# HEALTH & IMMUNITY: A NATURAL PERSPECTIVE FOR A NOVEL TIME

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# YOU CAN 'T CONTROL THE VIRUS, BUT YOU CAN *CONTROL* THE *HOST*



# Factors that make us more likely to contract COVID-19

- CVD
- Diabetes
- Obesity
- Hypertension
- Age
- Chronic pulmonary disease
- Chronic liver or kidney disease
- Radiation therapy
- Autoimmune conditions
- Chronic neurological diseases



#### Underlying conditions among adults hospitalized with COVID-19



Note: Based on data from the COVID-19–Associated Hospitalization Surveillance Network for patients hospitalized in 99 counties in 14 states from March 1-30, 2020.

Source: MMWR. 2020 Apr 8:69(early release):1-7

#### Obesity linked to severe coronavirus, especially for younger patients

- Obesity important predictor of severe coronavirus illness
- The U.S. 1 of the highest obesity rates in the world
- Younger adults at particular risk\*

\*research is preliminary, and not peer reviewed



# Obesity linked to severe coronavirus, especially for younger patients (cont'd)

#### Hypotheses:

- Obesity:
  - May already have compromised respiratory function prior to infection
  - Abdominal obesity (more prominent in men) can cause compression of diaphragm, lungs and chest capacity
  - Causes chronic low-grade inflammation and an increase in circulating, proinflammatory cytokines plays role in worst COVID-19 outcomes

# Obesity and COVID-19: The role of visceral adipose tissue



30 patients – COVID-19 positive

- An increase in visceral fat area by 1 sq. decimeter associated with:
  - 22.53-fold increased risk for ICU
  - 16.11 mechanical ventilation
- Upper abdominal circumference, each additional cm show:
  - 1.13-fold increased risk for ICU
  - 1.25 mechanical ventilation
- No increased risks with subcutaneous fat or BMI

### Preventable lifestyle disease?



- Underlying chronic illness:
  - 42% obese
  - 75% overweight
  - 6/10 have 1 chronic illness
  - 4/10 have more than 1 chronic illness
  - Obesity increases the risk of death three times
- All the above lead to inflammation

### Preventable lifestyle disease? (cont'd)

- Belly fat
- Older metabolically challenged half over 65 pre/diabetic
- Older decreased immune function
- 12% population metabolically healthy



# Long term exposure to air pollution/COVID-19 mortality in the U.S.

- Coronavirus patients in areas that had high levels of air pollution before the pandemic more likely to die from infection than patients in cleaner parts of the country
- First link between long term exposure to pollution and COVID-19 death rates
- Particles PM 2.5 associated with increased death rates
- Person living for decades in a country with high levels of particulate matter:
  - 15% more likely to die from coronavirus
- Fine particulate matters comes from:
  - Fuel combustion: automobiles, refineries, power plants
  - Tobacco smoke

Harvard University, April 5, 2020 Xiao Wu, Rachel C. Nethery, Benjamin M. Sabath, Danielle Braun, Francesca Dominici. *medRxiv* 2020.04.05.20054502

### Smell and taste

- Loss of smell and taste strong association with COVID-19
- Include it in screening measure
- **Findings:** if you have smell and taste loss more than 10x more likely to have COVID-19
- Rate of recovery high 2-4 weeks





## Why does SARS-CoV-2 spread so easily?

https://www.medicalnewstoday.com/articles/why-does-sars-cov-2-spread-so-easily

ACE-2 is the host cell receptor responsible for mediating infection by SARS-CoV-2, the novel coronavirus responsible for coronavirus disease 2019 (COVID-19). Treatment with anti-ACE-2

antibodies disrupts the interaction between virus and receptor.



### The ACE2, gut microbiota and cardiovascular health

**Conclusion:** Association between RAS and gut microbiota seems to have strong influence on the genesis of CVD, through direct mechanisms – nerve stimulation, or indirectly on metabolic parameters – weight, adiposity, and lipid profile



Oliveira Andrade JM, et al. *Protein Pept Lett*. 2017 Nov 17;24(9):827-832

### ACE2 expression in human heart/SAR-CoV-2

- ACE2 cellular distribution in human heart not clearly illuminated
- Pericytes with high expression of ACE2 act as the target cardiac cell
- Pericytes injury due to virus infection may result in capillary endothelial cells dysfunction inducing microvascular dysfunction
- If infected by the virus these patients may have higher risk of HA

Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis

- 202 patients with COVID-19:
  - NAFLD
  - liver injury observed
  - 50% admission
  - 75.2% during hospitalization
- Abundant ACE2 receptors in small intestine and liver
- Liver contains largest amount of macrophages
- Gut-liver axis
- Obesity implicated

#### THE IMMUNE SYSTEM PROVIDES THREE LEVELS OF DEFENSE AGAINST DISEASE-CAUSING ORGANISMS



BARRIERS Prevent entry

- Skin and mucus membranes
- Stomach acid and digestive enzymes
- Beneficial bacteria that live in the colon (the gut microbiota)



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• WBCs called neutrophils and macrophages engulf and destroy foreign invaders and damaged cells



#### **ACQUIRED IMMUNITY** Specific defense

- WBCs called T lymphocytes (T cells) target and destroy infected or cancerous cells
- WBCs called B lymphocytes (B cells) and plasma cells produce antibodies that target and destroy infected or cancerous cells

#### Innate vs. acquired immunity

## The humoral and cell-mediated branches of the immune response



J. Bárcena & E. Blanco (2013). *Sub-cellular biochemistry*. 68. 631-65. 10.1007/978-94-007-6552-8\_21



- Immune support
- Immune boosting
- Immunosenescence
- Senolytics
- Immuno-rejuvenation
- Immunophenotyping

### Support your immune system

- Avoid certain foods:
  - GPS
  - DNA
  - Follow an anti-inflammatory diet
  - Detect or avoid food sensitivities

### Diet for immune resilience

## Proper diet = enhanced immunity vs. Poor diet = impaired immunity

### Support your immune system

- Make clean-eating a priority:
  - Wild SMASH fish
  - Plant-based diet
  - Fruits and vegetables
  - Grass-fed meats
  - High fiber
  - Nuts and seeds
  - Chicken soup

- Snack organic dark chocolate
- Herbals ginger, turmeric
- Bone broth
- Appropriate fluid intake
- Organic coffee, tea
- Oils EVOO, avocado, macadamia nut
- Mushrooms shiitake, reishi, chaga, turkey tail, maitake, oyster, lion's main
- Include nuts, avocado, olive oil in your diet
- Oleic acid from these foods stimulate SIRT1 the defense enzyme

#### Support your immune system

- Consider a time-restrictive eating (intermittent fasting) fast for 12-16 hours
- Get sufficient sleep aim for 7-8 good quality hours
- Home exercise plan work with a practitioner online
- Humidity keep humidity up at home to maintain airway health and mucus

# The impact of nutrition on COVID-19 susceptibility and long-term consequences

- High rate consumption in diets high in:
  - Saturated fats
  - Sugar

Western diet (WD)

- Refined carbs
- Lead to:
  - Obesity
  - Type-2 diabetes
- WD consumption activates:
  - Innate immune system
  - Impairs adaptive immunity
  - Leads to:
    - Chronic inflammation
    - Impaired host defense versus viruses

# The impact of nutrition on COVID-19 susceptibility and long-term consequences (cont'd)

- WD (saturated fatty acids (SFAs) can lead to chronic activation of innate immune system and inhibition of the adaptive
- Excessive SFAs induce lipotoxic state and activate innate immune system via TLR 4 (seen in macrophages, dendritic cells and neutrophils)
- WD/SFAs consumption:
  - Inhibits T & B function
  - Induces B cell apoptosis
  - Leading to B cell immunodepression
- Increased innate and decreased adaptive leads to chronic inflammation and impaired defense against viral pathogens

# The impact of nutrition on COVID-19 susceptibility and long-term consequences (cont'd)

 Increased peripheral inflammation (COVID-19) leads to increased neurodegenerative disease – complicated by unhealthy diet

#### Conclusion:

- Critical to consider impact of lifestyle habits in susceptibility to COVID-19 and recovery
- Authors recommend individuals refrain from a poor diet and consume high amounts of nutrients to boost immune function

#### Immune support supplements

- Vitamin C
- Zinc citrate
- Mixed mushroom complex
- Vitamin D3
- Probiotics

- N-Acetyl Cysteine
- Beta-glucans
- Omega-3 fatty acid
- Elderberry
- Vitamin A





# New York hospitals utilizing vitamin C

 COVID-19 intensive care patients immediately receiving 1500 mgs intravenously and re-administer exact amounts 3-4 times/day

"The patients who received vitamin C did significantly better than those who did not get vitamin C. It helps a tremendous amount, but it is not highlighted because it's not a sexy drug. "

Dr. Andrew G. Weber, pulmonologist and critical-care specialist





Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients*. 2015;7(6):4240–4270. Published 2015 May 29



Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta analysis of individual participant data

#### **Conclusions:**

Vitamin D supplementation safe and protected against acute respiratory tract infection overall.

Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.



# Vitamin D/VDR and microbiome in intestine and other putative organs



### First Data to be Published on **COVID-19 Severity** and **Vitamin D** Levels

#### COVID-19 Severity by Vitamin D Level (N=212)



### Influence of Microbiota on Viral Infections



Wilks J, Golovkina T. (2015): An overview of how the commensal microbiota influence viral pathogenesis.. *PLOS Pathogens*. https://doi.org/10.1371/journal.ppat.1002681.g001

### Probiotics

- 12-week study
- Participants had contracted a cold 4X in the past year

**Conclusion:** Consumption of probiotics significantly reduced incidence of upper respiratory infection and flu-like symptoms. They had increased slgA in the gut

Hong Z, Chiajung Y, Zonglian J, et al. Synth Syst Biotechnol, June 2018;3(2):113-120. Published online 2018 March 12

### Glutathione - COVID-19 pneumonia

**Conclusion:** Oral and IV glutathione, glutathione precursors (NAC) and alpha-lipoic acid may represent treatment approach for blocking NFKappaB and addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia

## Elderberry

- Contains several functional bioactive compounds:
  - Flavonoids
  - Phenolic acids
- Phenolic compounds are potent modulators of the immune response inflammation
- Shown to reduce production:
  - IL-16
  - IL-6
  - TNF-a
  - ROS

Putra WE, Rifa'i M. *Adv Pharm Bull*, 2019 Oct;9(4):619-623 Tiralongo E, Wee SS, Lea RA. *Nutrients*, 2016 Mar 24;8(4):182


Treating IBV with *S*. *nigra* extracts prior to infection is necessary for full virus inhibition and works synergistically with treating cells after infection



Christie C, David MZ, Susanna B, et al. *BMC Vet Res*. 2014;10:24. Published online 2014 Jan 16. doi: <u>10.1186/1746-6148-10-24</u>

### **IMMUNE SUPPORT SUPPLEMENTS**





Liposomal C	2 teaspoons daily
Zinc Lozenge	2 per day
D3 5000	1-2 caps daily
Acute Immune Benefits	1ml- 4 times daily
MegaProbiotic ND 50	1 cap daily
N-Acetyl Cysteine	2 caps daily
Immuno-DMG chewable	2 chewables daily

### Viral and cellular membrane

- Any virus must enter a human cell, replicate, and damage the cell, escaping to infect adjacent cells
- For viruses, there are 3 enzymes that play critical role in this sequence:
  - 1. ACE2



NLRP3 inflammasome

3. 3CL<sup>pro</sup>

2. Furin

### Viroporins activity and activation of inflammasomes



Farag NS, Breitinger U, Breitinger HG, El Azizi MA. Viroporins and inflammasomes: A key to understand virus-induced inflammation. Int J Biochem Cell Biol. 2020;122:105738. doi:10.1016/j.biocel.2020.105738

#### Cytokines – dangerous double-edged sword exploited by coronavirus

## Imagery of a cytokine storm

Jennifer RT, Marcus JK, Cameron PS, et al. *Microbiol Mol Rev*. 2012 Mar;76(1):16-32

### Mediators of the cytokine storm and the associated phenotypes with infection outcome



Jennifer RT, Marcus JK, Cameron PS, et al. *Microbiol Mol Rev*. 2012 Mar;76(1):16-32

### Acute respiratory distress syndrome (ARDS) Acute lung injury (ALI)

- Accumulation of neutrophils in lungs an increased production of:
  - inflammatory cytokines
  - chemokines
- ARDS/ALI dependent upon activation of inflammasome
- ARDS/ALI from cytokine storm + NLRP3 inflammasome
- Inflammasome part of our innate immune system IL-1 $\beta$  and IL-18

### Activation of the NLRP3 Inflammasome



### NLRP3 inflammasome

- EGCG/green tea
- Quercetin
- Resveratrol
- Curcumin
- Ginger
- Boswelia

- Aloe vera
- Sulforaphane
- Omega-3 fatty acid
- Vitamin D
- Melatonin
- Alpha-lipoic acid

### NLRP3 INFLAMMASOME PROTOCOL







Green Tea 70	1 cap daily
Olivir 15	1 tab BID
Curcumin C3 Complex	2 caps daily
Omega HP-D	2 sg BID
Phyto Benefits	2 caps daily
Liposomal Melatonin	2 sprays TID
Resveratrol-50	2 caps daily
Alpha Lipoic Acid	1 cap daily







Identification of dietary molecules as therapeutic agents to combat COVID-19 using molecular docking studies

- Molecular docking of 7 proteins of SARS-CoV-2 tested
- 18 compounds compared with 2 FDA drugs used in COVID-19
- Remdisivir and chloroquine
- EGCG lead compound that fits well into binding docks

**Conclusion:** EGCG should be explored as a drug candidate for treatment of COVID-19

#### Curcumin suppression of cytokine release/storm



- Results:Curcumin bl
- Curcumin block cytokine release, most importantly the key proinflammatory cytokines, IL-1, IL-6 and TNF-a
- Suppression of cytokine release by curcumin correlates with clinical improvement models of disease conditions where a cytokine storm plays a significant role in mortality



# Vitamin D deficiency contributes directly to ARDS

#### **Conclusions:**

Vitamin D deficiency common in people who develop ARDS. This deficiency appears to contribute to development of the condition. Approaches to correct vitamin D deficiency in patients at risk of ARDS should be developed.



### Vitamin D receptor inhibits NLRP3

- VDR is a negative regulator of NLRP3 activation
- VDR physically binds an NLRP3
- Blocks association of NLRP3 three with BRCC3
- Allows for NLRP3 inhibition

## Mechanisms for innate and adaptive immune responses to vitamin D



Barbara P, Gerlies T, Thomas RP, Karin A. Nutrients. 5 July 2013;5(7):2502-21

Evidence that vitamin D supplementation could reduce risk of influenza an COVID-19 infections and deaths

- Mechanisms vitamin D plays in reducing respiratory tract infections:
  - Cathelicidins and defensins lower viral replication rates
  - Reduce concentration of cytokines
- Reduce risk of infection:
  - 10,000 IU per day vitamin D3 for a few weeks
  - Then 5000 IU per day
  - Goal: raise concentration to above 40-60 ng/mL

#### **Conclusion:** For treatment of COVID-19, higher D3 will be useful

### Alpha-lipoic acid

- Naturally occurring disulfide compound
- Cellular co-enzyme
- Contains multiple antioxidant properties
- Enhances intracellular GSH levels
- Shown to attenuate the increased susceptibility to human coronavirus 229E infection

Putative pathogenesis of COVID-19 and potential adjuvant use of melatonin.



R. Zhang, X. Wang, L. Ni, et al. COVID-19: Melatonin as a potential adjuvant treatment, Life Science, 1 June 2020 online

## Overexpression of IL-6 and its potential negative consequences on the viral immune response



L. Velazquez-Salinas, A. Verdugo-Rodriguez, L. Rodriguez, M. Borca. Frontiers in Microbiology, 2019;10:1057

### IL-6 in severe case of COVID-19

- 9 severe COVID-19 patients
- Symptoms in order: fever, cough, dyspnea, fatigue
- Common comorbidity is hypertension
- IL-6 was increased with body temperature
- IL-6 was increased with CRP, LDH, D-dimer

### **Conclusion:** the dynamic change of IL-6 can be used as a marker for severe COVID-19

### Nrf2 inhibits *IL6* expression and alleviates inflammation *in vivo*



Kobayashi EH, Suzuki T, Funayama R, et al. **Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription**. *Nat Commun*. 2016;7:11624. Published 2016 May 23

### Stimulate Nrf2 pathway

- DHA
- Calorie restriction
- Curcumin
- Green tea extract
- Milk thistle
- Alpha-lipoic Acid
- Sulforaphane
- Ashwagandha
- Coffee





Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Preexisting Type 2 Diabetes



### Diabetes/Coronavirus risk

- Coronavirus enter the body
- Outcome:
  - the total amount of viruses
  - how much the virus replicates
  - how much replications happens on lung tissue
  - amount of cytokines utilized for immune response
- individuals with diabetes usually have a delayed immune response

Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors

- Females, generally, mount more robust immune responses to viral challenges than males
- Can result in more efficient virus clearance
- Estrogenic compounds found to reduce influenza

# Majority of male patients with COVID-19 have low T

- ICU patients positive COVID-19
- Male patients:
  - Low T (68.6%)
  - Low dihydrotestosterone (48.6%)
- Female patients:
  - Elevated T levels (60%) without alterations in dihydrotestosterone levels
- Male patients:
  - testosterone levels negatively correlate with inflammatory IL-2 and IFN- $\!\gamma$
  - estradiol levels positively correlate with inflammatory cytokine IL-6
- Female patients:
  - testosterone levels positively correlate with inflammatory cytokines (e.g. IL-6)

# Majority of male patients with COVID-19 have low T (cont'd)

- Critically ill male COVID-19 patients suffer from severe testosterone and dihydrotestosterone deficiencies
- Both androgens required to mount antiviral immune responses to combat infection in males



Maria S, Berfin T, Dominik J, et al. medRxiv 2020.05.07.20073817

### Men versus women

- Use of swab test
- 68 subjects, median age 37 years
- 48 males, 20 females
- Females able to achieve viral clearance significantly earlier than males
- Family members studied
- ACE2 in specific repositories were considered
- Testes one of the highest sites of ACE2 expression
- High ACE2 expression in testes suggest possible existence of gender specific viral reservoirs

### Fecal/oral transmission

- Fecal/oral transmission may be part of COVID-19 clinical picture
- Significant portion of Coronavirus patients experienced diarrhea, nausea, vomiting, and/or abdominal discomfort before onset of respiratory symptoms
- Researchers found RNA and proteins from SARS-CoV-2 (viral cause of COVID-19) are shed in feces early in infection and persist after respiratory symptoms abate

Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology, Feb. 27, 2020 online

### Fecal/oral transmission (cont'd)

- Mild GI discomfort diarrhea: 10% of people have GI symptoms
- GI manifestations consistent with distributor of ACE2 receptors which serve as entry points for SARS-CoV-2
- Receptors most abundant in cell membranes of lung AT2 cells as well as in enterocytes in the ileum and colon

Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology, Feb. 27, 2020 online

### GI track – possible route of viral transmission

- 53.4% of patients had SARS-CoV-2 RNA in stool
- 23% of patients tested positive in stool despite testing negative for the virus in respiratory samples

Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology, Feb. 27, 2020 online

## GI track – possible route of viral transmission (cont'd)

- The small but growing body of clinical evidence indicates digestive system may serve as an alternative route of SARS-CoV-2 infection
- In addition to respiratory track, they stressed adding that clinicians should be careful to promptly identify the patients with initial GI symptoms





### **GUT-LUNG CONNECTION**



### Pulmonary microbiome in health and critical illness



Samiran M, Dusan H. Yale J Biol Med, 2018 Jun; 91(2): 143–149
### Population-Based Gut Microbiome Associations With Hypertension



Hamdi J, David MK, Francine ZM. Circulation Research, 8 Nov 2018;123(11):1185-87

## Gut-hypertension

Study:

- 41 patients ideal blood pressure
- 99 patients hypertension
- 56 patients pre-hypertension

**Conclusion:** Patients with pre or hypertension had reduction in bacteria diversity

## Gut-hypertension (cont'd)

#### Phase 2

- Scientists transplanted fecal matter from patients into germ-free mice
- Mice that received fecal matter from hypertensive patients also developed hypertension

## Gut-hypertension (cont'd)

**Conversely:** Researchers transplanted feces from mice without hypertension into mice with hypertension

**Result:** Reduction in blood pressure in mice with hypertension



- SCFA link from gut-hypertension e.g.
  - Dietary fiber
  - Gut bacteria produce SFCA
- Bacterial populations: patients with higher blood pressure had lower levels of species that produce SCFA

# THE SUPPOR 7(R) ACTION PLAN

- Reset diet/lifestyle/mindset
- 2 Remove unwanted pathogens
- 3 **Replace** needed digestive enzymes and stomach acid
- 4 Regenerate damaged intestinal mucosa
- 5 Re-inoculate with quality pre and probiotics
- 6 Reintroduce certain foods removed in step 2
  - **Retain** your health and GI integrity

## Dr. Rob's 1-Month Gut Protocol

G.I. Benefits	1 scp bid
MegaProbiotic ND 50	1 cap daily
Enzyme Benefits	1 cap per meal
Amyloid Benefits	3 caps daily









### Keep an eye out...



# "Take care of your body, it's the only place you have to live".

Jim Rohn



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