The Functional Medicine Approach to COVID-19: Virus-Specific Nutraceutical and Botanical Agents

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Abstract

As the novel infection with SARS-CoV-2 emerges, objective assessment of the scientific plausibility of nutraceutical and botanical interventions for prevention and treatment is important. We evaluate twelve such interventions with mechanisms of action that modulate the immune system, impair viral replication, and/or have been demonstrated to reduce severity of illness. These are examples of interventions that, mechanistically, can help protect patients in the presence of the prevalent and infectious SARS-CoV-2 virus. While there are limited studies to validate these agents to specifically prevent COVID-19, they have been chosen based upon their level of evidence for effectiveness and safety profiles, in the context of other viral infections. These agents are to be used in a patient-specific manner in concert with lifestyle interventions known to strengthen immune response (see related article in this issue of *IMCJ*).

Background and Introduction

Health professionals and the public must be well informed about the SARS-CoV-2 virus, the disease it causes (COVID-19), and how it spreads. This information is readily available and not within the scope of this document. At this time, there are no specific vaccines or uniformly successful treatments for COVID-19. In this context of insufficient evidence, the scope of this document will be to assess the scientific plausibility of promising prevention approaches and therapeutic (nutraceutical and botanical) interventions and then to offer clinical recommendations.

With respect to interventions, 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:

- Adherence to all health recommendations from official sources to decrease viral transmission.
- Optimizing modifiable lifestyle factors in order to improve overall immune function (an introductory document on boosting immunity is available[i]). This should reduce progression from colonization to illness.
- Personalized consideration of therapeutic 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.
- Treatment of confirmed COVID-19 illness (as per conventional standards and practice):
  - May reduce the severity and duration of acute symptoms and complications.
  - May support recovery and reduce long-term morbidity and sequelae.

Additional references are being collated and will be made available in the future.

i. https://www.ifm.org/news-insights/boosting-immunity-functional-medicine-tips-prevention-immunity-boosting-covid-19-coronavirus-outbreak/

Clinical Recommendations and Mechanisms of Action

Background and Mechanisms of Action

We encourage practitioners to learn about the mechanism of invasion, replication, and pathophysiology of the SARS-CoV-2 virus. Much of what we know has been extrapolated from basic science research on SARS-CoV-2. Excellent resources are available online, including the free YouTube lectures through Dr. Roger Seheult.[ii]

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-1β production" notes that "resveratrol, curcumin, EGCG [epigallocatechin gallate], and quercetin are potent inhibitors of NLRP3 inflammasome-mediated IL-1β 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-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate were the natural compounds that appeared to have the best potential to act as COVID-19 Mpro 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, we 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. Our 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.

Download COVID-19: Nutraceutical and Botanical Recommendations for Patients[iii]

Recommended Interventions

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: 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 effects on illness from other viral strains	Reduction of symptoms
Strength of evidence	Moderate
Risk of harm[16,17]	Mimimal

ii. https://www.youtube.com/user/MEDCRAMvideos/feed
iii. https://p.widencdn.net/kvdwlh/COVID-19_Nutraceutical-and-Botanical-Recommendations-for-Patients_v4

Curcumin

Curcumin has been shown to modulate the NLRP3 inflammasome,[5] and a preprint suggests that curcumin can target the SARS-CoV-2 main protease to reduce viral replication.[18]

Intervention	**Curcumin**
Suggested dose	**500–1,000 mg po bid (of absorption-enhanced curcumin)**
Mechanism(s) of action against non-COVID-19 viruses	*Favorably modulate viral-induced pathological cellular processes:* • Modulation of NLRP3 inflammasome activation[5,19-21]
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm[22-27]	Mimimal

Epigallocatechin Gallate (EGCG)

Green tea, in addition to modulating the NLRP3 inflammasome and, based on a preprint, potentially targeting the SARS-CoV-2 main protease (M^{pro})[7] to reduce viral replication, has also been shown to prevent influenza in healthcare workers.[28]

Intervention	**Epigallocatechin gallate (EGCG)**
Suggested dose	**4 cups daily or 225 mg po qd**
Mechanism(s) of action against non-COVID-19 viruses	*Favorably modulate viral-induced pathological cellular processes:* • Modulation of NLRP3 inflammasome activation[5,28,29]
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm[30-35]	Significant (rare)—Hepatotoxicity

***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:* • 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[37-41]	Mimimal

Resveratrol

Resveratrol, a naturally occurring polyphenol, shows many beneficial health effects.[42] It has been shown to modulate the NLRP3 inflammasome.[5] In addition, resveratrol was shown to have in vitro activity against MERS-CoV.[43]

Intervention	**Resveratrol**
Suggested dose	**100–150 mg po qd**
Mechanism(s) of action against non-COVID-19 viruses	*Favorably modulate viral-induced pathological cellular processes* • Modulation of NLRP3 inflammasome activation[5]
Outcomes data supporting their mitigating effects on illness from other viral strains	MERS-CoV[43] Influenza[44,45]
Strength of evidence	Conditional
Risk of harm[46-53]	Mimimal

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] However, there is some controversy as to whether it should be used and the laboratory value that should be achieved. Research suggests that concerns about vitamin D (increased IL-1beta in cell culture) are not seen clinically. The guidance we suggest is that a laboratory range of >50 and < 80ng/mL serum 25-hydroxy vitamin D may help to mitigate morbidity from COVID-19 infection.

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[55-78]	*Favorably modulate cellular defense and repair mechanisms:* • Activation of macrophages • 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[79-82]	Mimimal

Melatonin

Melatonin has been shown to have an inhibitory effect on the NLRP3 inflammasome.[83] This has not gone unnoticed by the COVID-19 research community, with two recent published papers proposing the use of melatonin as a therapeutic agent in the treatment of patients with COVID-19.[84,85]

Intervention	**Melatonin**
Suggested dose	**5–20 mg qd**
Mechanism(s) of action against non-COVID-19 viruses[83,84]	*Favorably modulate viral-induced pathological cellular processes* • Modulation of NLRP3 inflammasome activation[83,84]
Outcomes data supporting their mitigating effects on illness from other viral strains	Research in progress
Strength of evidence	Conditional
Risk of harm[86-94]	Mimimal

Vitamin A

Vitamin A is a micronutrient that is crucial for maintaining vision, promoting growth and development, and protecting epithelium and mucus integrity in the body. Vitamin A is known as an anti-inflammation vitamin because of its critical role in enhancing immune function. Vitamin A is involved in the development of the immune system and plays regulatory roles in cellular immune responses and humoral immune processes through the modulation of T helper cells, sIgA, and cytokine production. Vitamin A has demonstrated a therapeutic effect in the treatment of various infectious diseases.[95]

Intervention	**Vitamin A**
Suggested dose	**Up to 10 000–25 000 IU/d**
Mechanism(s) of action against non-COVID-19 viruses[95,96]	*Favorably modulate cellular defense and repair mechanisms:* • Modulation of helper T cells • Modulation of sIgA *Favorably modulate viral-induced pathological cellular processes:* • Modulation of cytokine production
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm[97-102]	Mimimal, if does not exceed this dose; caution: pregnancy

Elderberry

Elderberry (*Sambucus nigra*) is seen in many medicinal preparations and has widespread historical use as an anti-viral herb.[103] Based on animal research, elderberry is likely most effective in the prevention of and early infection with respiratory viruses.[104] One in-vitro study reported an increase in TNF-alpha levels related to a specific commercial preparation of elderberry,[105] leading some to caution that its use could initiate a "cytokine storm." However, these data were not confirmed when the same group performed similar studies, which were published in 2002.[106] 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 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[103,107-112]	*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 with autoimmune disease; uncooked/unripe plant parts toxic; USDA GRAS

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	PEA = conditional (treatment) PEA = strong (prevention)
Risk of harm[116-119]	Mimimal

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.

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]	Mimimal

Zinc

Zinc contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. There is also evidence that it suppresses viral attachment and replication. Zinc deficiency is common, especially in those populations most at risk for severe SARS-CoV-2 infections, and is challenging to accurately diagnosis with laboratory measures. Supplementation with zinc is supported by evidence that it both prevents viral infections and reduces their severity and duration. Moreover, it has been shown to reduce the risk of lower respiratory infection, which may be of particular significance in the context of COVID-19.

Intervention	Zinc
Suggested Dose	**30–60 mg daily in divided doses** Zinc acetate, citrate, picolinate or glycinate orally. Zinc gluconate as lozenge.
Mechanism(s) of action against non-COVID-19 viruses[120-127]	*Favorably modulate innate and adaptive immune system* *Favorably modulate viral-induced pathological cellular processes, attachment and replication*
Outcomes data supporting their mitigating effects on illness from other viral strains	Prevention, reduced severity of symptoms, reduced duration of illness, prevention of lower respiratory tract infection
Strength of evidence	Strong
Risk of harm[128]	Mimimal

Evaluative Criteria

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

Strength of Evidence	Risk of Harm
Strength of Evidence **Conditional** Clinical experience and/or expert opinion and/or conflicting studies; biological mechanism at least partly explained.	**Risk of Harm** **Mimimal** Risk of self-limited symptoms; no risk of loss of function or corrective intervention anticipated; observation only.
Strength of Evidence **Limited** One study showing correlation between intervention and outcome; compelling ATMs and/or PCFs; biological mechanism at least partly explained.	**Risk of Harm** **Mild** Risk of symptoms; no risk of loss of function or quality of life; minor evaluative and/or therapeutic intervention needed.
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.	**Risk of Harm** **Significant** Risk of temporary loss of function or quality of life; significant evaluative and/or therapeutic intervention needed.
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** **Severe** Risk of permanent symptoms, loss of function, quality of life, or death; long-term evaluative and/or therapeutic intervention needed.

Note: This resource is only intended to identify botanical and nutraceutical and botanical agents that may boost your immune system. It is not meant to recommend any treatments, nor have any of these been proven effective against coronavirus. None of these practices are intended to be used in lieu of other recommended treatments. Always consult your physician or healthcare provider prior to initiation. For up-to-date information on COVID-19, please consult the Centers for Disease Control and Prevention at www.cdc.gov.

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