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## Letter to the Editor

## Supplements for COVID-19: A modifiable environmental risk



We have read with great interest the review by Gasmi A et al. exploring risk factors associated with disease severity in patients with COVID-19 [1]. The authors discuss an individualized patient approach to mitigating risk, especially regarding environmental factors over which patients and providers have some control. We were intrigued by the discussion of herbs with suspected anti-viral properties as a potential therapy for COVID-19. The authors present data regarding possible therapeutic effects of some herbal supplements. Herbal or “natural” supplements are used around the world for a myriad of reasons. Evidence supporting their clinical utility is limited, with a non-significant risk of harm [2]. Patient rationale for using supplements is multifactorial and includes a desire for “natural” treatments, cultural traditions, and/or a distrust of conventional medicine. We would like to note that some over the counter supplements may have unrecognized deleterious effects on the host immune and metabolic status, which could negatively alter disease severity of COVID-19.

COVID-19 is the disease caused by the SARS-CoV-2 virus, a novel highly pathogenic coronavirus that most often causes symptoms of upper respiratory infection. While many cases are mild, in some, SARS-CoV-2 is able to infect lower respiratory epithelial cells and induce a pathogenic immune response that can ultimately lead to hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), and death. The underlying pathophysiology surrounding this progression is unknown, and risk factors including hypertension, obesity, and diabetes are currently under investigation. However, rapid worsening of disease severity likely involves an uncontrolled immune response resulting in cytokine storm. Data from prior coronavirus outbreaks including SARS-CoV and MERS-CoV suggest that delayed release of interferons followed by recruitment of macrophages with rapid production of pro-inflammatory cytokines and chemokines play a central role in disease morbidity. These include but are not limited to interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), tumor necrosis factor (TNF), chemokine ligand-2 (CCL-2), chemokine ligand-3 (CCL-3), and chemokine ligand-5 (CCL-5) [3]. This cytokine storm is thought to be responsible for the recruitment of a large number of inflammatory cells, tissue infiltration, and ultimately organ injury. Although our understanding of the pathophysiology of SARS-CoV-2 is evolving, patients with COVID-19 have serum elevation of a number of pro-inflammatory cytokines including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , which positively correlate with disease severity [3]. Blunting this response has become a mainstay of treatment, with systemic steroids and inhibitors of cytokines such as IL-6 commonly being employed.

Gasmi et al. discuss nutrition in treating coronavirus. Zinc may have a possible therapeutic benefit and many hospitals and practitioners are prescribing zinc to patients with COVID-19. While there are reports of anti-viral effects of zinc clinically as well as *in vitro* data suggesting that zinc may slow the replication of coronaviruses [4], its effect on the clinical outcomes of COVID-19 patients remains to be elucidated. The use of other supplements, many of which have little to no data on clinical effectiveness or safety, is more concerning.

Many herbal supplements are currently being promoted in the lay media as “immune-boosters” against coronavirus. These so called “immune-boosting” agents may in fact have precisely the opposite effect in treating and mitigating the deleterious effects of the coronavirus, as described above. *Echinacea purpurea*, for example, is a supplement commonly taken for alleviation of upper respiratory infections and is believed to have immunomodulatory properties via enhancement of the innate immune system. However, some evidence suggests that it may stimulate macrophage production of pro-inflammatory cytokines including IL-1, IL-6, and TNF- $\alpha$  [5], which could worsen the cytokine storm and lung injury observed in COVID-19. Studies have suggested similar findings with garlic extract supplementation [6]. Astragalus is an herb whose root is commonly used in traditional Chinese medicine for a number of indications including immune stimulation in patients with malignancy. It has an unknown mechanism of action, although it is implicated in promoting macrophage production of TNF- $\alpha$  and IL-6 *in vitro* as well [7]. Other culprits which physicians should be aware of include elderberry extract, andrographis, *Pelargonium sidoides*, curcumin, and propolis. While the risk of these products worsening disease severity in COVID-19 is theoretical, at a time when disease pathophysiology is poorly understood and therapeutic options are limited, cessation of supplements may represent an additional environmental risk that can be modified. Moreover, patients may cling to such remedies as protection or cure and undervalue other reported measures such as social distancing and hand hygiene. These and many other supplements marketed as “immune-boosting” have little to no data on their *in vivo* immunomodulatory activity in humans, and avoiding them may be best practice until more is known.

Gasmi et al. adroitly summarize the possible therapeutics for coronavirus. We would be remiss to dismiss the potential utility of herbs for COVID-19, provided robust clinical trial data. Licorice (*Glycyrrhiza glabra*) root for example, has been proposed as a potential therapy for highly pathogenic coronaviruses because it contains large amounts of glycyrrhizin—the namesake of the plant responsible for its distinct flavor. During the 2002–2004 SARS outbreak, glycyrrhizin was found to inhibit SARS-CoV replication *in vitro* more than any other studied compound including ribavirin [8]. Although these reports may herald a promising therapeutic option for COVID-19, it would be premature to recommend its use without further studies given the potential risk of harm with herbal supplements.

Our understanding of the pathophysiology of SARS-CoV-2 infection is limited and continues to evolve. In this time of uncertainty, mitigating individual risks is essential. Gasmi et al. highlight many modifiable risks. We add that certain herbal supplements have the potential to worsen severity of disease in COVID-19 and practitioners should counsel patients to eliminate such supplements in an effort to optimize personal environmental factors. Further studies on the effectiveness and safety should be conducted before supplements can confidently be recommended to patients.

<https://doi.org/10.1016/j.clim.2020.108465>

Received 11 May 2020; Accepted 12 May 2020

Available online 15 May 2020

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## Funding

None.

## Declaration of Competing Interest

Dr. Zampella is a consultant for X4 Pharmaceuticals.

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