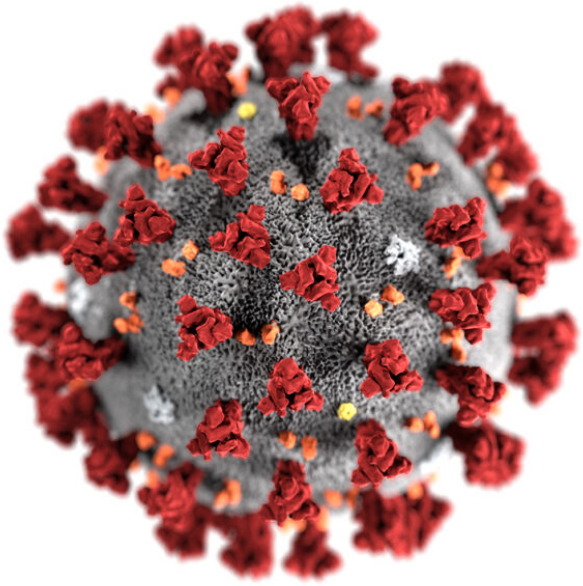
Nutritional support and COVID-19



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Lecture objectives

- Discuss typical targets for intervention in infectious disease
- Discuss the role of nutrition in immune system function
- Describe dietary components including supplements that have been studied in relation to COVID infection
- Identify concerns with dietary supplements used in COVID treatment

Overview

- The SARS-CoV-2 virus is a pathogen that causes a wide range of symptoms, primarily respiratory
- In addition to potentially-life-threatening acute symptoms, COVID-19 sufferers can experience ongoing health challenges
- Increased age and/or preexisting health conditions such as obesity, diabetes, and lung disease can exacerbate risk

Typical targets for intervention in Infectious disease

- Immune support*
- Antimicrobial or anti-infective treatment
- Symptomatic support
  - Acute symptoms
  - Effects on inflammation*
  - Post-recovery symptoms

*Key foci

Typical targets for intervention in infectious disease: Immune support

- Adequate nutrition supports the optimal functioning of the immune system
- Enhancement of immune system function and natural defenses most effectively allows the body to fight off infection
- Note that increased immune activity is not the same as increased immune function

Typical targets for intervention in infectious disease: Inflammation

- Inflammation is part of innate immunity
- Immune dysregulation could result in the hyperinflammatory state known as “cytokine storm” which is associated with severe acute lethal symptoms
- Chronic inflammation also underlies the health conditions that predispose to and/or result from COVID infection
- Note that free radicals and oxidative stress correlate with inflammation and can be important mediators of damage

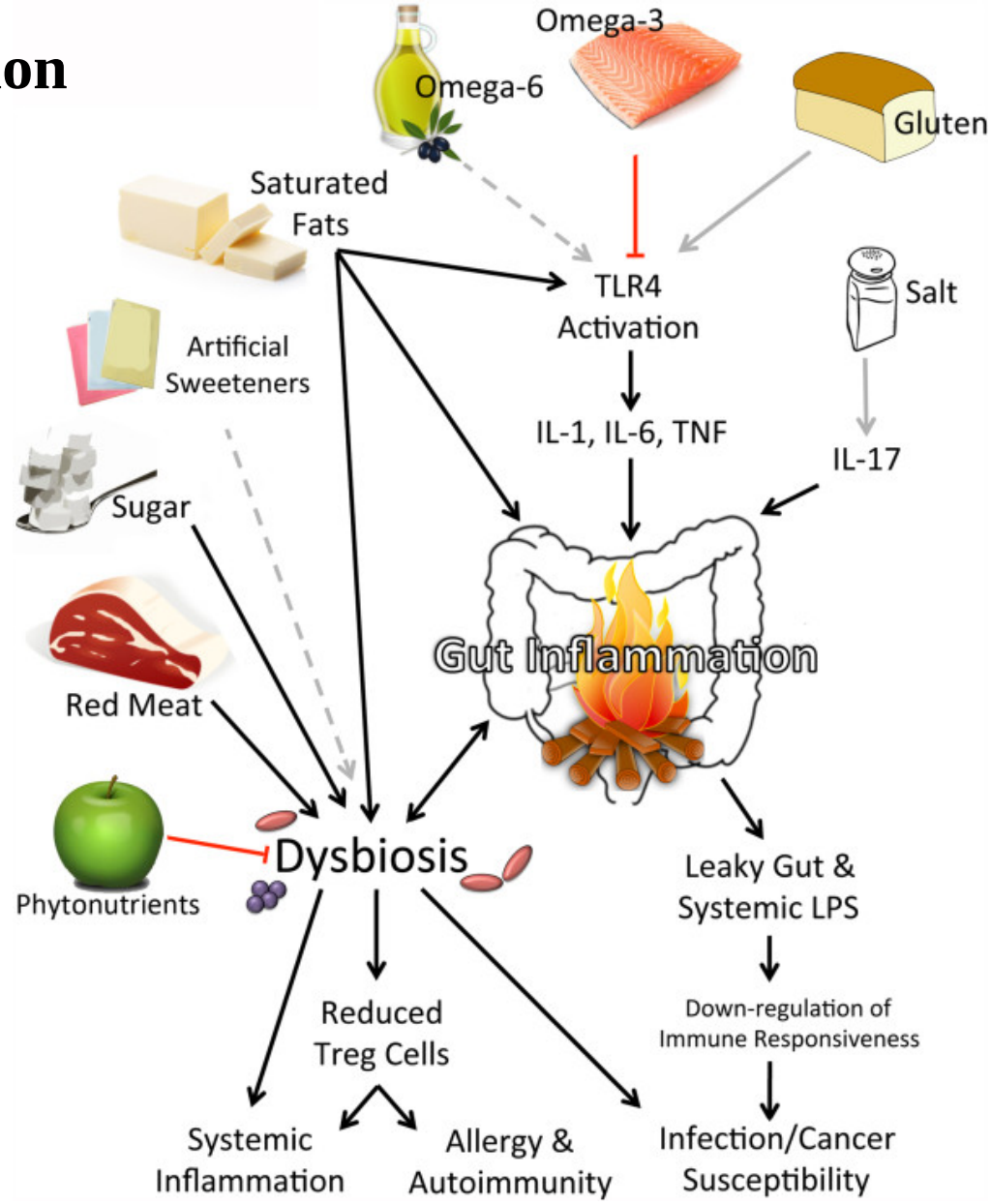
Role of nutrition in immune system function

- Good nutrition is a foundation of health and optimal functioning of all systems, including the immune system
- Additionally, nutrition and lifestyle are key factors in preexisting conditions such as metabolic syndrome
- However, quarantine conditions can adversely affect food access and food choice, as well as other lifestyle factors such as exercise

Role of nutrition of immune system function: Lifestyle

- Moderate levels of exercise enhance immune function, but intensive training can impair function
- Psychological stress increases susceptibility to infections
- Increased social support is protective against upper respiratory infections
- Components of the typical Western diet can have an adverse effect on immunity, as well as affecting obesity, diabetes, and other conditions increasing vulnerability
  - Sugar
  - Saturated fat
  - Red meat
  - Salt

Role of nutrition in immune system function



Red=human studies show inhibition
Grey=animal/in vitro studies
Dashed=scientific disagreement

Nutr J. 2014 Jun 17;13:61.

Role of nutrition in immune system function: Inflammation

- As previously described, acute inflammatory response can play a role in COVID-19 mortality via cytokine storm
- Furthermore, chronic inflammation plays a role in both preexisting conditions promoting risk as well as chronic sequela of infection

- Lifestyle factors affecting inflammation
  - Obesity promotes low-grade inflammation
  - Gut microflora can affect inflammation
  - Regular exercise decreases inflammation
  - Diet can play a role in chronic inflammation

Dietary approaches to addressing immune and inflammatory

Diet: Decreased inflammation

- Healthy diet: whole grains, fruits and vegetables, fish
- Vitamin C
- Vitamin E
- Carotenoids
- Zinc
- Omega three fatty acids
- Magnesium
- Mediterranean diet and other similarly healthy diets have anti-inflammatory effects

Diet: Increased inflammation

- Saturated and trans fat
- High glucose/high fat meals

Dietary components studied in relation to COVID infection

- Due to the complexity of the immune system, it is not surprising that a number of nutrients play a role in optimal immune function
- In general, while deficiency of a particular nutrient can clearly impair function, the benefits of supplementation are less clear
- Consumption of nutrients in foods, especially as fruits and vegetables, is likely to provide the most benefit
- However, as nutritional adequacy could be affected by quarantine conditions, supplementation could be helpful

Dietary components studied in relation to COVID infection

Micronutrients

- Vitamin A
- Vitamin C
- Vitamin D
- Zinc

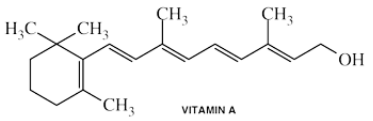
Macronutrients

- Protein
- Omega-three fatty acids

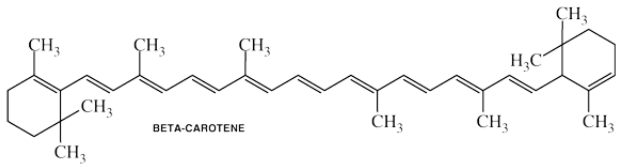
Other

- Probiotics
- Echinacea
- Elderberry
- N-acetyl cysteine

Vitamin A: Background



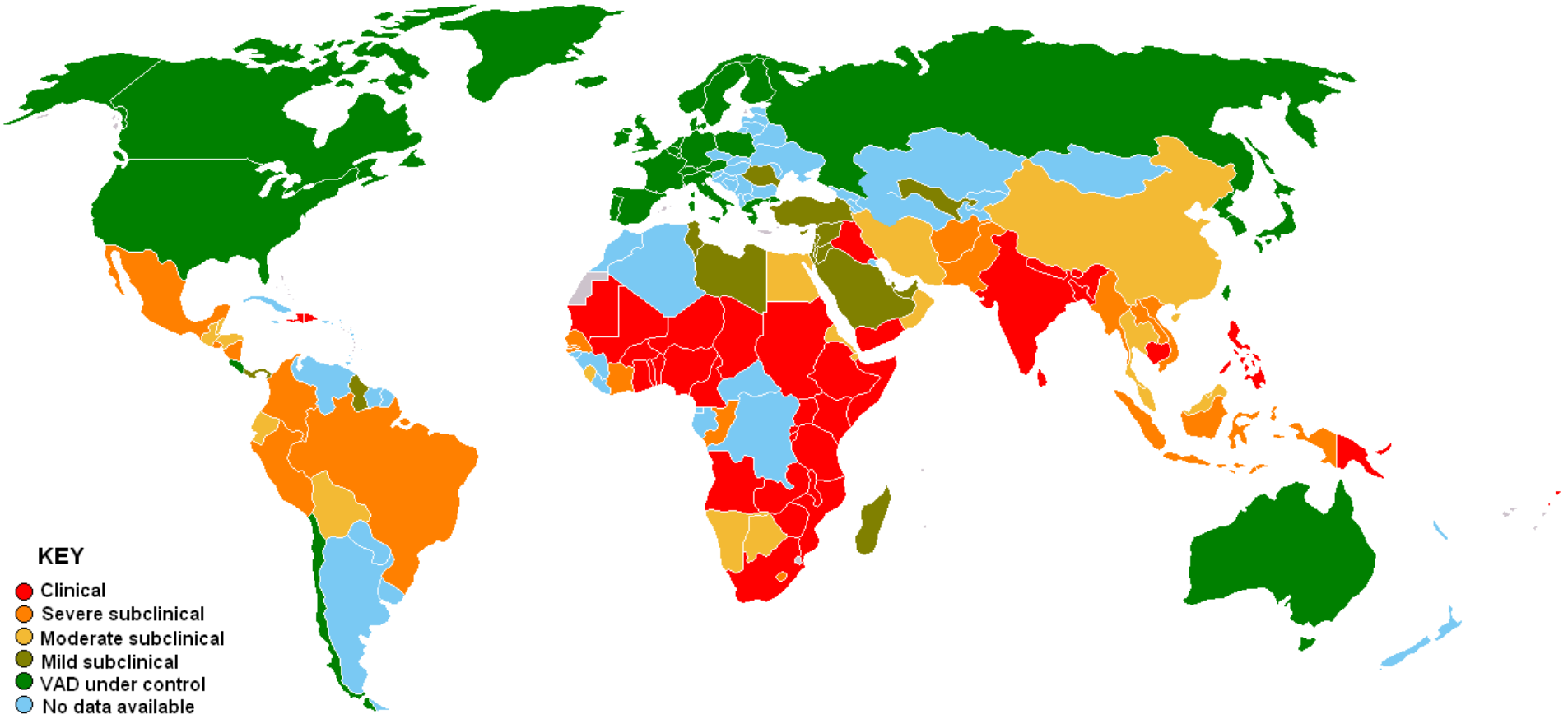
VITAMIN A



BETA-CAROTENE

- Enhances innate immunity
  - Needed for mucosal membrane integrity and function in producing mucus and clearing pathogens
- Binds nuclear receptor that alters transcription of immune-related genes
  - Increases regulatory T-cells
  - Increases IgA production
- Also alters immunoglobulin secretion in breast milk
- Present in foods as vitamin A and as the precursor beta-carotene

Global distribution of vitamin A deficiency

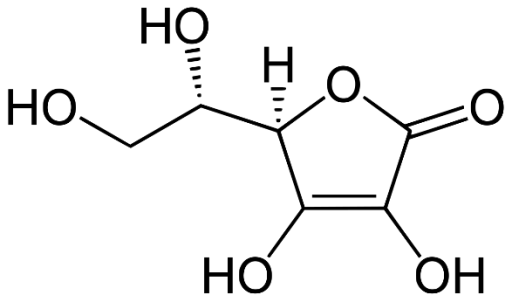


Calif Agr 65(3):130-135.

Vitamin A and COVID

- Prevention of vitamin A deficiency is likely helpful
- Benefit suggested for COVID via effects on type 1 interferons
- Note that vitamin A toxicity is a concern, especially in pregnancy, but beta carotenes do not have this risk

Vitamin C: Effects



- Needed for immune function
  - May increase phagocyte and lymphocyte function
  - Has antioxidant effect
- Widely used for common cold
  - May shorten duration of common cold
  - May be more effective in individuals with physical stress, children
  - Does not appear to be protective for cold prevention
- Also has antioxidant effects

Vitamin C and COVID

- Vitamin C deficiency impairs immune function, so vitamin C adequacy is important
- There is interest in supplemental Vitamin C for COVID due to its use for the common cold
- Searching the National Institutes of Health ClinicalTrials.gov website for “COVID” and “vitamin C" yielded twenty-one randomized controlled trials for COVID and vitamin C alone or in combination as treatment
  - The majority of these trials are in early stages
- High doses of vitamin C are widely used with relative safety, although increased risk of kidney stones is a possible consequence

Examples of registered clinical trials involving vitamin C and COVID

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Not yet recruiting	Pharmacologic **Ascorbic Acid** as an Activator of Lymphocyte Signaling for COVID-19 Treatment	• **COVID-19**	• Drug: **Ascorbic Acid**
2	☐	Not yet recruiting	Preventing **COVID-19** in Healthcare Workers With HCQ: A RCT	• **Covid-19**	• Drug: Hydroxychloroquine • Other: **Vitamin C**
3	☐	Recruiting	Use of **Ascorbic Acid** in Patients With **COVID 19**	• Hospitalized Patients With **Covid-19** Pneumonia	• Dietary Supplement: **Vitamin C**
4	☐	Recruiting	Lessening Organ Dysfunction With **VITamin C - COVID-19**	• **Vitamin C** • **COVID-19** • Hospitalized Patients	• Drug: **Vitamin C** • Drug: Control
5	☐	Recruiting	The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and **Vitamin C** on the Clinical Outcomes of Patients Infected With **COVID-19**	• **Covid-19**	• Drug: Quercetin • Dietary Supplement: bromelain • Drug: Zinc • Drug: **Vitamin C**
6	☐	Not yet recruiting	International ALLIANCE Study of Therapies to Prevent Progression of **COVID-19**	• **COVID19**	• Dietary Supplement: **Vitamin C** • Drug: Hydroxychloroquine • Drug: Azithromycin • (and 3 more...)
7	☐	Recruiting	Administration of Intravenous **Vitamin C** in Novel Coronavirus Infection (**COVID-19**) and Decreased Oxygenation	• **COVID-19** • Hypoxia	• Drug: L-**ascorbic acid**
8	☐	Not yet recruiting	Early Infusion of **Vitamin C** for Treatment of Novel **COVID-19** Acute Lung Injury (EVICT-CORONA-ALI)	• **COVID-19** • Lung Injury, Acute	• Drug: L-**ascorbic acid** • Other: Placebo
9	☐	Enrolling by invitation	Coronavirus 2019 (**COVID-19**)- Using **Ascorbic Acid** and Zinc Supplementation	• **COVID** • Corona Virus Infection	• Dietary Supplement: **Ascorbic Acid** • Dietary Supplement: Zinc Gluconate • Dietary Supplement: **Ascorbic Acid** and Zinc Gluconate • Other: Standard of Care

ClinicalTrials.gov

Vitamin D: Effects

- Most known for its effects on calcium regulation and maintenance of bone strength
- However, receptors are found on many other cells in the body, including the immune system
- Low vitamin D could predispose to respiratory infections
  - Supplementation could help in cases of severe vitamin D deficiency

Vitamin D and COVID

- Vitamin D deficiency has been correlated with increased COVID severity
- In regard to mechanism, Vitamin D could increase protection against infection in the respiratory tract as well as decreasing inflammation contributing to cytokine storm
- ClinicalTrials.gov cites four trials including vitamin D in COVID treatment

Zinc: Effect

- Essential mineral used as a cofactor for multiple enzymes, considered antioxidant
- Deficiency produces a number of adverse effects on growth, immune function, and cognition
- Used topically and orally for multiple purposes
- Commonly used for decreasing severity and duration of common cold but evidence is conflicting
- Might decrease incidence of pneumonia in undernourished children
- Elderly might be more likely to be zinc-deficient

Zinc and COVID

- ClinicalTrials.gov cites fifteen randomized controlled trials for COVID and zinc alone or in combination as treatment
- Note that nasal zinc gel can damage the sense of smell, which can be a sign of COVID
- Oral zinc can affect the sense of taste and cause GI upset, also COVID symptoms

- Note that deficiencies in selenium and iron have similarly been shown to correlate with increased COVID mortality

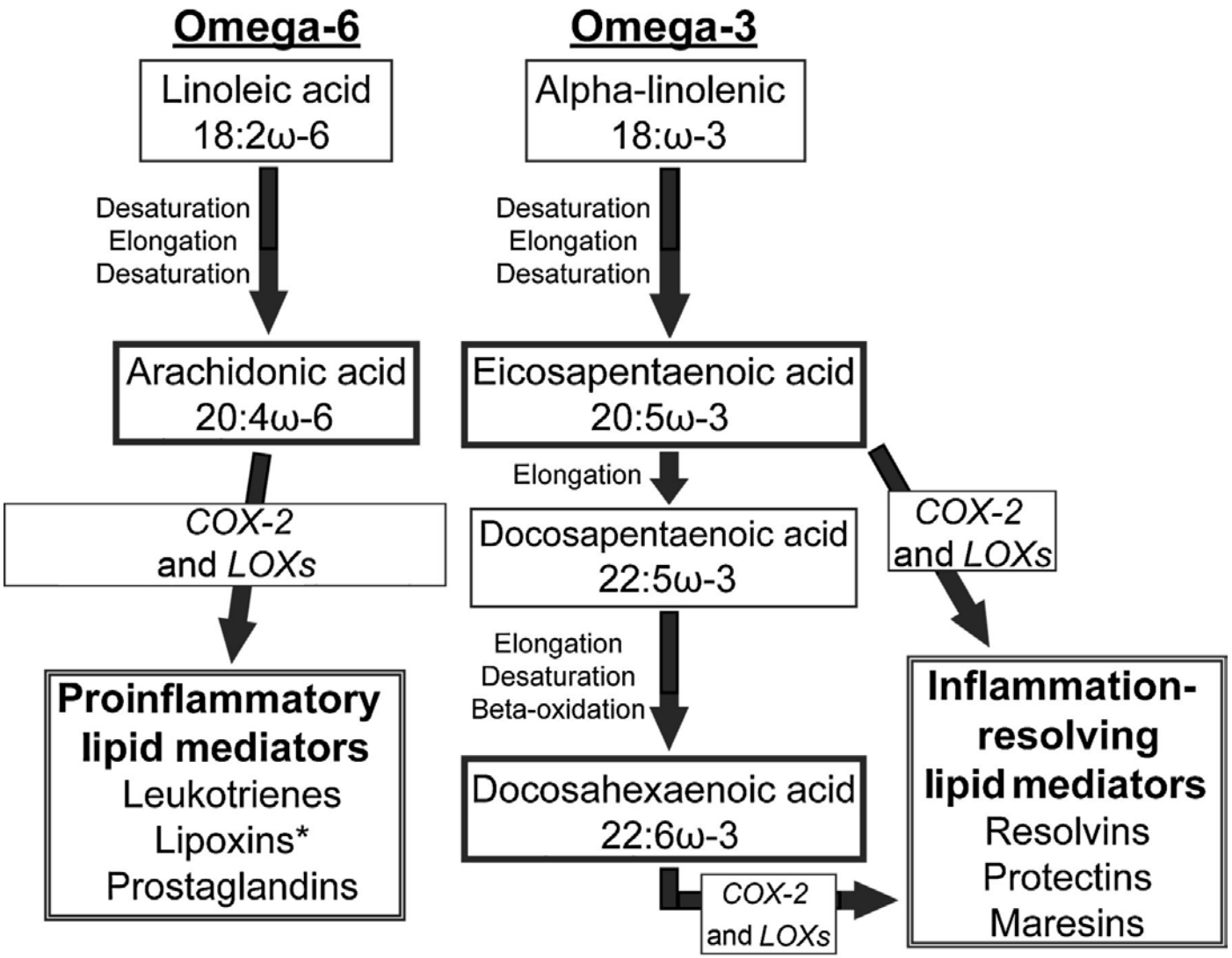
Protein: Effects

- Protein deficiency is known to impair immune function, particularly immunoglobulins and gut-associated lymphoid tissue
- Specific amino acids such as arginine and glutamine plays a particularly important role in immune cell function
- Protein deficiency has been associated with increased viral susceptibility and decreased response to influenza vaccination
- High quality protein is of course important for general health

Omega-3 fatty acid: Effects

- Omega-3 fatty acids are essential dietary components that are widely used for decreasing serum triglycerides
  - Prescription fish oil is presumed to be more effective due to higher concentrations and greater purity
- Needed for neurological development and function, especially in children
- Can also modulate the inflammatory cascade by serving as precursors to anti-inflammatory mediators

Omega-3 fatty acid: Effects on inflammation



Cancer Prev Res May 1 2015 (8) (5) 359-364

Omega-3 fatty acid: Effects

- Fish oil contains the omega 3 fatty acids DHA and EPA (docosahexanoic acid and eicosapentanoic acid)
- Krill oil is also a source of of DHA and EPA

- Plant-derived *alpha-linolenic acid* can be converted in part to EPA and DHA
  - Flaxseed
  - Walnuts
  - Chia

Omega-3 fatty acid and COVID

- Omega-3 fatty acid supplementation, in particular the fish oils DHA and EPA, has been suggested as having a benefit in cytokine storm
  - Oral, enteral, and intravenous lipid emulsions are possible dosage forms
- The cardiovascular benefits of omega-3 fatty acids could also play a role in decreasing risk factors and mitigating chronic sequelae of COVID
  - E.g., Deep vein thrombosis
- ClinicalTrials.gov lists seven trials containing omega-3 fatty acids, three with the prescription EPA product icosopent ethyl
- Omega-3 fatty acids are generally considered beneficial and are fairly safe

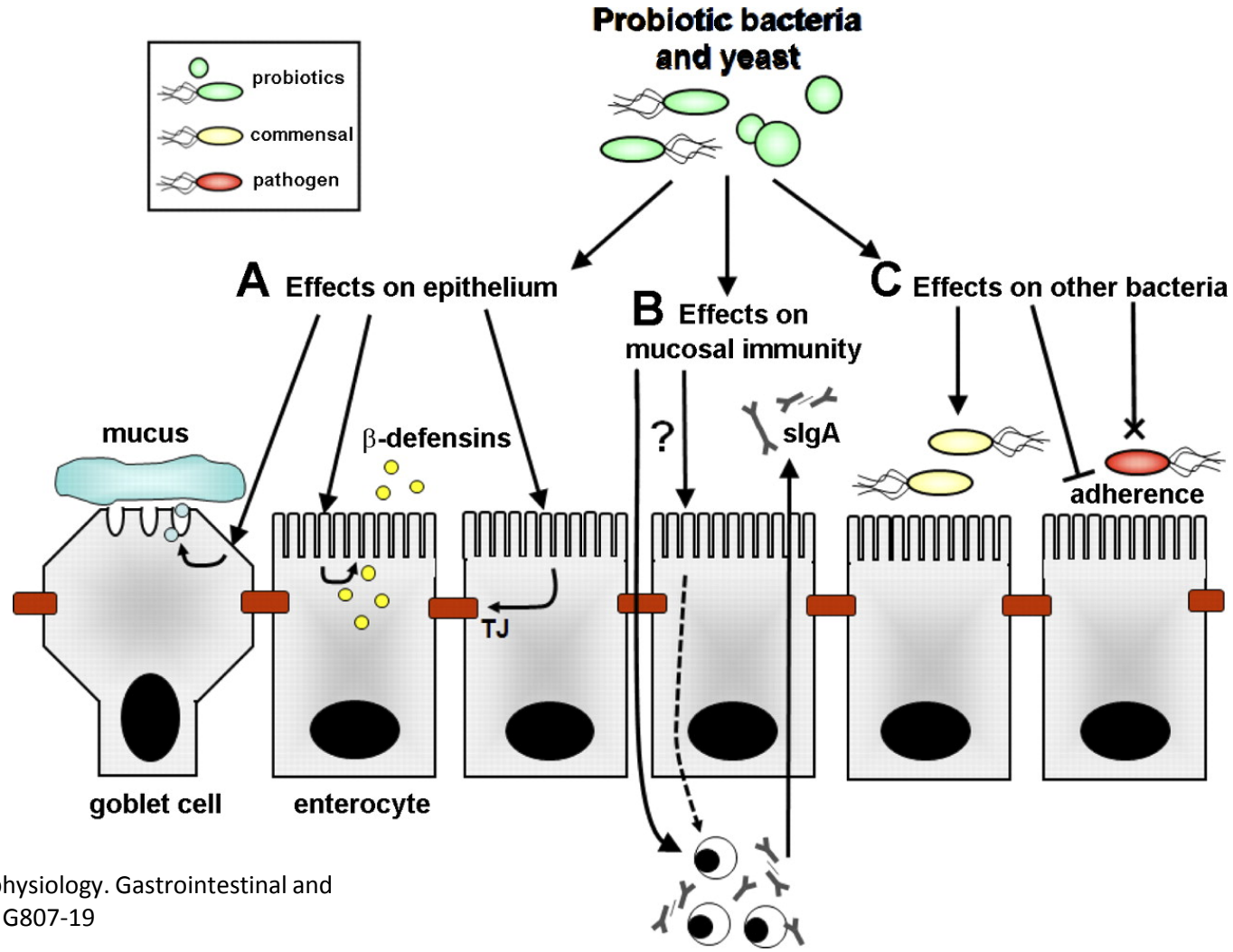
Probiotics: Effects

- Probiotics have traditionally been used in treating various forms of infectious diarrhea
- Less directly, the immune system can be affected by altering gut microflora
  - Alters immune regulation
  - Alters intestinal permeability (leaky gut)
- Effects depend greatly on the type, amount, and viability of the probiotic being used

Probiotics: Effect

- *Prebiotics* make the gut more welcoming for probiotic growth
  - Prebiotics such as fiber have shown beneficial effects
  - For example, both probiotics and prebiotics have demonstrated increases in the effectiveness of influenza vaccine
- Increased prebiotic effects could contribute to the health benefits of whole grains, legumes, and other plant products
- Use of the prebiotics fructan and galactan in particular have been cited

Typical targets for intervention in immune and inflammatory disorders:



American journal of physiology. Gastrointestinal and liver physiology. 298. G807-19

Probiotics and COVID

- A number of studies demonstrate benefits of specific probiotic products for respiratory tract infections though not for COVID specifically
  - ClinicalTrials.gov lists nine trials of probiotic products
- Note that COVID can also result in GI symptoms, which are a more typical application of probiotics
- Benefits are likely to depend on the use of specific strains and not common probiotics available commercially
- Relatively safe although possible risk of infection in immunocompromised patients
  - Prebiotics do not have this risk

Echinacea: Effect

- Commonly used for prevention/treatment of common cold
- Can have effects on both specific and non-specific immunity, affects cytokine production
- Also may have direct antimicrobial and anti-inflammatory activity
- Some studies suggest decreased severity and duration of cold symptoms if started immediately and used 7-10 days
- Evidence of benefit is not established, especially in children

Echinacea and COVID

- Not studied directly but based on effects in other respiratory diseases, has been suggested as promising
- Concern with increasing autoimmune effects and exacerbating cytokine storm, but decreases in proinflammatory cytokines have been reported

Elderberry: Effect

- Used alone or in combination for upper respiratory infections
- Immunomodulatory and possibly antiviral effects
- Increases cytokine production
- Has been reported to reduce flu symptoms and duration when given within 48 hrs of initial symptoms

Elderberry and COVID

- Not studied directly but based on effects in other respiratory diseases, has been suggested as promising
- Elderberry lectins have been postulated to interfere with coronavirus spike proteins
- Relatively safe

N-Acetyl Cysteine: Effect

- Sulfur-containing antioxidant used in-hospital as mucolytic agent and antidote for acetaminophen toxicity
- Also available as a dietary supplement
- Increases levels of the antioxidant glutathione, can increase T-cell proliferation, decrease inflammatory cytokines
- As a supplement, decreased incidence of incidence and severity of influenza symptoms

N-Acetyl Cysteine and COVID

- Can increases levels of the antioxidant glutathione that is depleted in COVID
- Could inhibit binding of coronavirus spike proteins to functional receptor used for entry into cells
- Relatively safe
- Potential use as a supplement in prevention, high dose use in treatment
- ClinicalTrials.gov lists 7 trials including NAC

Concerns with dietary supplements used in COVID treatment

Concerns with dietary supplements used in COVID treatment

FDA list of COVID-19 related fraudulent products

Date Issued	Firm Name	Product Name and Image[1]
04/01/2020	Health Mastery Systems DBA Pure Plant Essentials	Essential oil products
04/01/2020	Homeomart Indibuy	Homeopathic drug products
04/01/2020	Gaia's Whole Healing Essentials, LLC	Colloidal silver products
03/31/2020	NeuroXPF	Cannabidiol (CBD) products
03/30/2020	JRB Enterprise Group Inc. DBA Anti Aging Bed	Colloidal silver products
03/30/2020	Halosense Inc.	Salt therapy products
03/30/2020	Bioactive C60/FullerLifeC60 LLC	FullerLifeC60
03/26/2020	Corona-cure.com	Corona-Cure Coronavirus Infection Prevention Nasal Spray
03/26/2020	Carahealth	Herbal products, including Carahealth Immune
03/06/2020	Xephyr LLC dba N-ergetics	Colloidal Silver 1100 PPM, Colloidal Silver 500 PPM, Colloidal Silver 30 PPM, Colloidal Silver Advanced 20 PPM

https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products

Concerns with dietary supplements used in COVID treatment

FDA list of COVID-19 related fraudulent products (continued)

Date Issued	Firm Name	Product Name and Image[1]
03/06/2020	GuruNanda, LLC	Essential oil products
03/06/2020	Quinessence Aromatherapy Ltd	Essential oil products
03/06/2020	Vivify Holistic Clinic	Formula #1, Formula #2, Formula #3, and *Eupatorium perfoliatum* (Boneset)
03/06/2020	Colloidal Vitality LLC	Products labeled to contain silver
03/06/2020	The Jim Bakker Show	Silver Sol Liquid and products labeled to contain silver
03/06/2020	Herbal Amy Inc.	Coronavirus Protocol (Coronavirus Boneset Tea, Coronavirus Cell Protection, Coronavirus Core tincture, Coronavirus Immune System, and Elderberry Tincture)

https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products

Concerns with dietary supplements used in COVID treatment: Essential oils

- Used topically, by inhalation, or orally (diluted) as antimicrobial agents
- Many oils do have antiseptic properties and molecules that could have antiviral activity, especially due to their high concentrations
- Despite interest in use for COVID, studies thus far are theory-based or *in vitro*
- However, the concentrated nature of the oils makes them potentially toxic when taken internally
- Many oils are also irritating to the skin

Colloidal Silver: Effect

- Sub-microscopic/nano particles of metallic silver
- Used topically and internally for antibiotic effect
  - Historically, silver nitrate, and silver sulfadiazine have been used as topical anti-infectives
  - Silver has multiple possible antibacterial effects including binding to cell membrane to initiate apoptosis, proteins, and DNA
- Increased surface area by decreasing particle size increases efficacy of binding
- Could result in argyria, bluish color in skin (not reversible) even when used as a nose drop or topically
- Could also result in neurological, renal damage, deposits in other organs

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