Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Explore 16 (2020) 354–356

Contents lists available at ScienceDirect

Explore

journal homepage: www.elsevier.com/locate/jsch

Review Article

Integrative considerations during the COVID-19 pandemic

Lise Alschuler[a,b,*], Andrew Weil[b,c], Randy Horwitz[a,b], Paul Stamets[d], Ann Marie Chiasson[a,b], Robert Crocker[a,b], Victoria Maizes[a,b]

[a] University of Arizona College of Medicine, United States
[b] Andrew Weil Center for Integrative Medicine, United States
[c] University of Arizona, United States
[d] Fungi Perfecti, LLC, United States

There is a high level of interest in integrative strategies to augment public health measures to prevent COVID-19 infection and associated pneumonia. Unfortunately, ***no integrative measures have been validated in human trials as effective specifically for COVID-19.*** Notwithstanding, this is an opportune time to be proactive. Using available in-vitro evidence, an understanding of the virulence of COVID-19, as well as data from similar, but different, viruses, we offer the following strategies to consider. Again, we stress that these are supplemental considerations to the current recommendations that emphasize regular hand washing, physical distancing, stopping non-essential travel, and obtaining testing in the presence of symptoms.

While the pathogenicity of COVID-19 is complex, it is important to understand the role of inflammation in this disease. The virulence and pathogenicity (including acute respiratory distress syndrome) associated with SARS corona viruses develops as the result of viral activation of cytoplasmic NLRP3 inflammasome. This inflammasome within activated (upregulated NFkB) macrophages and Th1 immune cells releases proinflammatory cytokines, namely IL-1B and IL-18, which dictate the pathogenic inflammation responsible for the virulence and symptoms of COVID-19.[1] Understanding this component of COVID-19 infection provides a mechanistic underpinning to several of the following.

Risk reduction

- **Adequate sleep**: Shorter sleep duration increases the risk of infectious illness. One study found that less than 5 h of sleep (monitored over 7 consecutive days) increased the risk of developing rhinovirus associated cold by 350% (odds ratio [OR] = 4.50, 95% confidence interval [CI], 1.08–18.69) when compared to individuals who slept at least 7 h per night.[2] Important specifically to COVID-19 infection, sleep deprivation increases CXCL9 levels. CXCL9 is a monokine, induced by interferon, which increases lymphocytic infiltration,[3] and which is implicated in NLRP3 inflammasome activation.[4] Adequate sleep also ensures the secretion of melatonin, a molecule which may play a role in reducing coronavirus virulence (see **Melatonin** below).
- **Stress management**: Psychological stress disrupts immune regulation and is specifically associated with increased proinflammatory cytokines such as IL-6.[5] Acute stress in mice increases IL-1B via NLRP3 inflammasome activation.[6] Various mindfulness techniques such as meditation, breathing exercises, guided imagery, etc. reduce stress, reduce activated NFkB, may reduce CRP and do not appear to increase inflammatory cytokines.[7]
- **Zinc**: Coronavirus appear to be susceptible to the viral inhibitory actions of zinc. Zinc may prevent coronavirus entry into cells[8] and appears to reduce coronavirus virulence.[9] Typical daily dosing of zinc is 15 mg–30 mg daily with lozenges potentially providing direct protective effects in the upper respiratory tract.
- **Vegetables and fruits +/- isolated Flavonoids**: Many flavonoids have been found, in vitro, to reduce NLRP3 inflammasome signaling, and consequently NFkB, TNF-a, IL-6, IL-1B and IL-18 expression.[10] Some of the specific flavonoids which have been shown to have this effect, and which can be found in the diet and/or dietary supplements include:

  - **baicalin**[11] and **wogonoside**[12] from **Scutellaria baicalensis** (Chinese skullcap);
  - **liquiritigenin**[13] from **Glycyrrhiza glabra** (licorice)
  - **dihydroquercetin**[14] and **quercetin**[15] found in **onions** and **apples**. Of note, **quercetin** also functions as a **zinc ionophore**, **chelating zinc** and transporting it into the **cell cytoplasm**.[16] This could, theoretically, enhance the anti-viral actions of **zinc**.
  - **myricetin**[17] found in **tomatoes, oranges, nuts,** and **berries**
  - **apigenin**[18] (found in **Matricaria recutita (Chamomile), parsley** and **celery**.
  - **curcumin**[19,20] (found in **turmeric** root)
  - **epigallocatechine gallate (EGCG)** from green tea. EGCG has been found to have antiviral activity against a wide range of DNA and RNA viruses, especially in the early stages of infection by preventing viral attachment, entry and membrane fusion[21] EGCG, link **quercetin**, is a **zinc ionophore**,[16] thereby potentially enhancing the antiviral actions of zinc.

* Corresponding author
E-mail address: alschuler@email.arizona.edu (L. Alschuler).

https://doi.org/10.1016/j.explore.2020.03.007

At least 5–7 servings of vegetables and 2–3 servings of fruit daily provide a repository of flavonoids and are considered a cornerstone of an anti-inflammatory diet.

- **Vitamin C**: Like flavonoids, ascorbic acid inhibits NLRP3 inflammasome activation.[22] Clinical trials have found that vitamin C shortens the frequency, duration and severity of the common cold and the incidence of pneumonia.[23] Typical daily dosing of vitamin C ranges from 500 mg to 3000 mg daily with even higher doses utilized during times of acute infection.
- **Melatonin**: Melatonin has been shown to inhibit NFkB activation and NLRP3 inflammasome activation.[24] In fact, the age-related decline in melatonin production is one proposed mechanism to explain why children do not appear to have severe symptoms as frequently as do older adults. Melatonin also reduces oxidative lung injury and inflammatory cell recruitment during viral infections.[25] Typical dosing of melatonin varies widely from 0.3 mg to 20 mg (the latter used in the oncological setting).
- **Sambucus nigra (Elderberry):** There is preclinical evidence that elderberry inhibits replication and viral attachment of Human coronavirus NL63 (HCoV-NL63),[26] which although different than COVID-19, is still a member of the same coronavirus family. Sambucus appears most effective in the prevention or early stage of corona virus infections.[27] Of note, Sambucus significantly increases inflammatory cytokines, including IL-B1[28] so should be discontinued with symptoms of infection (or positive test). An evidence-based systematic review of elderberry conducted by the Natural Standard Research Collaboration concluded that there is level B evidence to support the use of elderberry for influenza[29] which may or may not be relevant to COVID-19 prevention. Typical dosing of 2:1 elderberry extract is 10 mL–60 mL daily for adults and 5mL–30 mL daily for children.
- **Vitamin D:** In certain conditions, vitamin D has been found to decrease NLRP3 inflamasome activation[30] and vitamin D receptor activation reduces IL-1b secretion.[31] However, 1,25(OH)vitamin D has also been found to increase IL-1b levels,[32,33] and should, therefore, be used with caution and perhaps discontinued with symptoms of infection.

During symptoms of infection or positive test for COVID-19

To avoid: Given the integral role of inflammatory cytokines (namely IL-1B and IL-18) in the pathogenicity of COVID-19, as well as the impossibility of predicting which individuals are susceptible to the "cytokine storm", technically called secondary hemophagocytic lymphohistiocytosis, or sHLH, it appears to be prudent to avoid high and regular use of immunostimulatory agents which increase these cytokines. Again, in the absence of human clinical data, **caution is warranted with the following immune activating agents** due to preclinical evidence of increased IL-1B and/or IL-18 production in infected immune cells:

- ! Sambucus nigra (Elderberry)[34] (i.e. Elderberry may be used for prevention but should be stopped if any symptoms of infection appear.)
- ! Isolated polysaccharide extracts from medicinal mushrooms or mycelium[35,36]
- ! Echinacea angustifolia and E. purpurea[37,38]
- ! Larch arabinogalactan[39]
- ! Vitamin D[40,41]

Likely safe: Other commonly used natural immunostimulatory and antiviral agents including the following do not appear to increase IL-1B or IL-18 as a part of their immunomodulatory actions. Several of these, in fact, reduce these cytokines and may restore immune homeostasis. These are, therefore, likely safe to use both prior to, and during, COVID-19 infection. Whether these agents mitigate the symptoms or virulence of COVID-19 is unknown and therefore the benefit of these agents during COVID-19 infection is unknown.

- Allium sativum (garlic)[42]
- Quercetin[43]
- Astragalus membranaceus[44,45]
- Mycelium mushroom extracts[46,47] as well as fruiting body extract of Agaricus blazeii[48]
- Mentha piperita (peppermint)[49]
- Andrographis paniculata[50]
- Green tea and green tea extracts[51,52]
- Zinc[53]
- Vitamin A[54] [note: This study found that 25,000iu daily for 4 months in 84 women resulted in lower serum IL-1b and IL-1b/IL-4 ratios in obese women. Oral vitamin A can causes hypervitaminosis A especially at doses greater than 25,000 IU daily for more than 6 years or 100,000iu daily for more than 6 months.[55] Monitoring liver function tests for hepatotoxicity during vitamin A dosing of any duration, even at lower doses, is advised given variable individual sensitivity.]
- Vitamin C[56]

The information and understanding of COVID-19 continues to change rapidly. We encourage you to make integrative recommendations carefully and with consideration of the underlying mechanisms of both the COVID-19 infection and the intended intervention. **It is also important to reiterate that to date there are no clinically evidence-based integrative prevention or treatment strategies for COVID-19 infection.**

References

1 Chen I-Y, et al. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Front Microbiol*. 2019;10:50.
2 Prather AA, et al. Behaviorally assessed sleep and susceptibility to the common cold. *Sleep*. 2015;38(9):1353–1359.
3 Gorbachev AV, et al. CXC chemokine ligand 9/monokine induced by IFN-gamma production by tumor cells is critical for T cell-mediated suppression of cutaneous tumors. *J Immunol*. 2007;178:2278–2286.
4 Romero JM, et al. A four-chemokine signature is associated with a T-cell-Inflamed phenotype in primary and metastatic pancreatic cancer. *Clin Cancer Res*. 2020 Jan 21. online ahead of print].
5 Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. *J Neuroimmune Pharmacol*. 2006;1(4):421.
6 Iwata M, et al. Psychological stress activates the inflammasome via release of adenosine triphosphate and stimulation of the purinergic type 2X7 receptor. *Biol Psychiatry*. 2016;80(1):12.
7 Black D, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann NY Acad Sci*. 2016;1373(1):13.
8 Phillips JM, et al. Neurovirulent murine coronavirus jhm.sd uses cellular zinc metalloproteases for virus entry and cell-cell fusion. *J Virol*. 2017;91(8).
9 Han Y-S, et al. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization, and inhibition. *Biochemistry*. 2005;44(30):10349.
10 Lim H, et al. Flavonoids interfere with NLRP3 inflammasome activation. *Toxicol Appl Pharmacol*. 2018;355:93.
11 Fu S, et al. Baicalin suppresses NLRP3 inflammasome and nuclear factor-kappa b (NF-κB) signaling during haemophilus parasuis infection. *Vet Res*. 2016;47(1):80.
12 Sun Y, et al. Wogonoside protects against dextran sulfate sodium-induced experimental colitis in mice by inhibiting nf-κb and NLRP3 inflammasome activation. *Biochm Pharmacol*. 2015;94(2):142.
13 Zhu X, et al. Liquiritigenin attenuates high glucose-induced mesangial matrix accumulation, oxidative stress, and inflammation by suppression of the nf-κb and NLRP3 inflammasome pathways. *Biomed Pharmacother*. 2018;106:976.
14 Ding T, et al. Kidney protection effects of dihydroquercetin on diabetic nephropathy through suppressing ROS and NLRP3 inflammasome. *Phytomedicine*. 2018:(41):45.
15 Choe J-Y, et al. Quercetin and ascorbic acid suppress fructose-induced NLRP3 inflammasome activation by blocking intracellular shuttling of txnip in human macrophage cell lines. *Inflammation*. 2017;40(3):980.
16 Dabbagh-Bazarbachi H. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from hepa 1-6 cells to a liposome model. *J Agric Food Chem*. 2014;62(32):8085–8093.

17 Chen H, et al. Myricetin inhibits NLRP3 inflammasome activation via reduction of ROS-dependent ubiquitination of ASC and promotion of ROS-independent NLRP3 ubiquitination. *Toxicol Appl Pharmacol*. 2019;365:19.
18 Yamagata K, et al. Dietary apigenin reduces induction of LOX-1 and NLRP3 expression, leukocyte adhesion, and acetylated low-density lipoprotein uptake in human endothelial cells exposed to trimethylamine-n-oxide. *J Cardiovasc Pharmacol*. 2019;74(6):558.
19 Yin H, et al. Curcumin suppresses IL-1β secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. *J Immunol*. 2018;200(8):2835.
20 Wen CC, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem*.. 2007;50(17):4087.
21 Kaihatsu K, et al. Antiviral mechanism of action of epigallocatechin-3- o-gallate and its fatty acid esters. *Molecules*. 2018;23(10):2475.
22 Choe J-Y, et al. Quercetin and ascorbic acid suppress fructose-induced NLRP3 inflammasome activation by blocking intracellular shuttling of txnip in human macrophage cell lines. *Inflammation*. 2017;40(3):980.
23 Hemila H. Vitamin c supplementation and respiratory infections: a systematic review. *Mil Med*. 2004;169(11):90.
24 Hardeland R. Melatonin and inflammation – story of a double-edged blade. *J Pineal Res*. 2018;65(4):e12525.
25 Silvestri M, Rossi GA. Melatonin: its possible role in the management of viral infections – a brief review. *Ital J Pediatr*. 2013;39:61.
26 Weng J-R, et al. Antiviral activity of sambucus formosananakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. *Virus Res*. 2019;273: 197767.
27 Chen C, et al. Sambucus nigra extracts inhibit infectious bronchitis virus at an early point during replication. *BMC Vet Res*. 2014;10:24.
28 Barak V, et al. 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.
29 Ulbricht C, et al. An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the natural standard research collaboration. *J Dietary Suppl*. 2014;11(1):80.
30 Lu L, et al. Vitamin d 3 protects against diabetic retinopathy by inhibiting high-glucose-induced activation of the ROS/TXNIP/NLRP3 inflammasome pathway. *J Diabetes Res*. 2018. 8193523.
31 Rao Z, et al. Vitamin D receptor inhibits NLRP3 activation by impeding its BRCC3-Mediated deubiquitination. *Front Immunol*. 2019;10:2783.
32 Verway M, et al. Vitamin d induces interleukin-1β expression: paracrine macrophage epithelial signaling controls M. tuberculosis infection. *PLoS Pathog*. 2013;9:(6) e1003407.
33 Tulk SE, et al. Vitamin D_3 metabolites enhance the NLRP3-dependent secretion of IL-1β from human THP-1 monocytic cells. *J Cell Biochem*. 2015;116(5):711.
34 Barak V, et al. 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.
35 Yang Y, et al. Protein-bound polysaccharide-K induces IL-1β via TLR2 and NLRP3 inflammasome activation. *Innate Immun*.. 2014;20(8):857.
36 Ma XL, et al. Immunomodulatory activity of macromolecular polysaccharide isolated from Grifola frondosa. *Chin J Nat Med*. 2015;13(12):906.
37 Burger RA, et al. Echinacea-induced cytokine production by human macrophages. *Int J Immunopharmacol*. 1997;19(7):371.
38 Senchina DS, et al. Human blood mononuclear cell in vitro cytokine response before and after two different strenuous exercise bouts in the presence of bloodroot and echinacea extracts. *Blood Cells Mol Dis*. 2009;43(3):298.
39 Hauer J, Anderer FA. Mechanism of stimulation of human natural killer cytotoxicity by arabinogalactan from larix occidentalis. *Cancer Immunol Immunother*. 1993;36(4):237.
40 Verway M, et al. Vitamin D induces interleukin-1β expression: paracrine macrophage epithelial signaling controls M. tuberculosis infection. *PLoS Pathog*. 2013;9:(6) e1003407.
41 Tulk SE, et al. Vitamin D_3 metabolites enhance the NLRP3-dependent secretion of IL-1β from human THP-1 monocytic cells. *J Cell Biochem*. 2015;116(5):711.
42 Arreola R, et al. Immunodulation and anti-inflammatory effects of garlic compounds. *J Immunol Res*. 2015;2015: 401630.
43 Mlcek J, et al. Quercetin and its anti-allergic immune response. *Molecules*. 2016;21 (5):623.
44 He X, et al. Inhibitory effect of astragalus polysaccharides on lipopolysaccharide-induced TNF-a and IL-1β production in THP-1 cells. *Molecules*. 2012;17(3):3155.
45 Li H., et al. Astragaloside inhibits IL-1β-induced inflammatory response in human osteoarthritis chondrocytes and ameliorates the progression of osteoarthritis in mice immunopharmacol immunotoxicol. 2019;421(4):497.
46 Davis R, et al. Differential immune activating, anti-inflammatory, and regenerative properties of the aqueous, ethanol, and solid fractions of a medicinal mushroom blend. *J Inflammation Res*. 2020;13:117.
47 Benson KF. The mycelium of the trametes versicolor (Turkey tail) mushroom and its fermented substrate each show potent and complementary immune activating properties in vitro. *MC Complement Alternat Med*. 2019;19:342.
48 Tangen J-M. Immunomodulatory effects of the agaricus blazei murrill-based mushroom extract andosan in patients with multiple myeloma undergoing high dose chemotherapy and autologous stem cell transplantation: a randomized, double blinded clinical study. *BioMed Res Int*. 2015;2015:: 718539.
49 Li Y, et al. In vitro antiviral, anti-inflammatory, and antioxidant activities of the ethanol extract of mentha piperita l. *Food Sci Biotechnol*. 2017;26(6):1675.
50 Chandrasekaran CV, et al. In vitro comparative evaluation of non-leaves and leaves extracts of andrographis paniculata on modulation of inflammatory mediators. *Antiinflamm Antiallergy Agents Med Chem*. 2012;11(2):191.
51 Ge M, et al. Multiple antiviral approaches of (-)-epigallocatechin-3-gallate (EGCG) against porcine reproductive and respiratory syndrome virus infection *in vitro*. *Antiviral Res*. 2018;158:52–62.
52 Ahmed S, et al. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. *Free Radic Biol Med*. 2002;33(8):1097.
53 Han Y-S, et al. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization, and inhibition. *Biochemistry*. 2005;44(30):10349.
54 Farhangi MA, et al. Vitamin a supplementation and serum Th1- And Th2-associated cytokine response in women. *J Am Coll Nutr*. 2013;32(4):280.
55 Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr*. 2006;83(23):191.
56 Choe J-Y, et al. Quercetin and ascorbic acid suppress fructose-induced NLRP3 inflammasome activation by blocking intracellular shuttling of txnip in human macrophage cell lines. *Inflammation*. 2017;40(3):980.