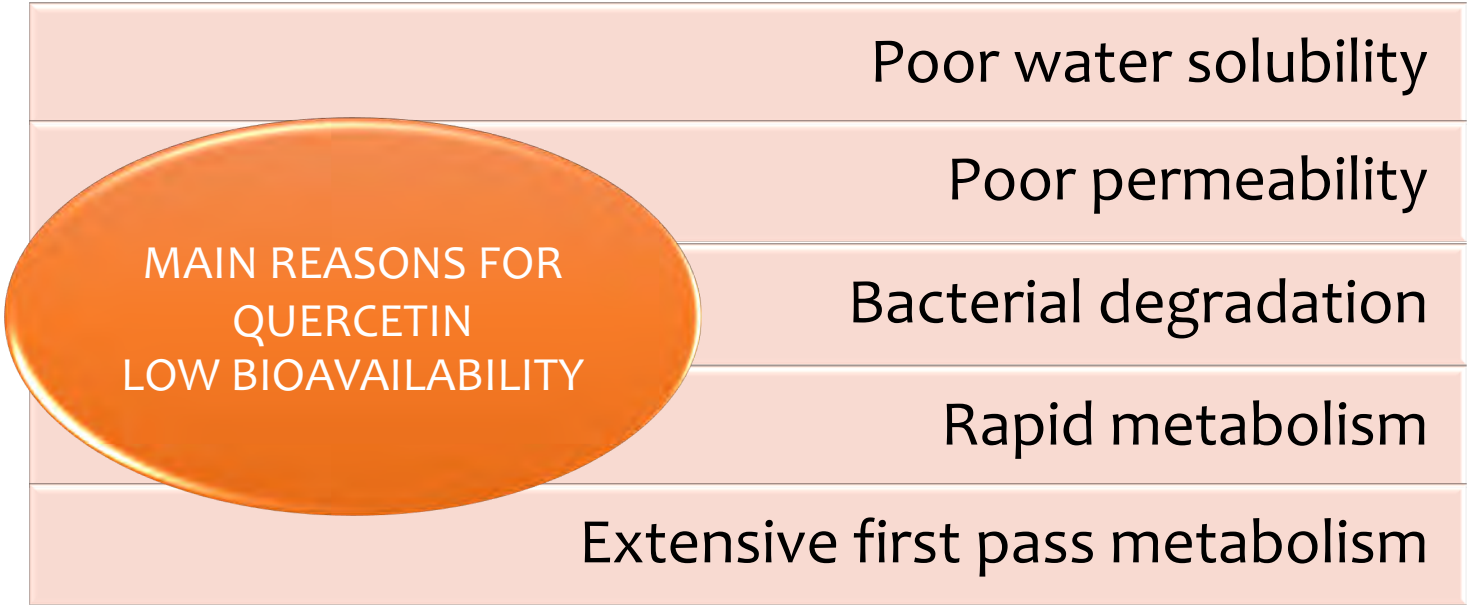
- Quercetin
- EMIQ
- Quercetin Phytosome® (a.k.a., QuerceFit)

Quercetin and Athletic Performance
Results from double-blind studies

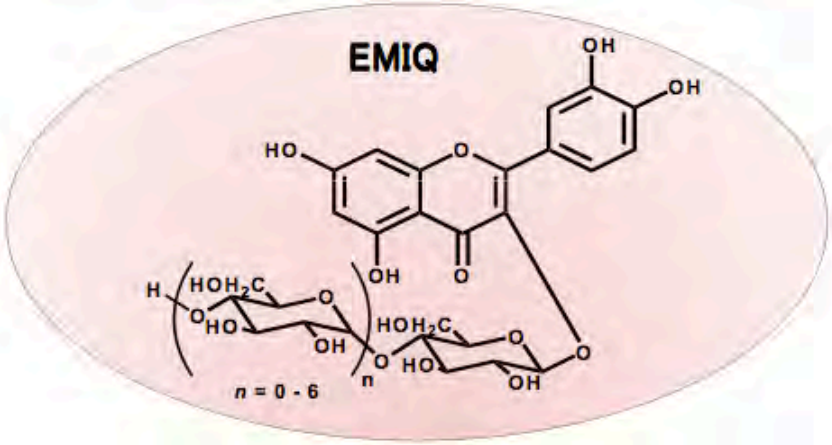
- Quercetin at dosages of 1 g/day:
  - Increases net distance in a 12 min treadmill by 2.9%
  - In cyclists, increase in VO2max (3.9%) along with a substantial (13.2%) increase in ride time to fatigue.
  - Increases skeletal muscle messenger RNA expression (range = 16-25%) for sirtuin 1 and other markers.
  - Reduces upper respiratory infections in moderately trained individuals - only 1/20 developed symptoms in the quercetin group compared to 9/20 in the placebo group.

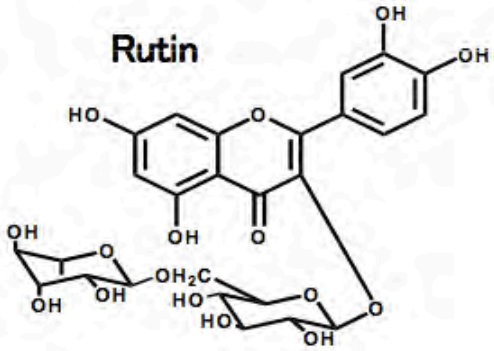
Curr Sports Med Rep. 2009 Jul-Aug;8(4):206-13.

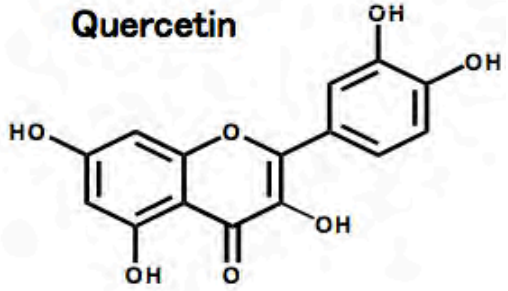
QUERCETIN: POOR ORAL ABSORPTION



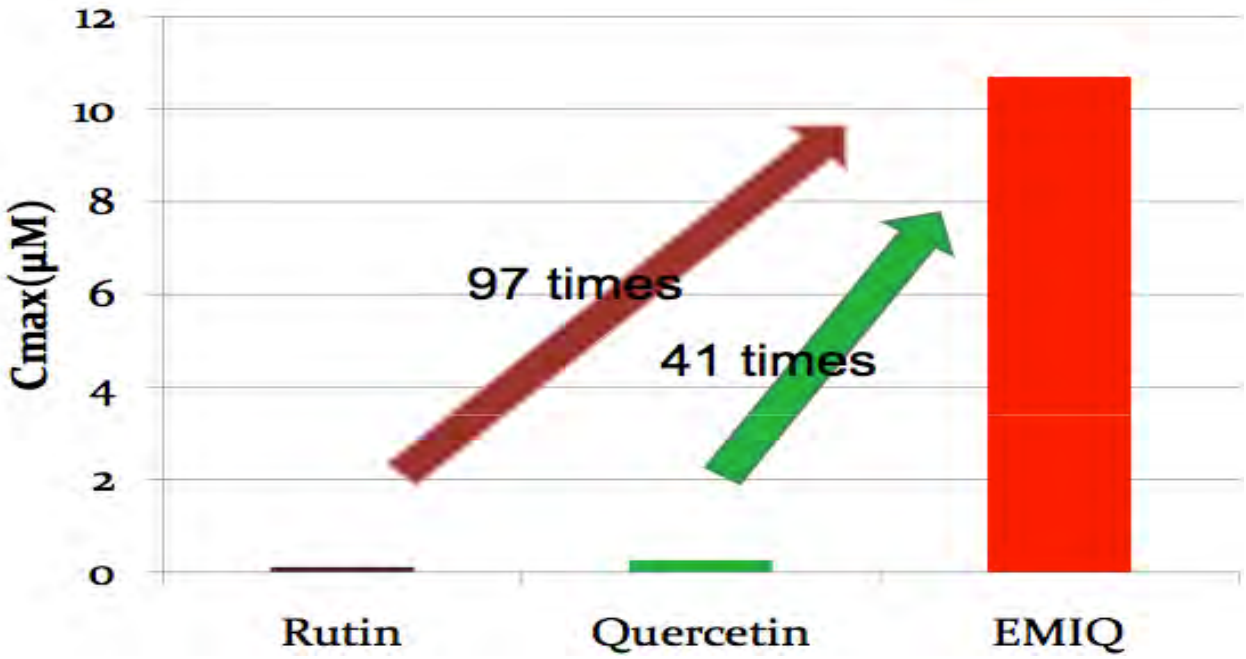
Enzymatically Modified Isoquercitrin







EMIQ Effectively Increases Serum Quercetin Levels



Note: Total AUC increases 15X with EMIQ

Arch Biochem Biophys. 2010 Sep 1;501(1):91-7.

Dosage of Commercially Available Forms of Quercetin

- Quercetin – 1,000 to 2,000 mg daily
- EMIQ – 75 to 150 mg daily

Selenium and Immune Function

- Selenium is critical to all components of the immune system
- Selenium deficiency is common in many parts of the world and results in depressed immune function.
- Selenium supplementation (200 mcg/day) has been shown to stimulate white blood cell and thymus function in selenium deficient individuals.
- Selenium supplementation (200 mcg/day) to individuals with normal selenium concentrations in their blood resulted in a 118% increase in the ability of white blood cells to kill tumor cells and 82.3% increase in natural killer cell activity.

Selenium

- All cause mortality ↓ 17%
- Total cancer mortality ↓ 50%
- Total cancer incidence ↓ 37%
- Prostate cancer incidence ↓ 63%
- Lung cancer incidence ↓ 46%

- Selenium plays a pivotal role in antioxidant protection.
- Low selenium levels linked to higher risk for infections, cancer, cardiovascular disease, inflammatory diseases, premature aging and cataract formation.

Other Natural Products for Immune Support

- N-Acetylcysteine
- Proteolytic Enzymes

N-Acetylcysteine (NAC) and Respiratory Health

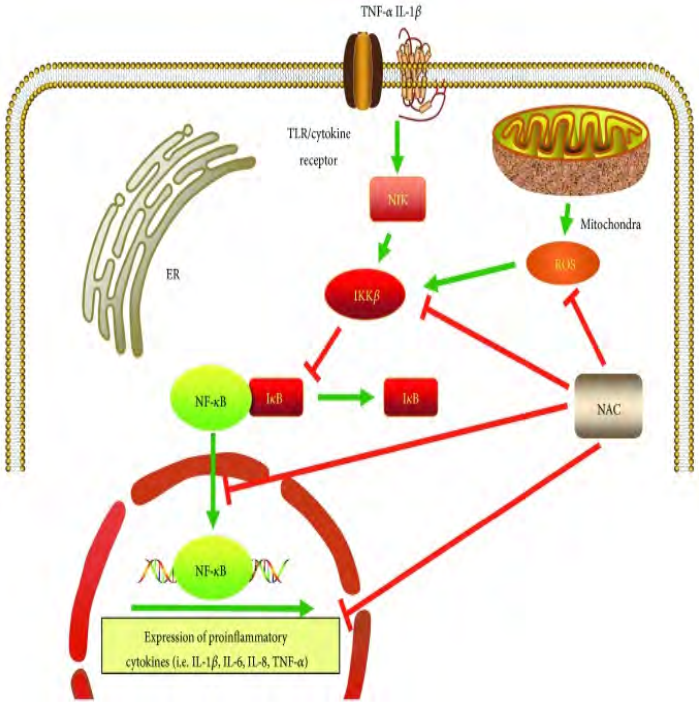
NAC is a source of cysteine and is a glutathione (GSH) precursor.

- Replenishing glutathione levels. Accepted medical treatment of acetaminophen toxicity.
- Reducing inflammation and relieving symptoms of respiratory congestion by acting as a mucolytic in loosening and expectorating mucus
- In respiratory tract infection or inflammation, the mucus has higher viscosity and elasticity and is not easily cleared. NAC hydrolyzes the disulfide bonds of mucus proteins to decrease mucus viscosity, thereby facilitating ciliary clearance.
- NAC is used in hospitals in pneumonia and in compromised cases such as COPD, chronic bronchitis, and intubated or post-operative patients.

Dosage: For mild to moderate conditions, 600 mg daily. For more severe conditions and COPD, 1,200 mg daily. Divided dosages are recommended.

Oxid Med Cell Longev. 2018; 2018: 2835787.

N-Acetylcysteine (NAC) and the Respiratory Tract



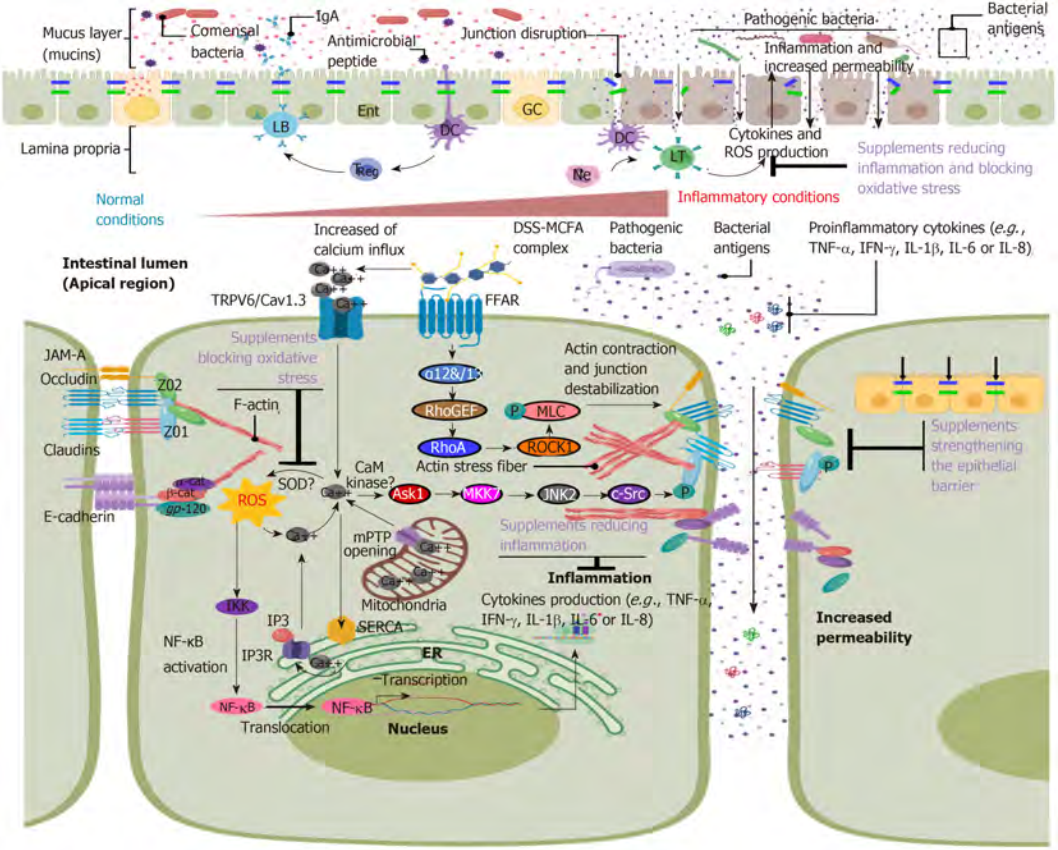
NAC produces:

- Mucus modifying effects:
  - Improvement in rheological properties of mucus, reduction of excess mucin production, and restoration of mucociliary clearance.
- Immune enhancement and anti-inflammatory actions:
  - Via antioxidant effects and glutathione boosting.
  - Via effects on sIgA and suppression of excess production of IgE and IgG4.
  - Regulation of the production of pro-inflammatory and profibrotic cytokines.
- Antimicrobial actions:
  - Suppression of adhesion of pathogens to epithelial cells.
  - Destruction of biofilms and inhibition of biofilm formation.

N-Acetylcysteine (NAC) and the Gastrointestinal Tract

NAC produces beneficial effects on:

- Intestinal morphology
- Absorptive and barrier function
- Antioxidative capacity
- Inflammation
- Improved energy status in the intestinal mucosa
- Promotion of cell survival a
- Regulation of tight junction protein expression (claudin-1 and occludin)



Front Biosci 2015 Jan 1;20:872-91.

N-acetylcysteine in Meta-analysis in Chronic Bronchitis and COPD

Summary: The results of the meta-analysis (13 studies, 4155 COPD patients) showed that patients treated with NAC had significantly and consistently fewer exacerbations of chronic bronchitis or COPD (relative risk reduction of 25%). However, higher doses of NAC were more effective in COPD. NAC was well tolerated and the risk of adverse reactions was not dose-dependent.

In COPD, NAC should be given at a dose of ≥1200 mg per day to prevent exacerbation. In patients with chronic bronchitis, without airway obstruction, 600 mg per day is sufficient.

European Respiratory Review 2015 24: 451-46

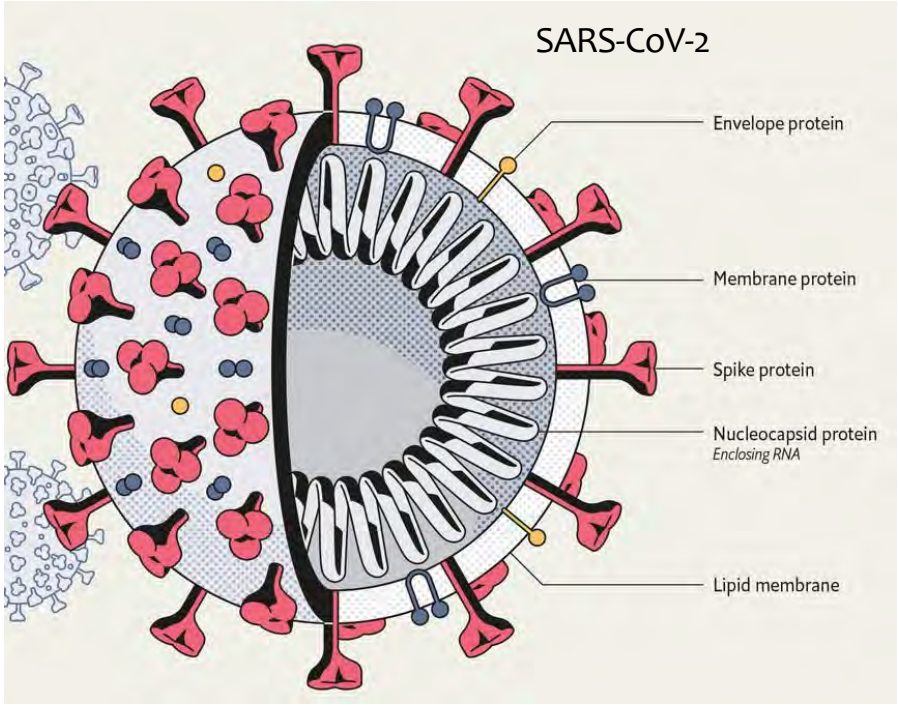
Pharmacological Actions of Supplemental Proteolytic Enzymes

- ✓ Digestive aid
- ✓ Antimicrobial
- ✓ Anti-inflammatory
- ✓ Activation of complement
- ✓ Mucolytic
- ✓ Regress atherosclerotic plaque
- ✓ Fibrinolytic
- ✓ Complex anticancer effects

"Proteolytic enzyme preparations are among the most valuable therapeutic agents in natural medicine, yet they remain significantly underutilized by physicians and the public."

Michael T. Murray, N.D.

Do Proteolytic Enzymes Digest Proteins on Viruses? Sometimes….

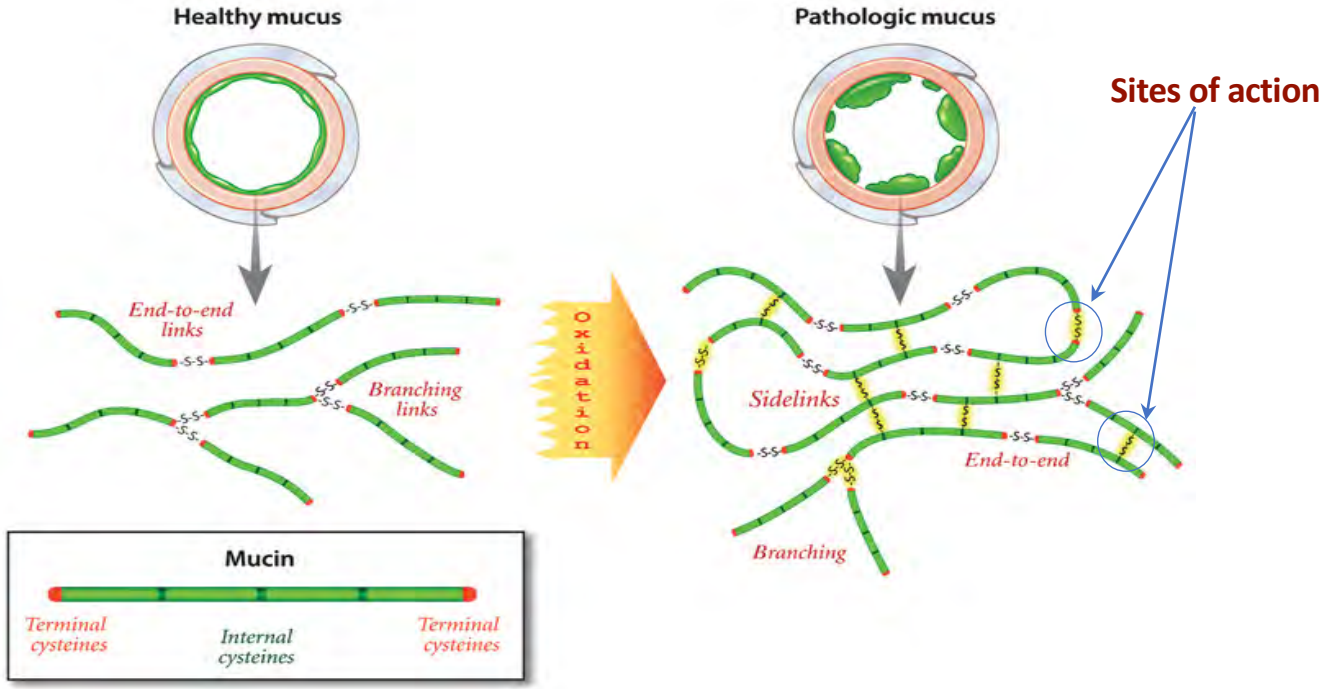


- Viruses contain various proteins on cellular surfaces that are critical to their attachment and infectivity.
- Endogenous enzymes secreted by the stomach, pancreas and intestinal epithelium are part of the host defense mechanisms against microbial infection.
- Serine proteases such as bromelain and trypsin are used in the production of vaccines to both neutralize the virus and expose antigens.

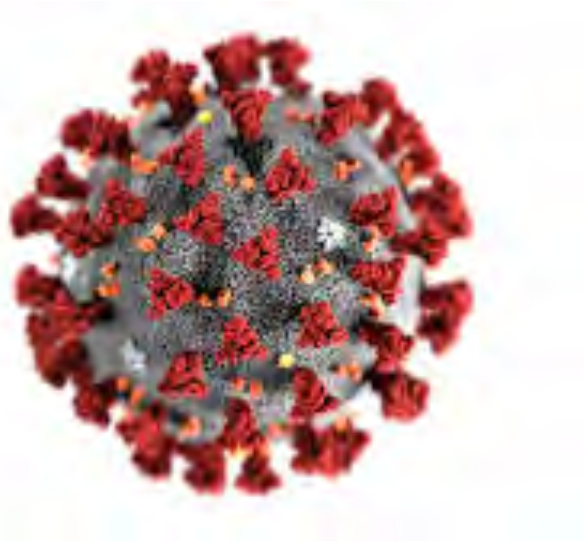
Can Serine Proteases Increase the Production of Endogenous Protease Inhibitors?

- There is a balance of protease to protease inhibitors in the body. An increase in the level of supplemental serine proteases may be offset by an increase in the level of endogenous serine protease inhibitors.
- Protease inhibitors secreted by our own white blood cells as well as in drug form are known antiviral agents.
- In particular, macrophages within the lining of the mucosa of the gut and respiratory tract secrete a protease inhibitor that protects the epithelial cells from microbial serine proteases that promote infection and spreading.
- Secretory leukocyte protease inhibitor (SLPI) is particularly important in airway secretions because of its broad-spectrum antibiotic activity including its antiviral effects.
- SLPI also blocks viral attachment and protects the lungs against attack by our own immune system.

Proteolytic Enzymes Break Disulfide Bonds in Mucus to Improve Viscosity



Questions



Thank you!