LAZARUS WELLNESS
Functional Medicine • Clinical Nutrition
Spinal Therapy • Fitness & Rehabilitation

COVID-19 ANTIVIRAL PROTOCOL

The practice of Functional Medicine emphasizes the primacy of safety, validity, and effectiveness. In the novel context of COVID-19, validity in the form of published evidence is lacking. Therefore, "validity" relies upon inferences from the mechanisms of action of individual agents and/or published outcomes data supporting their mitigating effects on illness from other viral strains.

Likewise, data for the "effectiveness" of interventions targeting the viral mechanisms of COVID-19 are nascent and rapidly emerging. In this context, the following recommendations represent the Functional Medicine approach to the COVID-19 crisis:

1. **Adherence to all health recommendations from official sources to decrease viral transmission.**
2. **Optimizing modifiable lifestyle factors in order to improve overall immune function.**
    - Reduces progression from colonization to illness.
3. **Personalized consideration of therapeutic nutritional agents that may:**
    - Favorably modulate cellular defense and repair mechanisms.
    - Favorably modulate viral-induced pathological cellular processes.
    - Promote viral eradication or inactivation.
    - Mitigate collateral damage from other therapeutic agents.
    - Promote resolution of collateral damage and restoration of function.
4. **Treatment of confirmed COVID-19 illness (as per conventional standards and practice):**
    - May reduce the severity and duration of acute symptoms and complications.
5. **May support recovery and reduce long-term morbidity and sequelae.**

BACKGROUND AND MECHANISMS OF ACTION

This document discusses the mechanisms of action of a number of different botanical and nutraceutical agents. These agents can be considered as immunoadjuvants, defined as substances that act to accelerate, prolong, or enhance antigen-specific immune responses by potentiating or modulating the immune response.[1]

A coronavirus such as SARS-CoV-2 can be deadly because of its ability to stimulate a part of the innate immune response called the inflammasome, which can cause uncontrolled release of pro-inflammatory cytokines, leading to cytokine storm and severe, sometimes irreversible, damage to respiratory epithelium.[2] The SARS-CoV-2 virus has been shown to activate the NLRP3 inflammasome.[3,4]

A 2016 review article[5] entitled "Natural compounds as regulators of NLRP3 inflammasome-mediated IL-beta production" notes that "resveratrol, curcumin, EGCG [epigallocatechin gallate], and quercetin are potent inhibitors of NLRP3 inflammasome-mediated IL-1beta production, typically acting at more than one element of the involved pathways. However, it should be noted that these polyphenols have an even much broader biological effect, as they influence a variety of pathways." For example, these polyphenols modulate NF-kB upregulation, which is useful to counteract the COVID-19 'hyper-inflammation.[6]

A preprint released on March 23, 2020, identified the ability of plant bioactive compounds to inhibit the COVID-19 main protease (M^{pro}),[7] which is necessary for viral replication. There is much excitement surrounding the recent identification of M^{pro}, and it is a current potential pharmaceutical drug target. Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate were the natural compounds that appeared to have the best potential to act as COVID-19 M^{pro} inhibitors. Though further research is necessary to prove their efficacy, this study provides the biologic plausibility and mechanistic support (COVID-19 protease inhibition) to justify their use.

For these reasons, I recommend the following compounds, at standard dosages, to prevent activation of the NLRP3 inflammasome, to decrease NF-kB activation, and to potentially inhibit COVID-19 replication. There is no literature to support a regimen of a single vs. multiple agents. My recommendation is to use higher dosing and/or multiple agents when patient contextual factors (e.g., patient desire, pre-existing inflammation, multiple co-morbidities, higher risk, etc.) and/or therapeutic decision-making warrant such use.

ALL COMPOUNDS LISTED BELOW REQUIRE AN Rx FROM A BOARD-CERTIFIED CLINICAL NUTRITIONIST TO ENSURE PROPER DOSAGE AND NO INTERACTIONS WITH CURRENT MEDICATIONS/SUPPLEMENTS.

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VITAMIN D

Activated vitamin D,1,25(OH) D, a steroid hormone, is an immune system modulator that reduces the expression of inflammatory cytokines and increases macrophage function. Vitamin D also stimulates the expression of potent antimicrobial peptides (AMPs), which exist in neutrophils, monocytes, natural killer cells, and epithelial cells of the respiratory tract.[54] Vitamin D increases anti-pathogen peptides through defensins and has a dual effect due to suppressing superinfection. Evidence suggests vitamin D supplementation may prevent upper respiratory infections.[55]

Intervention	**Vitamin D**
Suggested Dose	**5,000 IU po qd in the absence of serum levels**
Mechanism(s) of action against non-COVID-19 viruses[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78]	*Favorably modulate cellular defense and repair mechanisms:* •Activation of macrophages Stimulation of anti-microbial peptides •Stimulation of anti-microbial peptides •Modulation of defensins •Modulation of TH17 cells *Favorably modulate viral-induced pathological cellular processes:* •Reduction in cytokine expression •Modulation of TGF beta
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms and complications
Strength of evidence	Limited
Risk of harm:[79],[80],[81],[82]	Mild

VITAMIN C

Vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. Supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections.[120] Vitamin C has been used in hospital ICUs to treat COVID-19 infection.

Intervention	**Vitamin C**
Suggested Dose	**1-3 grams po qd**
Mechanism(s) of action against non-COVID-19 viruses [120]	*Favorably modulate cellular defense and repair mechanisms* *Favorably modulate viral-induced pathological cellular processes*
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm[121]	Mild

PALMITOYLETHANOLAMIDE (PEA)

PEA is a naturally occurring anti-inflammatory palmitic acid derivative that interfaces with the endocannabinoid system. There was a significantly favorable outcome in five of six double blind placebo-controlled trials looking at acute respiratory disease due to influenza.[115] Dosing was generally 600 mg three times daily for up to three weeks. There are multiple mechanisms of action associated with PEA, from inhibition of TNF-alpha and NF-kB to mast cell stabilization. In influenza, it is thought that PEA works by attenuating the potentially fatal cytokine storm.

Intervention	**Palmitoylethanolamide (PEA)**
Suggested Dose	**300 mg po bid to prevent infection, 600 mg po tid x two weeks to treat infection**
Mechanism(s) of action against non-COVID-19 viruses[115]	*Favorably modulate cellular defense and repair mechanisms* *Favorably modulate viral-induced pathological cellular processes*
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional (treatment) Strong (prevention)
Risk of harm:[116],[117],[118],[119]	Mild

N-ACETYLCYSTEINE (NAC)

N-acetylcysteine promotes glutathione production, which has been shown to be protective in rodents infected with influenza. In a little-noticed six-month controlled clinical study enrolling 262 primarily elderly subjects, those receiving 600 mg NAC twice daily, as opposed to those receiving placebo, experienced significantly fewer influenza-like episodes and days of bed confinement.[36]

Intervention	**N-Acetylcysteine (NAC)**
Suggested Dose	**600-900 mg po bid**
Mechanism(s) of action against non-COVID-19 viruses:[36]	*Favorably modulate cellular defense and repair mechanisms:* •Hypothetical: repletion of glutathione and cysteine
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms
Strength of evidence	Limited
Risk of harm:[37],[38],[39],[40],[41]	Mild

QUERCETIN

Quercetin has been shown to have antiviral effects against both RNA (e.g., influenza and coronavirus) and DNA viruses (e.g., herpesvirus). Quercetin has a pleiotropic role as an antioxidant and anti-inflammatory, modulating signaling pathways that are associated with post-transcriptional modulators affecting post-viral healing.[8]

Intervention	**Quercetin**
Suggested Dose	**Regular 1 gm po bid, phytosome 250-500 mg bid**
Mechanism(s) of action against non-COVID-19 viruses	*Promote viral eradication or inactivation:*[9],[10],[11],[12],[13] •Inhibition of viral replication *Favorably modulate viral-induced pathological cellular processes:* •Modulation of NLRP3 inflammasome activation[5],[14],[15] *Mechanistically promote resolution of collateral damage and restoration of function:* •Modulation of mast cell stabilization (anti-fibrotic)
Outcomes data supporting their mitigating	Reduction of symptoms
Strength of evidence	Moderate
Risk of harm:[16],[17]	Mild

ELDERBERRY

Elderberry (*Sambucus nigra*) is an anti-viral herb [103] and likely most effective in the prevention of and early infection with respiratory viruses.[104] Therefore, these data suggest it is highly implausible that consumption of properly prepared elderberry products (from berries or flowers) would contribute to an adverse outcome related to overproduction of cytokines or lead to an adverse response in someone infected with COVID-19.

Intervention	**Elderberry**
Suggested Dose	**500 mg po qd (of USP standard of 17% anthocyanosides)**
Mechanism(s) of action against non-COVID-19 viruses[103],[107],[108],[109],[110],[111],[112]	*Favorably modulate cellular defense and repair mechanisms* *Favorably modulate viral-induced pathological cellular processes*
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm:[103],[107],[113],[114]	Mild; caution w/autoimmune disease; uncooked/unripe plant parts toxic; USDA GRAS

Evaluative Criteria

In the recommendations above, the following criteria are used to identify strength of evidence and risk of harm.

Strength of Evidence

Strength of Evidence
Conditional
Clinical experience and/or expert opinion and/or conflicting studies; biological mechanism at least partly explained.

Strength of Evidence
Limited
One study showing correlation between intervention and outcome; compelling ATMs and/or PCFs; biological mechanism at least partly explained.

Strength of Evidence
Moderate
Two independent studies (one of which is LOE = 1 or 2) showing correlation between intervention and outcome; biological mechanism at least partly explained.

Strength of Evidence
Strong
Two independent studies (both LOE = 1 or 2) showing correlation between intervention and outcome; biological mechanism fully explained or partly explained and having one additional correlative study.

Risk of Harm

Risk of Harm
Mild
Risk of self-limited symptoms; no risk of loss of function or corrective intervention anticipated; observation only.

Risk of Harm
Moderate
Risk of symptoms; no risk of loss of function or quality of life; minor evaluative and/or therapeutic intervention needed.

Risk of Harm
Significant
Risk of temporary loss of function or quality of life; significant evaluative and/or therapeutic intervention needed.

Risk of Harm
Severe
Risk of permanent symptoms, loss of function, quality of life, or death; long-term evaluative and/or therapeutic intervention needed.

Specific Antiviral Formulas

Bacticidx

TonicSea Bacticidx is an all-natural herbal immune support formula containing Echinacea root, elderflower/elderberry, and ginger root.◆

Proper immune function is critical for adults, especially if regularly in highly contagious environments such as schools or offices. Bacticidx by TonicSea is a great way to help you get the herbal ingredients you need for healthy immune function.◆

Bacticidx is formulated with three potent immune-supporting herbs: Echinacea, elderflower/elderberry, and ginger root. Research suggests that the Echinacea herb supports the body's immune function. For this reason, Echinacea is sometimes referred to as "nature's immune enhancer."◆

Bacticidx contains Ginger, which has also been used in traditional medicine throughout history as a means of aiding digestion, reducing nausea, and supporting immune function. Ginger contains fragrant polyphenols called gingerols that have been shown to have antioxidant and immune supporting roles in the body.◆

Bacticidx also contains elderflower and elderberry, which have polyphenols that help support healthy inflammatory response by inhibiting nitric oxide production in certain bodily tissues.◆

C Buffered With Bioflavonoids

C-Buffered with Bioflavonoids offers a wide range of support for the human body.* It offers potent support for antioxidant and free radical scavenging and supports the body's defense system by supporting white blood cell function and activity.* It supports the formation and maintenance of intercellular ground substance and collagen.* Vitamin C aids in the absorption of iron and the formation of red blood cells and converts folic acid to active folinic acid.* It supports healthy histamine release and supports lymphocyte formation.* Vitamin C is also required for the synthesis of carnitine and steroids.*

D3 10,000 With K2

High-Potency, Bioavailable Vitamin D Plus Vitamin K

NutriDyn D3 10,000 with K2 is a highly bioavailable form of Vitamin D3 (as cholecalciferol) and vitamin K2 (as patented MenaQ7®). Vitamin D3 and vitamin K2 are essential micronutrients with ubiquitous roles throughout the body, such as supporting stress levels, bone health, skin health, heart health, and immune function.◆

Vitamin K2 (menaquinone) comes in a variety of forms, with evidence suggesting that the form MK-7 is especially important for people that have chronic health issues causing nutrient malabsorption. Research also demonstrates that vitamin K2 is a crucial micronutrient for supporting the cardiovascular system and bone health.◆

Given the importance of adequate vitamin D levels in the body and many people's lack of exposure to direct sunlight, D3 10,000 with K2 supplementation can help users in a variety of ways. The most relevant researched-backed benefits derived from consumption of vitamin D3 and K2 include:

- Supports cardiovascular function◆
- Supports healthy mood and stress levels◆
- Supports bone and skin tissues◆
- Supports immune function◆

Lung Support

Support for Healthy Lung Function◆

Lung Support promotes healthy lung function through the potent antioxidant properties of vitamins A and C and nutrient-dense Raw Lung Concentrate.◆ By promoting healthy oxidative stress responses, Lung Support supplementation also promotes respiratory health.◆

Antioxidants are the first line of defense in supporting lung health as they scavenge free radicals in the extracellular fluid lining of the lungs.◆ Raw lung concentrate has been processed to preserve all of the nutrients, proteins, enzymes, cofactors, hormones, and vitamins to provide tissue-specific support for the lungs.◆

The ingredients in Lung Support are dosed in a manner that is congruous with what research suggests to be effective and safe, particularly for supporting healthy lung function.◆

Clinical evidence and research shows that the ingredients in Lung Support may:

- Promote healthy oxidative stress responses◆
- Promote respiratory health◆
- Supports healthy immune function◆
- Supports overall health and well-being◆

NAC-600

Antioxidant and Immune Support◆

NutriDyn NAC-600 contains pharmaceutical grade N-acetyl-L-cysteine (NAC) for supporting glutathione synthesis in the body, a key tripeptide that has important antioxidant roles in humans.◆ NAC is an acetylated version of the amino acid L-cysteine, which is the limiting factor to glutathione production since it is rarely found in foods.

Much of the L-cysteine ingested through diet and/or supplementation is suggested to be lost to first-pass metabolism. Moreover, supplementing with glutathione itself is imprudent as it is rapidly broken down by the intestines.

This is where NAC-600 comes into play, as its structural difference makes it more resistant to metabolism and thus more L-cysteine can be distributed to the body (resulting in increased glutathione production).

Since glutathione is one of the body's major endogenous antioxidants and also involved in many metabolic reactions, low levels of this peptide are associated with high levels of oxidative stress and impairments in nearly every system in the body.

Given the importance of sufficient glutathione levels in the body for supporting overall health and longevity, supplementation with NAC-600 can benefit users in a variety of ways.◆ The most relevant research-backed benefits derived from supplementation with NAC-600 include:

- Supports metabolic reactions in body systems, especially the immune, nervous, respiratory, and gastrointestinal systems◆
- Acts as an antioxidant in the body to regulate oxidative stress◆
- Supports nitric oxide production and vascular function◆

REFERENCES

1. Hotchkiss RS, Opal SM. Activating immunity to fight a foe – a new path. *N Engl J Med*. 2020;382(13):1270-1272. doi:10.1056/NEJMcibr1917242

2. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34(2):1. doi:10.23812/CONTI-E

3. Ding S, Xu S, Ma Y, Liu G, Jang H, Fang J. Modulatory mechanisms of the NLRP3 inflammasomes in diabetes. *Biomolecules.* 2019;9(12):E850. doi:10.3390/biom9120850

4. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Front Microbiol.* 2019;10:50. doi:10.3389/fmicb.2019.00050

5. T?zsér J, Benk? S. Natural compounds as regulators of NLRP3 inflammasome-mediated IL-1? production. *Mediators Inflamm.* 2016;2016:5460302. doi:10.1155/2016/5460302

6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0

7. Adem S, Eyupoglu V, Sarfraz I, Rasul A, Ali M. Identification of potent COVID-19 main protease (Mpro) inhibitors from natural polyphenols: an in silico strategy unveils a hope against CORONA. *Preprints.* Published online March 23, 2020. doi:10.20944/preprints202003.0333.v1

8. Dostal Z, Modriansky M. The effect of quercetin on microRNA expression: a critical review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2019;163(2):95-106. doi:10.5507/bp.2019.030

9. Wu W, Li R, Li X, et al. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses*. 2015;8(1):E6. doi:10.3390/v8010006

10. Kinker B, Comstock AT, Sajjan US. Quercetin: a promising treatment for the common cold. *J Anc Dis Prev Rem.* 2014;2:2:1000111. doi:10.4172/2329-8731.1000111

11. Somerville VS, Braakhuis AJ, Hopkins WG. Effect of flavonoids on upper respiratory tract infections and immune function: a systematic review and meta-analysis. *Adv Nutr*. 2016;7(3):488-497. doi:10.3945/an.115.010538

12. Qiu X, Kroeker A, He S, et al. Prophylactic efficacy of quercetin 3-?-O-D-glucoside against Ebola virus infection. *Antimicrob Agents Chemother*. 2016;60(9):5182-5188. doi:10.1128/AAC.00307-16

13. Wong G, He S, Siragam V, et al. Antiviral activity of quercetin-3-?-O-D-glucoside against Zika virus infection. *Virol Sin.* 2017;32(6):545-547. doi:10.1007/s12250-017-4057-9

14. Yi YS. Regulatory roles of flavonoids on inflammasome activation during inflammatory responses. *Mol Nutr Food Res.* 2018;62(13):e1800147. doi:10.1002/mnfr.201800147

15. Sun Y, Liu W, Zhang H, et al. Curcumin prevents osteoarthritis by inhibiting the activation of inflammasome NLRP3. *J Interferon Cytokine Res.* 2017;37(10):449-455. doi:10.1089/jir.2017.0069

16. Andres S, Pevny S, Ziegenhagen R, et al. Safety aspects of the use of quercetin as a dietary supplement. *Mol Nutr Food Res.* 2018;62(1). doi:10.1002/mnfr.201700447

17. O?arowski M, Miko?ajczak P?, Kujawski R, et al. Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: review of *in vitro*, *in vivo*, and clinical studies. *Evid Based Complement Alternat Med*. 2018;2018:7421489. doi:10.1155/2018/7421489

18. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential inhibitor of COVID-19 main protease (M^{pro}) from several medicinal plant compounds by molecular docking study. *Preprints.* Published online March 13, 2020. doi:10.20944/preprints202003.0226.v1

19. Yin H, Guo Q, Li X, et al. Curcumin suppresses IL-1? secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. *J Immunol.* 2018;200(8):2835-2846. doi:10.4049/jimmunol.1701495

20. Gong Z, Zhao S, Zhou J, et al. Curcumin alleviates DSS-induced colitis via inhibiting NLRP3 inflammsome activation and IL-1? production. *Mol Immunol.* 2018;104:11-19. doi:10.1016/j.molimm.2018.09.004

21. Zhao J, Wang J, Zhou M, Li M, Li M, Tan H. Curcumin attenuates murine lupus via inhibiting NLRP3 inflammasome. *Int Immunopharmacol.* 2019;69:213-216. doi:10.1016/j.intimp.2019.01.046

22. Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol*. 2017;174(11):1325-1348. doi:10.1111/bph.13621

23. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*). *J Altern Complement Med.* 2003;9(1):161-168. doi:10.1089/107555303321223035

24. Ng QX, Koh SSH, Chan HW, Ho CYX. Clinical use of curcumin in depression: a meta-analysis. *J Am Med Dir Assoc.* 2017;18(6):503-508. doi:10.1016/j.jamda.2016.12.071

25. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. A meta-analysis of the clinical use of curcumin for irritable bowel syndrome (IBS). *J Clin Med*. 2018;7(10):E298. doi:10.3390/jcm7100298

26. Bahramsoltani R, Rahimi R, Farzaei MH. Pharmacokinetic interactions of curcuminoids with conventional drugs: a review. *J Ethnopharmacol.* 2017;209:1-12. doi:10.1016/j.jep.2017.07.022

27. Xu J, Qiu JC, Ji X, et al. Potential pharmacokinetic herb-drug interactions: have we overlooked the importance of human carboxylesterases 1 and 2? *Curr Drug Metab.* 2019;20(2):130-137. doi:10.2174/1389200219666180330124050

28. Matsumoto K, Yamada H, Takuma N, Niino H, Sagesaka YM. Effects of green tea catechins and theanine on preventing influenza infection among healthcare workers: a randomized controlled trial. *BMC Complement Altern Med*. 2011;11:15. doi:10.1186/1472-6882-11-15

29. Lee HE, Yang G, Park YB, et al. Epigallocatechin-3-gallate prevents acute gout by suppressing NLRP3 inflammasome activation and mitochondrial DNA synthesis. *Molecules*. 2019;24(11):E2138. doi:10.3390/molecules24112138

30. Mereles D, Hunstein W. Epigallocatechin-3-gallate (EGCG) for clinical trials: more pitfalls than promises? *Int J Mol Sci*. 2011;12(9):5592-5603. doi:10.3390/ijms12095592

31. Chow HH, Cai Y, Hakim IA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res.* 2003;9(9):3312-3319.

32. Isomura T, Suzuki S, Origasa H, et al. Liver-related safety assessment of green tea extracts in humans: a systematic review of randomized controlled trials [published correction appears in *Eur J Clin Nutr.* 2016;70(11):1221-1229]. *Eur J Clin Nutr*. 2016;70(11):1340. doi:10.1038/ejcn.2016.78

33. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf.* 2008;31(6):469-484. doi:10.2165/00002018-200831060-00003

34. Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol Rep*. 2020;7:386-402. doi:10.1016/j.toxrep.2020.02.008

35. Younes M, Aggett P, Aguilar F, et al. Scientific opinion on the safety of green tea catechins. *EFSA J.* 2018;16(4):e05239. doi:10.2903/j.efsa.2018.5239

36. McCarty MF, DiNicolantonio JJ. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. *Prog Cardiovasc Dis*. Published online February 12, 2020. doi:10.1016/j.pcad.2020.02.007

37. Mokhtari V, Afsharian P, Shahhoseini M, Kalantar SM, Moini A. A review on various uses of N-acetyl cysteine. *Cell J*. 2017;19(1):11-17. doi:10.22074/cellj.2016.4872

38. Bauer IE, Green C, Colpo GD, et al. A double-blind, randomized, placebo-controlled study of aspirin and N-acetylcysteine as adjunctive treatments for bipolar depression. *J Clin Psychiatry.* 2018;80(1):18m12200. doi:10.4088/JCP.18m12200

39. Berk M, Turner A, Malhi GS, et al. A randomised controlled trial of a mitochondrial therapeutic target for bipolar depression: mitochondrial agents, N-acetylcysteine, and placebo [published correction appears in *BMC Med.* 2019;17(1):35]. *BMC Med*. 2019;17(1):18. doi:10.1186/s12916-019-1257-1

40. Clark RSB, Empey PE, Bay?r H, et al. Phase I randomized clinical trial of N-acetylcysteine in combination with an adjuvant probenecid for treatment of severe traumatic brain injury in children. *PLoS One*. 2017;12(7):e0180280. doi:10.1371/journal.pone.0180280

41. Bhatti J, Nascimento B, Akhtar U, et al. Systematic review of human and animal studies examining the efficacy and safety of *N*-acetylcysteine (NAC) and *N*-acetylcysteine amide (NACA) in traumatic brain injury: impact on neurofunctional outcome and biomarkers of oxidative stress and inflammation. *Front Neurol*. 2018;8:744. doi:10.3389/fneur.2017.00744

42. Brisdelli F, D'Andrea G, Bozzi A. Resveratrol: a natural polyphenol with multiple chemopreventive properties. *Curr Drug Metab*. 2009;10(6):530-546. doi:10.2174/138920009789375423

43. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis*. 2017;17(1):144. doi:10.1186/s12879-017-2253-8

44. Palamara AT, Nencioni L, Aquilano K, et al. Inhibition of influenza A virus replication by resveratrol. *J Infect Dis*. 2005;191(10):1719-1729. doi:10.1086/429694

45. Euba B, López-López N, Rodríguez-Arce I, et al. Resveratrol therapeutics combines both antimicrobial and immunomodulatory properties against respiratory infection by nontypeable *Haemophilus influenzae*. *Sci Rep*. 2017;7(1):12860. doi:10.1038/s41598-017-13034-7

46. Mendes da Silva D, Gross LA, Neto EPG, Lessey BA, Savaris RF. The use of resveratrol as an adjuvant treatment of pain in endometriosis: a randomized clinical trial. *J Endocr Soc*. 2017;1(4):359-369. doi:10.1210/js.2017-00053

47. Zhu CW, Grossman H, Neugroschl J, et al. A randomized, double-blind, placebo-controlled trial of resveratrol with glucose and malate (RGM) to slow the progression of Alzheimer's disease: a pilot study. *Alzheimers Dement (N Y)*. 2018;4:609-616. doi:10.1016/j.trci.2018.09.009

48. Roberts VH, Pound LD, Thorn SR, et al. Beneficial and cautionary outcomes of resveratrol supplementation in pregnant nonhuman primates. *FASEB J*. 2014;28(6):2466-2477. doi:10.1096/fj.13-245472

49. Klink JC, Tewari AK, Masko EM, et al. Resveratrol worsens survival in SCID mice with prostate cancer xenografts in a cell-line specific manner, through paradoxical effects on oncogenic pathways. *Prostate*. 2013;73(7):754-762. doi:10.1002/pros.22619

50. Shaito A, Posadino AM, Younes N, et al. Potential adverse effects of resveratrol: a literature review. *Int J Mol Sci.* 2020;21(6):E2084. doi:10.3390/ijms21062084

51. Salehi B, Mishra AP, Nigam M, et al. Resveratrol: a double-edged sword in health benefits. *Biomedicines*. 2018;6(3):E91. doi:10.3390/biomedicines6030091

52. Patel KR, Scott E, Brown VA, Gescher AJ, Steward WP, Brown K. Clinical trials of resveratrol. *Ann N Y Acad Sci.* 2011;1215:161-169. doi:10.1111/j.1749-6632.2010.05853.x

53. Brantley SJ, Argikar AA, Lin YS, Nagar S, Paine MF. Herb-drug interactions: challenges and opportunities for improved predictions. *Drug Metab Dispos*. 2014;42(3):301-317. doi:10.1124/dmd.113.055236

54. Mawson AR. Role of fat-soluble vitamins A and D in the pathogenesis of influenza: a new perspective. 2013;2013:246737. *Int Sch Res Notices.* doi:10.5402/2013/246737

55. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess*. 2019;23(2):1-44. doi:10.3310/hta23020

56. Zhou J, Du J, Huang L, Wang Y, Shi Y, Lin H. Preventive effects of vitamin D on seasonal influenza A in infants: multicenter, randomized, open, controlled clinical trial. *Pediatr Infect Dis J*. 2018;37(8):749-754. doi:10.1097/INF.0000000000001890

57. Tzilas V, Bouros E, Barbayianni I, et al. Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther*. 2019;55:17-24. doi:10.1016/j.pupt.2019.01.003

58. Ricca C, Aillon A, Viano M, Bergandi L, Aldieri E, Silvagno F. Vitamin D inhibits the epithelial-mesenchymal transition by a negative feedback regulation of TGF-? activity. *J Steroid Biochem Mol Biol*. 2019;187:97-105. doi:10.1016/j.jsbmb.2018.11.006

59. Fischer KD, Agrawal DK. Vitamin D regulating TGF-? induced epithelial-mesenchymal transition [published correction appears in *Respir Res*. 2015;16:139]. *Respir Res*. 2014;15:146. doi:10.1186/s12931-014-0146-6

60. Schrumpf JA, Ninaber DK, van der Does AM, Hiemstra PS. TGF-?1 impairs vitamin D-induced and constitutive airway epithelial host defense mechanisms. *J Innate Immun*. 2020;12(1):74-89. doi:10.1159/000497415

61. Liu RM, Gaston Pravia KA. Oxidative stress and glutathione in TGF-beta-mediated fibrogenesis. *Free Radic Biol Med*. 2010;48(1):1-15. doi:10.1016/j.freeradbiomed.2009.09.026

62. Lu L, Lu Q, Chen W, Li J, Li C, Zheng Z. Vitamin D_3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. *J Diabetes Res*. 2018;2018:8193523. doi:10.1155/2018/8193523

63. Rao Z, Chen X, Wu J, et al. Vitamin D receptor inhibits NLRP3 activation by impeding its BRCC3-mediated deubiquitination. *Front Immunol*. 2019;10:2783. doi:10.3389/fimmu.2019.02783

64. Hewison M. Vitamin D and immune function: an overview. *Proc Nutr Soc*. 2012;71(1):50-61. doi:10.1017/S0029665111001650

65. Fitch N, Becker AB, HayGlass KT. Vitamin D [1,25(OH)2D3] differentially regulates human innate cytokine responses to bacterial versus viral pattern recognition receptor stimuli. *J Immunol*. 2016;196(7):2965-2972. doi:10.4049/jimmunol.1500460

66. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol*. 2017;27(1). doi:10.1002/rmv.1909

67. Verway M, Bouttier M, Wang TT, et al. Vitamin D induces interleukin-1? expression: paracrine macrophage epithelial signaling controls *M. tuberculosis* infection. *PLoS Pathog*. 2013;9(6):e1003407. doi:10.1371/journal.ppat.1003407

68. Tulk SE, Liao KC, Muruve DA, Li Y, Beck PL, MacDonald JA. Vitamin D_3 metabolites enhance the NLRP3-dependent secretion of IL-1? from human THP-1 monocytic cells. *J Cell Biochem*. 2015;116(5):711-720. doi:10.1002/jcb.24985

69. Lee MT, Kattan M, Fennoy I, et al. Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease. *Blood Adv*. 2018;2(9):969-978. doi:10.1182/bloodadvances.2017013979

70. Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol*. 2017;5(12):986-1004. doi:10.1016/S2213-8587(17)30357-1

71. Sluyter JD, Camargo CA, Waayer D, et al. Effect of monthly, high-dose, long-term vitamin D on lung function: a randomized controlled trial. *Nutrients*. 2017;9(12):E1353. doi:10.3390/nu9121353

72. Scragg R. The vitamin D assessment (ViDA) study – design and main findings. *J Steroid Biochem Mol Biol*. 2020;198:105562. doi:10.1016/j.jsbmb.2019.105562

73. Turin A, Bax JJ, Doukas D, et al. Interactions among vitamin D, atrial fibrillation, and the renin-angiotensin-aldosterone system. *Am J Cardiol*. 2018;122(5):780-784. doi:10.1016/j.amjcard.2018.05.013

74. Zaheer S, Taquechel K, Brown JM, Adler GK, Williams JS, Vaidya A. A randomized intervention study to evaluate the effect of calcitriol therapy on the renin-angiotensin system in diabetes. *J Renin Angiotensin Aldosterone Syst*. 2018;19(1):1470320317754178. doi:10.1177/1470320317754178

75. Cremer A, Tambosco C, Corcuff JB, et al. Investigating the association of vitamin D with blood pressure and the renin-angiotensin-aldosterone system in hypertensive subjects: a cross-sectional prospective study. *J Hum Hypertens*. 2018;32(2):114-121. doi:10.1038/s41371-017-0005-2

76. Zittermann A, Ernst JB, Prokop S, et al. Effects of vitamin D supplementation on renin and aldosterone concentrations in patients with advanced heart failure: the EVITA trial. *Int J Endocrinol*. 2018;2018:5015417. doi:10.1155/2018/5015417

77. Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep*. 2014;4:7027. doi:10.1038/srep07027

78. Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep*. 2017;16(5):7432-7438. doi:10.3892/mmr.2017.7546

79. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA.* 2010;303(18):1815-1822. doi:10.1001/jama.2010.594

80. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med.* 2016;176(2):175-183. doi:10.1001/jamainternmed.2015.7148

81. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. *Clin Pharmacol Ther.* 2009;85(2):198-203. doi:10.1038/clpt.2008.165

82. Žofková I. Hypercalcemia. Pathophysiological aspects. *Physiol Res.* 2016;65(1):1-10. doi:10.33549/physiolres.933059

83. Favero G, Franceschetti L, Bonomini F, Rodella LF, Rezzani R. Melatonin as an anti-inflammatory agent modulating inflammasome activation. *Int J Endocrinol.* 2017;2017:1835195. doi:10.1155/2017/1835195

84. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov.* 2020;6:14. doi:10.1038/s41421-020-0153-3

85. Zhang R, Wang X, Ni L, et al. COVID-19: melatonin as a potential adjuvant treatment. *Life Sci*. Published online March 23, 2020. doi:10.1016/j.lfs.2020.117583

86. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: a critical systematic review of clinical evidence. *Complement Ther Med.* 2019;42:65-81. doi:10.1016/j.ctim.2018.11.003

87. Andersen LP, Gögenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. *Clin Drug Investig.* 2016;36(3):169-175. doi:10.1007/s40261-015-0368-5

88. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev.* 2002;2:CD001520. doi:10.1002/14651858.CD001520

89. Leite Pacheco R, de Oliveira Cruz Latorraca C, Adriano Leal Freitas da Costa A, Luiza Cabrera Martimbianco A, Vianna Pachito D, Riera R. Melatonin for preventing primary headache: a systematic review. *Int J Clin Pract.* 2018;72(7):e13203. doi:10.1111/ijcp.13203

90. Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. *Arch Dis Child.* 2018;103(12):1155-1162. doi:10.1136/archdischild-2017-314181

91. Besag FMC, Vasey MJ, Lao KSJ, Wong ICK. Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a systematic review. *CNS Drugs.* 2019;33(12):1167-1186. doi:10.1007/s40263-019-00680-w

92. Harpsøe NG, Andersen LP, Gögenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. *Eur J Clin Pharmacol.* 2015;71(8):901-909. doi:10.1007/s00228-015-1873-4

93. Wirtz PH, Spillmann M, Bärtschi C, Ehlert U, von Känel R. Oral melatonin reduces blood coagulation activity: a placebo-controlled study in healthy young men. *J Pineal Res.* 2008;44(2):127-133. doi:10.1111/j.1600-079X.2007.00499.x

94. McGlashan EM, Nandam LS, Vidafar P, Mansfield DR, Rajaratnam SMW, Cain SW. The SSRI citalopram increases the sensitivity of the human circadian system to light in an acute dose. *Psychopharmacology (Berl).* 2018;235(11):3201-3209. doi:10.1007/s00213-018-5019-0

95. Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. *J Clin Med*. 2018;7(9):E258. doi:10.3390/jcm7090258

96. Cui D, Moldoveanu Z, Stephensen CB. High-level dietary vitamin A enhances T-helper type 2 cytokine production and secretory immunoglobulin A response to influenza A virus infection in BALB/c mice. *J Nutr*. 2000;130(5):1132-1139. doi:10.1093/jn/130.5.1132

97. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. *N Engl J Med.* 1995;333(21):1369-1373. doi:10.1056/NEJM199511233332101

98. Bartlett H, Eperjesi F. Possible contraindications and adverse reactions associated with the use of ocular nutritional supplements. *Ophthalmic Physiol Opt.* 2005;25(3):179-194. doi:10.1111/j.1475-1313.2005.00294.x

99. Bendich A, Langseth L. Safety of vitamin A. *Am J Clin Nutr.* 1989;49(2):358-371. doi:10.1093/ajcn/49.2.358

100. Cruz S, da Cruz SP, Ramalho A. Impact of vitamin A supplementation on pregnant women and on women who have just given birth: a systematic review. *J Am Coll Nutr.* 2018;37(3):243-250. doi:10.1080/07315724.2017.1364182

101. Oliveira JM, Allert R, East CE. Vitamin A supplementation for postpartum women. *Cochrane Database Syst Rev.* 2016;3:CD005944. doi:10.1002/14651858.CD005944.pub3

102. García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. *Int J Mol Sci*. 2016;17(4):537. doi:10.3390/ijms17040537

103. Porter RS, Bode RF. A review of the antiviral properties of black elder (*Sambucus nigra* L.) products. *Phytother Res*. 2017;31(4):533-554. doi:10.1002/ptr.5782

104. Chen C, Zuckerman DM, Brantley S, et al. *Sambucus nigra* extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res*. 2014;10:24. doi:10.1186/1746-6148-10-24

105. Barak V, Halperin T, Kalickman I. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. *Eur Cytokine Netw*. 2001;12(2):290-296.

106. Barak V, Birkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J*. 2002;4(11 Suppl):919-922.

107. Ulbricht C, Basch E, Cheung L, et al. An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. *J Diet Suppl*. 2014;11(1):80-120. doi:10.3109/19390211.2013.859852

108. Frank T, Janssen M, Netzet G, Christian B, Bitsch I, Netzel M. Absorption and excretion of elderberry (*Sambucus nigra* L.) anthocyanins in healthy humans. *Methods Find Exp Clin Pharmacol*. 2007;29(8):525-533. doi:10.1358/mf.2007.29.8.1116309

109. Badescu M, Badulescu O, Badescu L, Ciocoiu M. Effects of *Sambucus nigra* and *Aronia melanocarpa* extracts on immune system disorders within diabetes mellitus. *Pharm Biol*. 2015;53(4):533-539. doi:10.3109/13880209.2014.931441

110. Curtis PJ, Kroon PA, Hollands WJ, et al. Cardiovascular disease risk biomarkers and liver and kidney function are not altered in postmenopausal women after ingesting an elderberry extract rich in anthocyanins for 12 weeks. *J Nutr*. 2009;139(12):2266-2271. doi:10.3945/jn.109.113126

111. Fallah AA, Sarmast E, Fatehi P, Jafari T. Impact of dietary anthocyanins on systemic and vascular inflammation: systematic review and meta-analysis on randomised clinical trials. *Food Chem Toxicol*. 2020;135:110922. doi:10.1016/j.fct.2019.110922

112. Li S, Wu B, Fu W, Reddivari L. The anti-inflammatory effects of dietary anthocyanins against ulcerative colitis. *Int J Mol Sci.* 2019;20(10):E2588. doi:10.3390/ijms20102588

113. Elderberry for influenza. *Med Lett Drugs Ther*. 2019;61(1566):32. [https://secure.medicalletter.org/w1566f]

114. Hawkins J, Baker C, Cherry L, Dunne E. Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials. *Complement Ther Med*. 2019;42:361-365. doi:10.1016/j.ctim.2018.12.004

115. Keppel Hesselink JM, de Boer T, Witkamp RF. Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold. *Int J Inflam*. 2013;2013:151028. doi:10.1155/2013/151028

116. Cordaro M, Cuzzocrea S, Crupi R. An update of palmitoylethanolamide and luteolin effects in preclinical and clinical studies of neuroinflammatory events. *Antioxidants (Basel)*. 2020;9(3):E216. doi:10.3390/antiox9030216

117. Davis MP, Behm B, Mehta Z, Fernandez C. The potential benefits of palmitoylethanolamide in palliation: a qualitative systematic review. *Am J Hosp Palliat Care*. 2019;36(12):1134-1154. doi:10.1177/1049909119850807

118. Gabrielsson L, Mattsson S, Fowler CJ. Palmitoulethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. *Br J Clin Pharmacol*. 2016;82(4):932-942. doi:10.1111/bcp.13020

119. Natural Medicines Database. Palmitoylethanolamide (PEA). Accessed March 30, 2020. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=1596

120. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*. 2017;9(11):E1211. doi:10.3390/nu9111211

121. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU: a meta-analysis. *Nutrients.* 2019;11(4):708. doi:10.3390/nu11040708